COMPREHENSIVE ORGANIC CHEMISTRY

The Synthesis and Reactions of Organic Compounds

Chairman and Deputy Chairman of the Editorial Board
SIR DEREK BARTON, F.R.S.
and
W. DAVID OLLIS, F.R.S.

COMPREHENSIVE ORGANIC CHEMISTRY

COMPREHENSIVE ORGANIC CHEMISTRY
EDITORIAL BOARD

Volume 1

Stereochemistry, Hydrocarbons, Halo Compounds, Oxygen Compounds

Edited by J. F. Stoddart, University of Sheffield

Volume 2

Nitrogen Compounds, Carboxylic Acids, Phosphorus Compounds

Edited by I. O. Sutherland, University of Liverpool

Volume 3

Sulphur, Selenium, Silicon, Boron, Organometallic Compounds

Edited by D. Neville Jones, University of Sheffield

Volume 4

Heterocyclic Compounds

Edited by P. G. Sammes, The City University, London

Volume 5

Biological Compounds

Edited by E. Haslam, University of Sheffield

Volume 6

Author, Formula, Subject, Reagent, Reaction Indexes

Edited by C. J. Drayton, Pergamon Press, Oxford

COMPREHENSIVE ORGANIC CHEMISTRY

The Synthesis and Reactions of Organic Compounds

CHAIRMAN AND DEPUTY CHAIRMAN OF THE EDITORIAL BOARD

SIR DEREK BARTON, F.R.S.

AND

W. DAVID OLLIS, F.R.S.

Volume 1 Stereochemistry, Hydrocarbons, Halo Compounds, Oxygen Compounds

Edited by J. F. STODDART

UNIVERSITY OF SHEFFIELD

PERGAMON PRESS

OXFORD · NEW YORK · TORONTO · SYDNEY · PARIS · FRANKFURT

U.K.	Pergamon Press Ltd., Headington Hill Hall, Oxford OX3 0BW, England
U.S.A.	Pergamon Press Inc., Maxwell House, Fairview Park, Elmsford, New York 10523, U.S.A.
CANADA	Pergamon of Canada, Suite 104, 150 Consumers Road, Willowdale, Ontario, M2 J1P9, Canada
AUSTRALIA	Pergamon Press (Aust.) Pty. Ltd, P.O. Box 544, Potts Point, N.S.W. 2011, Australia
FRANCE	Pergamon Press SARL, 24 rue des Ecoles, 75240 Paris, Cedex 05, France
FEDERAL REPUBLIC OF GERMANY	Pergamon Press GmbH, 6242 Kronberg-Taunus, Pferdstrasse 1, Federal Republic of Germany

First edition 1979

British Library Cataloguing in Publication Data
Comprehensive organic chemistry
1. Chemistry, Organic
I. Barton, *Sir*, Derek
547 QD251.2 78-40502

ISBN 0-08-021313-8
ISBN 0-08-021319-7 (set)

Printed in Great Britain by A. Wheaton & Co. Ltd., Exeter

Foreword

During more than a century, the development of organic chemistry has been associated with extensive documentation. Vast numbers of textbooks, monographs, and reviews have been published with the objective of summarizing and correlating the results obtained by many thousands of organic chemists working in academic and industrial research laboratories. However, out of this colossal literature there is but a relatively small number of textbooks and multi-volumed works which have become generally accepted as representing real steps forward in the presentation of our subject.

During the classical era of organic chemistry (1820–1940), textbooks which had a profound influence on the teaching of the subject included, for example, works by Armstrong (1874), van't Hoff (1875), Roscoe–Schorlemmer (1878), Richter (1888), Gattermann (1895), van't Hoff–Werner–Eiloart (1898), Meyer–Jacobson (1902), Schmidt–Rule (1926), Karrer (1928), Freudenberg (1933), Richter–Anschütz (1935), and Gilman (1938). These texts provide an opportunity to comment on the relationship between the history of organic chemistry and its associated publications. The *Treatise on Chemistry* by Roscoe and Schorlemmer consisted of three volumes (5343 pages) published in nine parts over the period 1878–1892: the major component was Volume III (6 parts, 3516 pages) which was devoted to organic chemistry. Another instructive example is the important work *Lehrbuch der Organischen Chemie*, produced by Victor Meyer and Paul Jacobson. The increase in size from the edition (1735 pages) published during 1902–1903 to the edition (5115 pages) published over the period 1913–1924 is striking.

Many have expressed concern about the problems of maintaining effective contact with the expanding literature of organic chemistry, but few have allowed themselves to become involved with attempted solutions. The decision to publish Comprehensive Organic Chemistry was not taken lightly. The absence of a work reflecting the current rapid development of modern organic chemistry has been lamented by many eminent chemists, including the late Sir Robert Robinson (1886–1975) who played an important role in the initiation of this project shortly before his death. Comprehensive Organic Chemistry was conceived, designed, and produced in order to meet this deficiency. We realised that the current rate of growth of organic chemistry demanded speedy publication and, furthermore, that its interaction with other subjects including biochemistry, inorganic chemistry, molecular biology, medicinal chemistry, and pharmacology required the collaboration of many authors. The selection of topics to be included in order to justify the work as being comprehensive has not been easy. We recognize that some areas of organic chemistry have not been given the detailed treatment which can be justified, but we have done our best to meet the expectations of the majority of readers. In particular, we have not made a special section for Theoretical Organic Chemistry. This is not because of any lack of appreciation on our part of the importance of Theory. It is because a correct treatment of Theory cannot be made comprehensible in an abbreviated form. It is also because Theory changes with time more rapidly than the facts of the subject. Theory is better treated in our view in specialist monographs. The same arguments apply equally to the fundamental subject of Stereochemistry. Any comments regarding errors and omissions will be appreciated so that they can be dealt with in future editions.

The contents of each volume have been brought together so as to reflect what are judged to be the truly important facets of modern organic chemistry. The information is presented in a concise and logical manner with mechanistic organic chemistry being adopted to provide a constant and correlative theme. The dominating intention of the Editorial Board has been to ensure the publication of a contribution to the literature of

organic chemistry which will be genuinely useful and stimulating. Emphasis has therefore been given throughout to the properties and reactions of all the important classes of organic compounds, including the remarkable array of different compounds prepared by synthesis as well as natural products created by biosynthesis. Of course, the study of natural products provided the original foundation stones on which modern synthetic organic chemistry now firmly stands.

As a major presentation of modern organic chemistry, Comprehensive Organic Chemistry will be doubly useful because we have provided, in a separate volume, an extensive index. Not only have the contents of the work been indexed in the ordinary way, but we have also added a substantial number of additional references from the original literature. These do not appear in the text itself. Thus, the reader who wishes to obtain additional information about reactions and reagents mentioned in the text will quickly be able to consult the original literature. The Index volume has been prepared by a team from Pergamon Press.

Our debt to the Authors and to the Volume Editors is considerable. We are very grateful to all our colleagues for the efficient way in which they have tried to meet the challenges (and the deadlines!) which have been presented to them. We hope that the Authors have enjoyed their association with this venture. In a lighter vein, we also trust that their feelings are different from the statement 'this task put system into my soul but not much money into my purse' attributed to Henry Edward Armstrong (1848–1937) after he had written his *Introduction to Organic Chemistry* in 1874.

We are delighted to acknowledge the masterly way in which Robert Maxwell, the Publisher, and the staff at Pergamon Press have supported the Volume Editors and the Authors in our endeavour to produce a work which correctly portrays the relevance and achievements of organic chemists and their contributions to knowledge by research.

D. H. R. Barton
Chairman

W. D. Ollis
Deputy Chairman

Contents

Part 1 Nomenclature and Stereochemistry **1**

1 Introduction and Stereochemistry 3
J. F. Stoddart, *University of Sheffield*

Part 2 Hydrocarbons **35**

2.1 Saturated Hydrocarbons 37
T. Clark, *Universität Erlangen-Nürnberg*, and M. A. McKervey, *University College, Cork*

2.2 Olefinic and Acetylenic Hydrocarbons 121
G. H. Whitham, *University of Oxford*

2.3 Dienes, Polyenes, and Acetylenic Hydrocarbons 171
G. Pattenden, *University of Nottingham*

2.4 Aromaticity 215
P. J. Garratt, *University College London*

2.5 Arenes and their Reactions 241
H. Heaney, *University of Technology, Loughborough*

2.6 Annulenes and Related Systems 361
P. J. Garratt, *University College London*

2.7 Carbocations and Carbanions 411
D. Bethell, *University of Liverpool*

2.8 Radicals, Carbenes, and Arynes 455
J. T. Sharp, *University of Edinburgh*

Part 3 Halo Compounds **491**

3 Halo Compounds 493
R. D. Chambers and S. R. James, *University of Durham*

Part 4 Alcohols, Phenols, Ethers, and Related Compounds **577**

4.1 Alcohols 579
S. G. Wilkinson, *University of Hull*

4.2 Phenols 707
D. A. Whiting, *University of Nottingham*

4.3 Ethers 799
N. Baggett, *University of Birmingham*

4.4 Cyclic Ethers 853
A. H. Haines, *University of East Anglia*

4.5 Alkyl Aryl and Diaryl Ethers 897
D. A. Whiting, *University of Nottingham*

4.6 Peroxides 909
D. Swern, *Temple University, Philadelphia*

Part 5 Aldehydes and Ketones 941

5.1 Aldehydes 943
R. Brettle, *University of Sheffield*

5.2 Ketones 1017
A. J. Waring, *University of Birmingham*

5.3 Aromatic Aldehydes 1105
T. Laird, *Imperial Chemical Industries Limited, Blackley, Manchester*

5.4 Aromatic Ketones 1161
T. Laird, *Imperial Chemical Industries Limited, Blackley, Manchester*

5.5 Quinones 1213
T. Laird, *Imperial Chemical Industries Limited, Blackley, Manchester*

Preface to Volume 1

Chemistry assumes a ubiquitous status amongst the natural sciences. Not only does it seek, through the investigation of molecular structure and reaction mechanism, to answer questions posed by physical and chemical phenomena, but it also provides, through the medium of synthesis, a challenge to the innovative spirit and creative genius of man. It should always be a science and is sometimes an art. Often, the curiosity of the chemist in his quest to understand natural phenomena is surpassed only by his desire to emulate the chemical works of Nature. Nowhere across the wide spectrum of chemical disciplines has so much been accomplished by the practitioners in such a relatively short time span as within the domain — whatever that might be — of organic chemistry. A consideration in this volume to a range of topics which leads the reader through a somewhat arbitrary maze from hydrocarbons to quinones must, of necessity, pay some allegiance to the past glories of the subject. However, earlier achievements in no way overshadow more recent triumphs by organic chemists in manipulating molecular events involving the more mundane functional groups which will always provide the staple diet for chemical reactivity in organic compounds. Moreover, the last three decades have witnessed a technological revolution in the tooling of chemistry with the widespread introduction of, for example, chromatography and spectroscopy in their many and varied forms. In addition, interpretative and predictive powers have been increased enormously with the advent of modern high-speed electronic computers.

Stereochemistry has always provided a focal point within organic chemistry. It seemed not only reasonable but logical to allow recent conceptual developments in stereochemistry, coupled with the inevitable proliferation in nomenclature surrounding these advances, to provide a short introduction to this volume in Part 1. Aside from their very considerable commercial importance, hydrocarbons, be they saturated or unsaturated, aliphatic or aromatic, have captured the imagination of theoreticians and experimentalists alike in recent years. Chapters 1–6 in Part 2 illustrate how the interplay of theory and practice has provided a much needed fillip to progress in this area. A discussion of reactive intermediates in Chapters 7 and 8 of Part 2 provides a useful bridge to the remainder of the volume. The early pre-eminence of carbocations has now given way to the recognition of the synthetic utility of other reactive species — particularly carbanions, but also radicals, carbenes, and arynes. Part 3 is given over entirely to halo compounds—a situation which reflects their importance from both academic and industrial viewpoints. In Part 4, alcohols, phenols, ethers, and peroxides are discussed in six separate chapters. Here, the importance of the oxygen atom in naturally occurring compounds is providing the organic chemist with the incentive, not only to understand, but also to mimic, *e.g.* the dramatic developments around crown ethers in a decade. Finally, of course, the carbonyl group is the centrepiece of organic chemistry. Chapters 1–5 in Part 5 must be viewed not only as individual contributions but also as introductions to much of the chemistry to be discussed in subsequent volumes of this work.

Circumstances eventually dictated that I was joined by no less than eighteen contributors in this mission to produce Volume 1 of Comprehensive Organic Chemistry. In so far as we are judged to have been successful in producing an interesting and readable account, the credit belongs to the authors. In so far as we are judged to have erred in our task through omissions or worse, the responsibility is mine. Whatever the judgement might be, I thank all those who have helped me to collate the material for this volume.

Sheffield J. F. STODDART

Contributors to Volume 1

Dr. N. Baggett
Department of Chemistry, University of Birmingham

Dr. D. Bethell
Robert Robinson Laboratories, University of Liverpool

Dr. R. Brettle
Department of Chemistry, University of Sheffield

Professor R. D. Chambers
Department of Chemistry, University of Durham

Dr. T. Clark
Institüt für Organische Chemie der Universität Erlangen-Nürnberg

Dr. P. J. Garrett
Christopher Ingold Laboratories, University College London

Dr. A. H. Haines
School of Chemical Sciences, University of East Anglia

Dr. H. Heaney
Organic Chemistry Laboratories, University of Technology, Loughborough

Dr. S. R. James
Department of Chemistry, University of Durham

Dr. T. Laird
Imperical Chemical Industries Ltd., Blackley, Manchester

Professor M. A. McKervey
Department of Chemistry, University College, Cork

Dr. G. Pattenden
Department of Chemistry, University of Nottingham

Dr. J. T. Sharp
Department of Chemistry, University of Edinburgh

Dr. J. F. Stoddart
Department of Chemistry, University of Sheffield

Professor D. Swern
Department of Chemistry, Temple University, Philadelphia

Dr. A. J. Waring
Department of Chemistry, University of Birmingham

Dr. D. A. Whiting
Department of Chemistry, University of Nottingham

Dr. G. H. Whitham
Dyson Perrins Laboratory, University of Oxford

Dr. S. G. Wilkinson
Department of Chemistry, University of Hull

Contents of Other Volumes

Volume 2

Part 6 Amines and Related Compounds
Part 7 Nitro and Nitroso Compounds
Part 8 Imines, Nitrones, Nitriles, and Isocyanides
Part 9 Carboxylic Acids and Related Compounds
Part 10 Phosphorus Compounds

Volume 3

Part 11 Organic Sulphur Compounds
Part 12 Organic Selenium and Tellurium Compounds
Part 13 Organic Silicon Compounds
Part 14 Organic Boron Compounds
Part 15 Organometallic Compounds

Volume 4

Part 16 Nitrogen Systems: The Azines
Part 17 Nitrogen Systems: The Azoles and other Systems
Part 18 Oxygen Systems
Part 19 Sulphur and Other Heteroatom Systems
Part 20 Mixed Heteroatom Systems

Volume 5

Part 21 Biological Chemistry: Introduction
Part 22 Nucleic Acids
Part 23 Proteins: Amino-acids and Peptides
Part 24 Proteins: Enzyme Catalysis and Functional Proteins
Part 25 Lipid Chemistry and Biochemistry
Part 26 Carbohydrate Chemistry
Part 27 Synthesis of Organic Macromolecules and their Uses in Organic Chemistry
Part 28 Bio-organic Chemistry
Part 29 Biosynthetic Pathways from Acetate
Part 30 Biosynthesis: A General Survey

Volume 6

Author Index
Formula Index
Subject Index
Reagent Index
Reaction Index

PART 1

NOMENCLATURE AND STEREOCHEMISTRY

1

Introduction and Stereochemistry

J. F. STODDART
University of Sheffield

1.1 SCOPE 3
1.2 SYMMETRY AND CHIRALITY 4
1.3 CHEMICAL TOPOLOGY 11
1.4 ISOMERISM 13
1.4.1 Some definitions 13
1.4.2 Designation of constitution 16
1.4.3 Designation of absolute configuration 16
1.4.4 Designation of relative configuration 19
1.4.5 Designation of conformation 21
1.4.6 Concept of isomerism 24
1.5 TOPISM 26
1.5.1 Some terminology 26
1.5.2 Prochirality 28
1.5.3 Pseudoasymmetry (Pseudochirality) 30
1.6 TOPOMERISM 31
1.7 DYNAMIC STEREOCHEMISTRY: A BRIEF COMMENT 31

1.1 SCOPE

There is little doubt that the emergence of stereochemical concepts over more than a century or so has been reflected intimately in the development of organic chemistry as a scientific discipline. Although stereochemistry is as old as organic chemistry itself, it provides, nonetheless, a suitable introductory theme to a treatise such as this devoted to modern organic chemistry. In more recent times, the advent of conformational analysis as a result of the pioneering paper[1] published in 1950 by Barton heralded a new era of growth in organic chemistry. During almost three decades now, conformational ideas in particular and stereochemical concepts in general have fostered major advances in (i) our approach to structural elucidations, (ii) our knowledge of reaction mechanisms, and (iii) our development of new synthetic methods. In this brief introductory section, the more recent conceptual advances in stereochemistry will be brought under scrutiny since they impinge most directly upon structural aspects. Thereafter, some contemporary aspects of dynamic stereochemistry will be highlighted very briefly as a forerunner to the remainder of the work. Inevitably, a short introduction must of necessity ignore many important stereochemical topics in specialized fields. Thus, at the outset, we refer the reader to a selection of numerous[2–19] textbooks, monographs, and reviews on various aspects of stereochemistry in the hope that he might find there what he will not find here in this introductory chapter.

1.2 SYMMETRY AND CHIRALITY

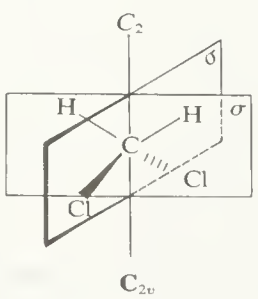
The symmetry properties of geometrical figures are characterized by symmetry operations which in turn define the symmetry elements (see Table 1) present in the particular simplex under examination.[6,20–24] If molecules can be assumed[20–28]—for the present at least—to generate geometrical figures, then it is possible to discuss their molecular structures in terms of their symmetry. In the first instance, it will be useful to restrict this discussion to (i) molecules which have defined structures by virtue of their rigidity and (ii) flexible molecules in which structures are defined as a consequence of selecting particular conformations. Basically, there are two kinds of symmetry elements — namely (i) axes of rotation and (ii) rotation-reflection axes — which a molecule can display through inspection

TABLE 1
Symmetry Elements and Symmetry Operations

Symmetry elements	*Symmetry operations*
C_n (Axis of symmetry)[a]	Rotation about an axis through $2\pi/n$ radians
σ (Plane of symmetry)[b]	Reflection in a plane
i (Centre of symmetry)[c]	Inversion through a centre
S_n (Rotation-reflection axis of symmetry)	Rotation about an axis through $2\pi/n$ radians followed by reflection in a plane perpendicular to the axis

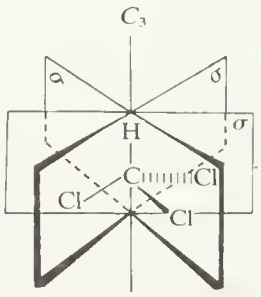
[a] All molecules have an infinite number of trivial axes which can be referred to collectively as the identity element, E. [b] A plane of symmetry corresponds to a S_1 symmetry element. [c] A centre of symmetry corresponds to a S_2 symmetry element.

of symmetry operations. Molecules that witness superimposition of structures upon their original structures as a consequence of rotation by $2\pi/n$ radians about an axis possess a so-called C_n axis (*n.b.* symmetry element descriptors are usually italicized). For example, dichloromethane (**1**) contains a C_2 axis and chloroform (**2**), a C_3 axis. All molecules, of course, contain an infinite number of trivial C_1 axes and, for this reason, they are often referred to collectively as the identity element, E. Molecules whose structures are indistinguishable from the original structures only after rotation by $2\pi/n$ radians followed by reflection in a plane perpendicular to the chosen axis of rotation possess a so-called S_n axis. When $n = 1$, the trivial S_1 axis corresponds to a plane of symmetry (σ) perpendicular to the rotation axis. A σ plane is most easily recognized as a mirror plane which bisects the molecule such that the ligands on one side of the plane are reflected exactly upon those on the other side. For example, dichloromethane (**1**) possesses two, and chloroform (**2**) three, σ planes. When $n = 2$, the S_2 axis corresponds to a centre of inversion (i) which demands that all ligands in the molecule are capable of inversion through a centre, *i.e.* any two particular ligands lie on a line going through the centre of the molecule such that the ligands are equidistant from the centre. The particular conformation (**3**) of *meso*-1,2-difluoro-1,2-dichloroethane contains a centre of symmetry. Higher order S_n (n must be an



C_{2v}

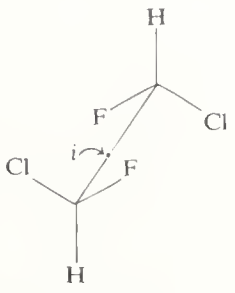
(**1**)



C_{3v}

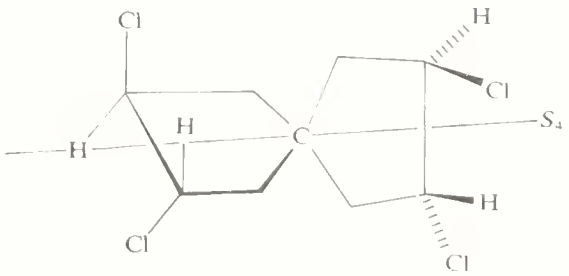
(**2**)

even number) axes are a relatively rare phenomenon but they do occur, for example, in spiro compounds of the type (**4**).



C_i

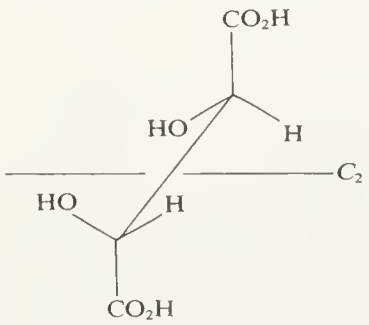
(**3**)



S_4

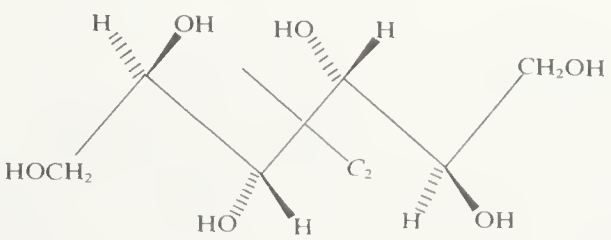
(**4**)

Molecules which contain S_n symmetry elements, *i.e.* a plane ($\sigma \equiv S_1$), or centre ($i \equiv S_2$) of symmetry, or a higher-order S_n ($n = 4$, 6, *etc.*) axis have reflection symmetry and are said[6,7,25–30] to be non-dissymmetric or achiral. Such molecules are devoid of handedness and therefore cannot exhibit enantiomerism and hence any of the chiroptical properties associated with this phenomenon. By contrast, molecules without reflection symmetry are said[6,7,25–30] to be dissymmetric or chiral. Such molecules are not superimposable upon their mirror images and therefore exhibit enantiomerism. This means that, in principle at least, these molecules can display optical activity. However, it should be recognized that the absence of measurable chiroptical properties is possible in chiral molecules[25,31] and that enantiomerism is not an empirically-based concept: it relates to a geometrical concept definable in terms of molecular symmetry. Thus, the description enantiomerism is always to be preferred to the term optical isomerism whose usage is not recommended.[30] It should be noted that chiral molecules can be symmetric by virtue of containing a C_n ($n > 1$) axis, *e.g.* in appropriate conformations, (+)-tartaric acid (**5**) and (−)-mannitol (**6**) both contain C_2 axes. When molecules are devoid of all symmetry elements apart from the identity element, *e.g.* (+)-α-pinene (**7**) and (−)-cholesterol (**8**), they are said to be asymmetric. Thus, all asymmetric molecules are chiral although not all chiral molecules are necessarily asymmetric. For this reason, the term asymmetric centre has been superseded[7,29,30,32] by the term chiral centre, or more precisely, centre of chirality. The word chiral is derived from *cheir*, the Greek word for hand, and was first employed in 1884 by the physicist, Lord Kelvin,[33] to describe geometrical figures or any group of points which exhibit handedness or what he preferred to call chirality. Although the meaning of the word had been discussed in a chemical context by Whyte[34] in the 1950s, it took many decades for the term chirality to be accepted finally into the chemical literature by Cahn, Ingold, and Prelog[29] in 1966 at the suggestion of Mislow.



C_2

(**5**)

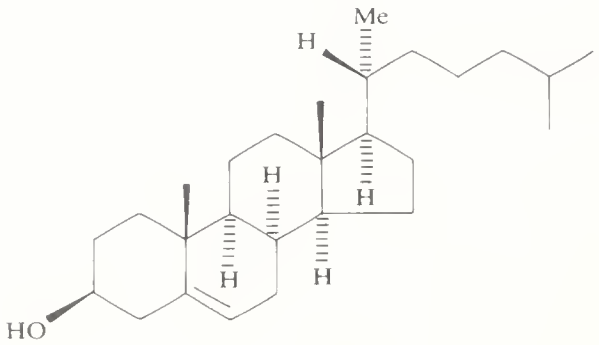


C_2

(**6**)

$\mathbf{C}_1$

(7)



$\mathbf{C}_1$

(8)

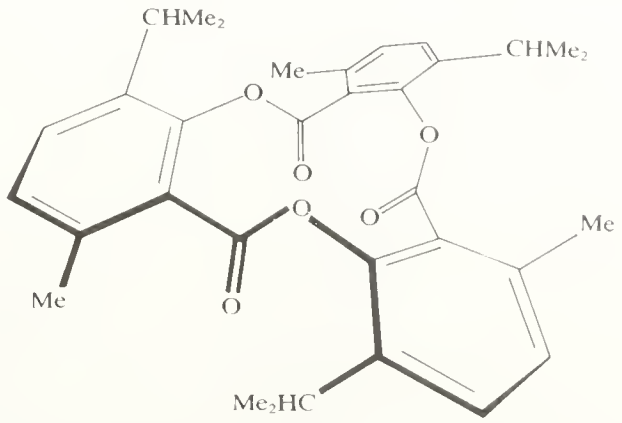
TABLE 2

The Important Symmetry Point Groups

Point group	*Symmetry elements*	*Symmetry number*[a]
$\mathbf{C}_1$[b]	E	1
$\mathbf{C}_n$[c]	E, C_n	n
$\mathbf{D}_n$	E, C_n, nC_2	$2n$
$\mathbf{C}_s$	E, σ	1
$\mathbf{C}_i$	E, i	1
$\mathbf{S}_n$	E, $C_{n/2}$, S_n (collinear with the $C_{n/2}$ axis)	$n/2$
$\mathbf{C}_{nv}$[d,e]	E, C_n, $n\sigma_v$	n ($n \neq \infty$)
$\mathbf{C}_{\infty v}$	E, C_∞, $\infty\sigma_v$	1
$\mathbf{C}_{2h}$[f]	E, C_2, σ_h, i	2
$\mathbf{D}_{2h}$[g]	E, $3C_2$ (mutually perpendicular), 3σ (mutually perpendicular), i	4
$\mathbf{D}_{3h}$[g]	E, C_3, $3C_2$ (all perpendicular to the C_3 axis), $3\sigma_v$, σ_h	6
$\mathbf{D}_{\infty h}$	E, C_∞, ∞C_2 (all perpendicular to the C_∞ axis), $\infty\sigma_v$, σ_h, i	2
$\mathbf{D}_{2d}$[h]	E, $3C_2$ (mutually perpendicular), $2\sigma_d$, S_4 (collinear with one of the C_2 axes)	4
$\mathbf{D}_{3d}$[h]	E, C_3, $3C_2$ (all perpendicular to the C_3 axis), $3\sigma_d$, i, S_6 (collinear with the C_3 axis)	6
$\mathbf{T}_d$	E, $4C_3$, $3C_2$ (mutually perpendicular), 6σ, $3S_4$ (coincident with the C_2 axis)	12
$\mathbf{O}_h$	E, $3C_4$ (mutually perpendicular), $4C_3$, $6C_2$, 9σ, $3S_4$, $4S_6$	24

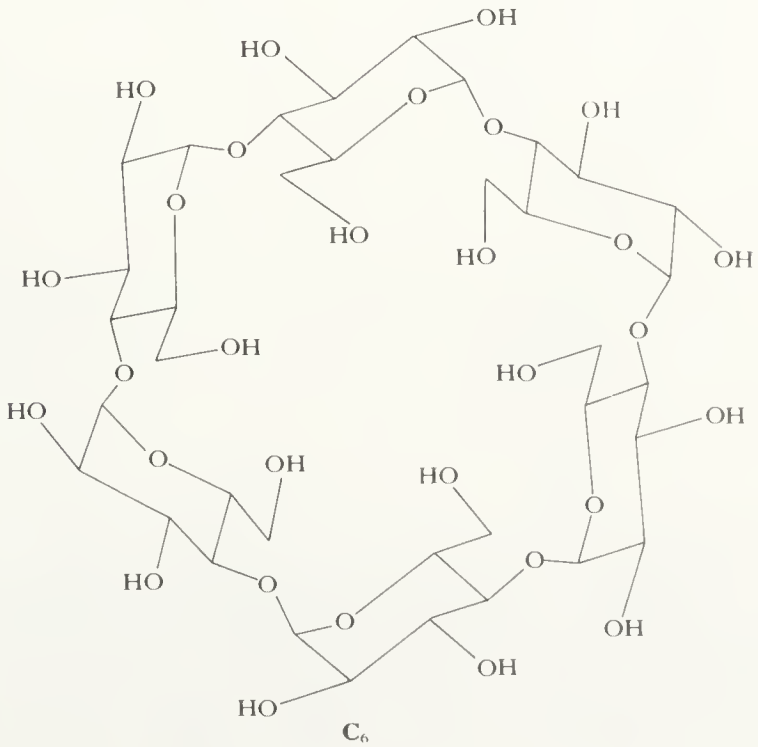
[a] The number of indistinguishable but non-identical positions through which a molecule may be rotated is known as the symmetry number. [b] These point groups are termed the non-axial point groups because they do not contain any C_n ($n > 1$) axes. All the other point groups are termed axial. [c] High symmetry chiral molecules have been reviewed recently by M. Farina and C. Morandi, *Tetrahedron*, 1974, **30,** 1819. [d] If there is only one C_n axis, and if n σ planes intersect at that C_n axis, then the planes are designated σ_v (where v means vertical). [e] The commonly occurring examples correspond to $n = 2$ and 3, *i.e.* $\mathbf{C}_{2v}$ and $\mathbf{C}_{3v}$. However, there are examples of molecules with $\mathbf{C}_{nv}$ symmetry where $n > 3$, *e.g.* the all-*cis*-1,2,3,4-tetrachlorocyclobutane belongs to point group $\mathbf{C}_{4v}$. Also, see Ref. 36. [f] If there is only one C_n axis and no intersecting σ planes, but instead a σ plane perpendicular to the C_n axis, then the plane is designated σ_h (where h means horizontal). The commonly occurring examples correspond to $n = 2$, *i.e.* to $\mathbf{C}_{2h}$ as indicated above. However, there are examples of molecules with $\mathbf{C}_{nh}$ symmetry where $n > 2$, *e.g.* iso-*cis*-perhydrotripticene has $\mathbf{C}_{3h}$ symmetry (see ref. in footnote c). [g] The commonly occurring examples correspond to $n = 2$ and 3, *i.e.* $\mathbf{D}_{2h}$ and $\mathbf{D}_{3h}$. However, there are examples of molecules with $\mathbf{D}_{nh}$ symmetry where $n > 3$, *e.g.* the eclipsed configuration of ferrocene belongs to point group $\mathbf{D}_{5h}$ and benzene has $\mathbf{D}_{6h}$ symmetry (see Refs. 21 and 22). [h] When a set of σ planes bisects the angles between a set of C_2 axes, the planes are designated σ_d (where d means diagonal). The commonly occurring examples correspond to $n = 2$ and 3, *i.e.* to $\mathbf{D}_{2d}$ and $\mathbf{D}_{3d}$ as indicated above. However, there are examples of molecules with $\mathbf{D}_{nd}$ symmetry where $n > 3$, *e.g.* the staggered configuration of ferrocene belongs to point group $\mathbf{D}_{5d}$.

Geometrical figures, and hence molecules, can be allocated[6,20–24] symmetry point groups according to the combination of symmetry elements they possess. Since this classification of molecules proves to be useful in a much wider context within organic chemistry, the so-called Schoenflies notation (*n.b.* crystallographers usually employ the alternative Herman–Mauguin notation) will now be discussed by reference to Table 2 which summarizes the important symmetry point groups in relation to organic molecules. It should be noted that the boldface symbol employed to denote a point group tends to have its origins in the principal symmetry element with the numerical and italicized subscripts helping to identify other symmetry elements. Asymmetric molecules, *e.g.* α-pinene (**7**) and cholesterol (**8**), which contain no symmetry elements other than the identity element belong to the point group $\mathbf{C}_1$. Molecules without reflection symmetry which possess a C_n ($n > 1$) axis belong to the $\mathbf{C}_n$ point groups. By far the most common point group in this collection is the point group $\mathbf{C}_2$, *e.g.* tartaric acid (**5**) and mannitol (**6**). Examples of molecules with $\mathbf{C}_n$ symmetry of order higher than two are rare; they are provided by tri-*o*-thymotide (**9**) with $\mathbf{C}_3$ symmetry[35] and cyclohexa-amylose (**10**) with $\mathbf{C}_6$ symmetry.[36] A



$\mathbf{C}_3$

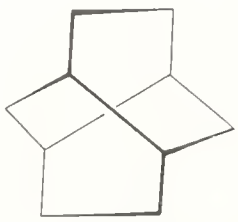
(**9**)



$\mathbf{C}_6$

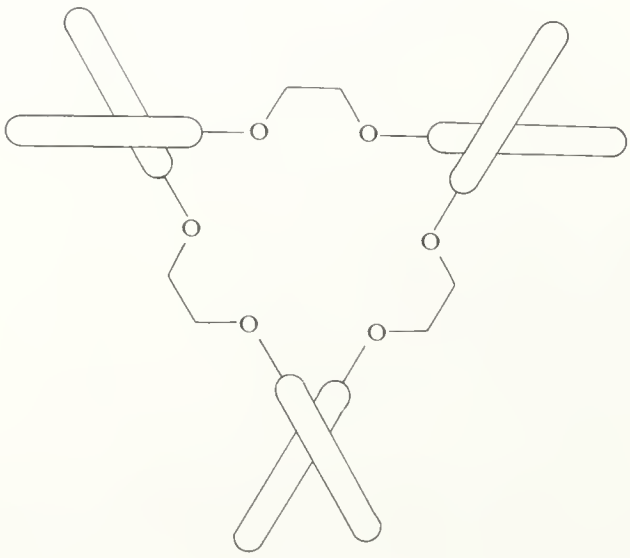
(**10**)

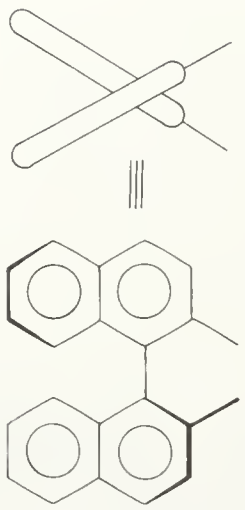
few chiral molecules possess more than one C_n axis. In such cases, the molecules are said to have dihedral symmetry and belong to the $\mathbf{D}_n$ point groups. They have a principal C_n axis with nC_2 axes perpendicular to it. The $\mathbf{D}_2$ point group is exemplified by twistane (**11**) and the rarely encountered $\mathbf{D}_3$ point group[37] by the trisbinaphthyl-24-crown-6 (**12**). Molecules belonging to the $\mathbf{C}_n$ (including $\mathbf{C}_1$) and $\mathbf{D}_n$ point groups are chiral. Indeed, the vast majority of chiral molecules belong to these point groups. Molecules with reflection symmetry can be classified into a wide range of symmetry point groups. The simplest cases are those with either (i) a σ plane (S_1 axis)—which have $\mathbf{C}_s$ symmetry—or (ii) an i inversion (S_2 axis)—which have $\mathbf{C}_i$ symmetry. For example, ethanol (**13**) has $\mathbf{C}_s$ symmetry whereas the dichlorodifluorocyclobutane (**14**) has $\mathbf{C}_i$ symmetry. In general, molecules which contain an S_n ($n>2$) axis in addition to collinear $C_{n/2}$ axes belong to the $\mathbf{S}_n$ point groups, *e.g.* the spiro compound (**4**) has $\mathbf{S}_4$ symmetry. Molecules which possess n σ planes which bisect a C_n axis belong to the $\mathbf{C}_{nv}$ point groups, *e.g.* dichloromethane (**1**) has $\mathbf{C}_{2v}$



$\mathbf{D}_2$

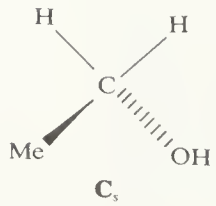
(**11**)





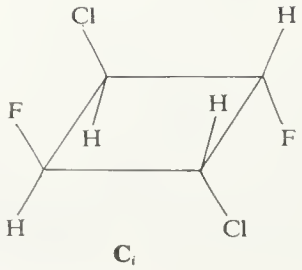
$\mathbf{D}_3$

(**12**)



$\mathbf{C}_s$

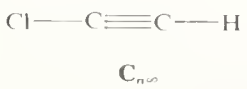
(**13**)



$\mathbf{C}_i$

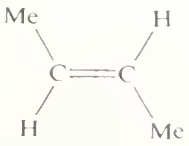
(**14**)

symmetry and chloroform (**2**) has $\mathbf{C}_{3v}$ symmetry. Linear molecules with conical symmetry such as chloroacetylene (**15**) belong to the point group $\mathbf{C}_{\infty v}$. Molecules which have a σ plane perpendicular to a C_n axis belong to the $\mathbf{C}_{nh}$ point groups, *e.g. trans*-but-2-ene (**16**) has $\mathbf{C}_{2h}$ symmetry. Molecules with reflection symmetry can also possess dihedral symmetry. When a σ plane is perpendicular to the principal C_n axis, the molecule belongs to the $\mathbf{D}_{nh}$ point groups, *e.g.* ethylene (**17**) has $\mathbf{D}_{2h}$ symmetry, cyclopropane (**18**) has $\mathbf{D}_{3h}$ symmetry, and benzene (**19**) has $\mathbf{D}_{6h}$ symmetry. Linear molecules with cylindrical symmetry such as acetylene (**20**) belong to the point group $\mathbf{D}_{\infty h}$. When σ planes intersect at a principal C_n axis and bisect the nC_2 axes, the molecule belongs to the $\mathbf{D}_{nd}$ point groups, *e.g.* allene (**21**) has $\mathbf{D}_{2d}$ symmetry and the chair conformation (**22**) of cyclohexane has $\mathbf{D}_{3d}$ symmetry. The highly symmetrical $\mathbf{T}_d$ and $\mathbf{O}_h$ point groups are exemplified by methane (**23**) and cubane (**24**), respectively.



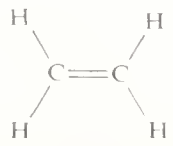
$\mathbf{C}_{n\infty}$

(**15**)



$\mathbf{C}_{2h}$

(**16**)



$\mathbf{D}_{2h}$

(**17**)

$\mathbf{D}_{3h}$

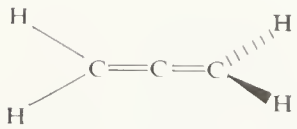
(**18**)

$\mathbf{D}_{6h}$

(**19**)

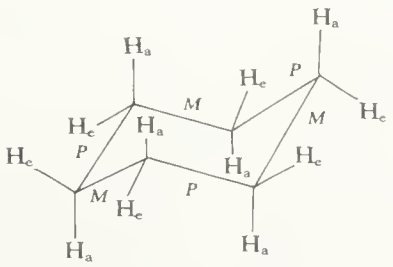
$\mathbf{D}_{\infty h}$

(**20**)



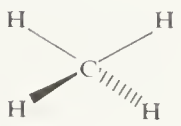
$\mathbf{D}_{2d}$

(**21**)



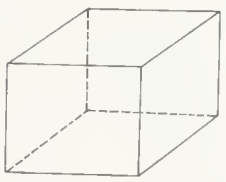
$\mathbf{D}_{3d}$

(**22**)



$\mathbf{T}_d$

(**23**)



$\mathbf{O}_h$

(**24**)

So far in this discussion, it has been assumed that molecules can be equated with models based on geometrical figures. More detailed thought and analysis reveals, however, that this portrayal of real molecules in terms of abstract models is not really justified. For a full and stimulating discussion of the problems, the reader is referred to 'an epistemological note on chirality' by Mislow and Bickart.[25] There now follows a summary of their appraisal of the problems and their conclusions. Let us begin by considering one mole of a monoatomic gas at room temperature. Although all possible means of measurement of the

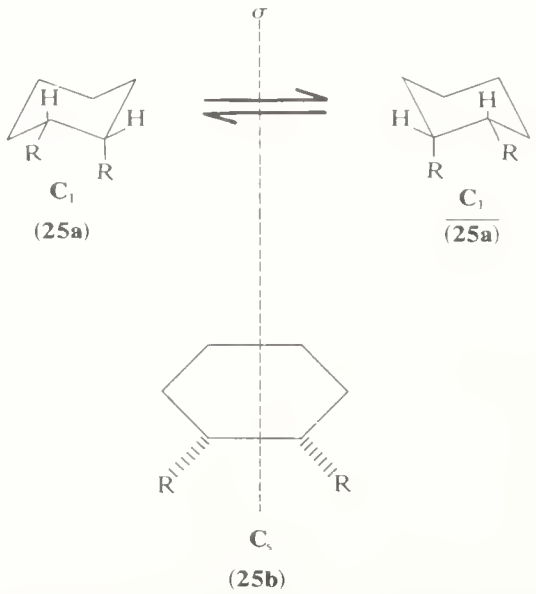
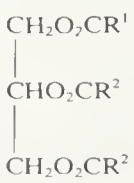


Figure 1 Ring inversion in *cis*-1,2-disubstituted cyclohexanes. A 'bar' over a number indicates its enantiomeric relationship to the 'unbarred' number

macroscopic sample indicate that it is achiral, it must, of course, at any particular instant be chiral. Statistical averaging on the time scale of any measurement made leads to the cancellation of the chiral effects and such a system is said to be stochastically achiral, *i.e.* the boundary between chirality and achirality is ill-defined for molecules. Similarly, the assignment of point groups to molecules very often represents the idealized situation which is probably never reached except on an averaging basis. For example, it has been stated already that the propeller conformation (**9**) of tri-*o*-thymotide has $\mathbf{C}_3$ symmetry. In fact, in the crystal structure,[38] deviations from $\mathbf{C}_3$ symmetry are quite large; not surprisingly, on statistical—and hence entropic—grounds a lopsided asymmetrical ($\mathbf{C}_1$) conformation is energetically more favourable. The fact that the low-temperature ^{1}H nuclear magnetic resonance (n.m.r.) spectra do not reveal[35] this lack of symmetry in solution no doubt reflects an averaging process by this means of observation. It can be said[39] that molecules of one chiral class, such as the propeller conformation (**9**) of tri-*o*-thymotide, are homochiral just in the way right hands belonging to different people are alike but not identical. By the same token, enantiomerically-related molecules which exhibit a spectrum of chirality characteristics are said to be heterochiral. Another example of stochastic achirality is met in the ring-inversion process which permits equilibration between enantiomeric chair conformations, (**25a**) and ($\overline{\mathbf{25a}}$), of *cis*-1,2-disubstituted cyclohexanes (see Figure 1). It is unlikely that the enantiomeric mixture will ever be equimolar. Nonetheless, averaging processes on the time scale of observation reveal that the system is achiral. Furthermore, dynamic n.m.r. spectroscopy shows that although molecules of many *cis*-1,2-disubstituted cyclohexanes exhibit $\mathbf{C}_1$ symmetry at low temperatures, they behave as if they had $\mathbf{C}_s$ symmetry (**25b**), *i.e.* they are achiral, at room temperature. Extrapolating to cyclohexane, it often behaves[40] as if it had $\mathbf{D}_{6h}$ symmetry rather than the $\mathbf{D}_{3d}$ symmetry of the chair conformation (**22**).

The absence of chirality can arise for reasons other than stochastic achirality. If chirality falls below the threshold of detection, as it would in $H(CH_2)_nCHD(CH_2)_nD$ as the magnitude of n increases, then a situation which is described as cryptochirality pertains. This phenomenon is met in the chemistry of triglycerides such as (**26**), which, although they are unquestionably chiral, do not exhibit chiroptical properties.[41]



(**26**)

Thus, it is not only permissible but realistic to refer to degrees of chirality. As often happens in chemistry, the situation regarding a concept—in this case, chirality—is not black and white. It is various shades of grey. Whilst observable chirality phenomena allow us to conclude that a sample, *i.e.* an ensemble of molecules, is chiral, the lack of such phenomena do not permit the designation achiral to be made.

1.3 CHEMICAL TOPOLOGY

Following the critique at the end of the previous section on the relationship between geometrical figures and molecules, this theme is now going to be considered again in more detail in order that different sources of chirality within molecules can be identified and classified in Section 1.4. The practicalities of chemistry have to be recognized. Whilst it may be sufficient (or even insufficient!) to associate chirality with certain molecular symmetry characteristics at an abstract level, the fact is that experimentalists are often concerned with introducing stereochemical modifications into portions of organic molecules. Thus, it is useful—indeed essential—to be able to locate and designate elements of chirality within a molecule.

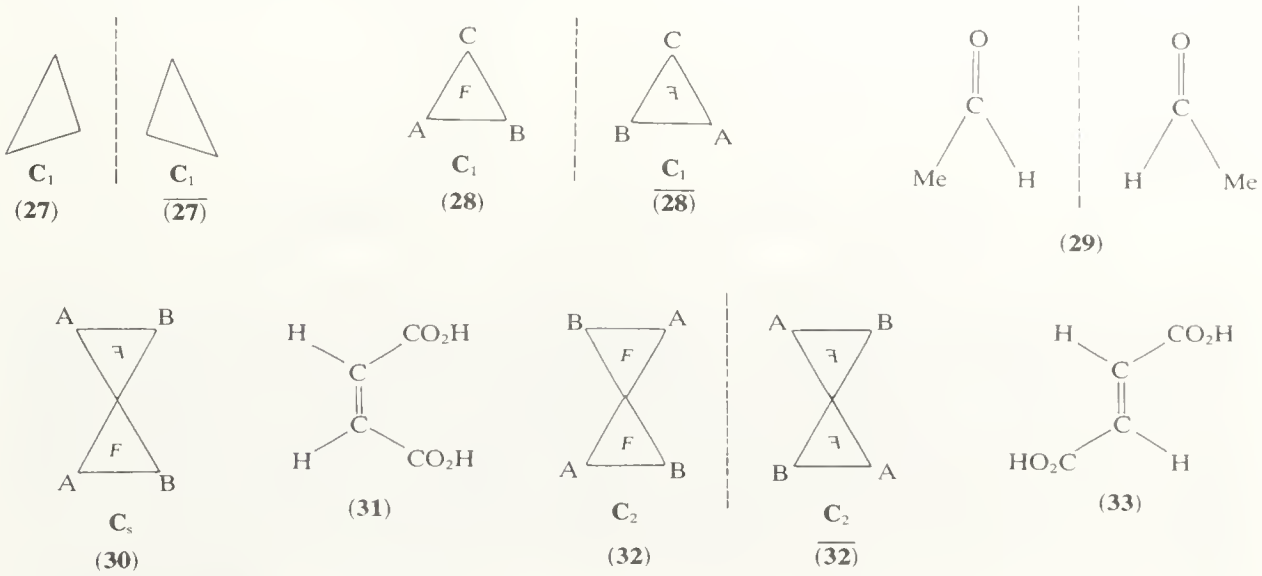


Figure 2 Some examples of two-dimensional chirality

Prelog[26–28] had drawn attention to the fact that chirality can be exhibited in either two- or three-dimensional space and has employed simplices in the form of triangles and tetrahedra to represent these situations. The irregular triangle (**27**) is chiral ($\mathbf{C}_1$ symmetry) in two-dimensional space since its mirror image by reflection across a straight line cannot be brought into congruence with it by translation or rotation in the plane (see Figure 2). Two-dimensional chirality, however, is lost in three-dimensional space. The block capital letters of the alphabet can be divided as shown in Figure 3 into those that are achiral and those that are chiral in two dimensions. In Figure 2, block capital letters have been introduced at the vertices of equilateral triangles to form different arrays; many of the simplices can be related to planar molecules, *e.g.* (**28**) to acetaldehyde (**29**), (**30**) to maleic acid (**31**), and (**32**) to fumaric acid (**33**). Thus, the chirality of acetaldehyde (**29**) and fumaric acid (**33**) in two dimensions can be recognized by us and by enzymes (see Section

Achiral: ABCDEHIKMOTUVWXY

Chiral: FGJLNPQRSZ ƧSЯQPИJLƆ⊣

Figure 3 The chirality of the block capital letters of the alphabet in two-dimensional space

1.5). Concepts such as stereoheterotopism and prochirality are a consequence of two-dimensional chirality. Eight point group symmetries are possible (see Figure 4) for the three-dimensional simplex, the tetrahedron. The regular $\mathbf{T}_d$ tetrahedron (**34**) is the simplex for the familiar chiral centre [see (**42**) in Figure 5] although simplices with $\mathbf{D}_2$

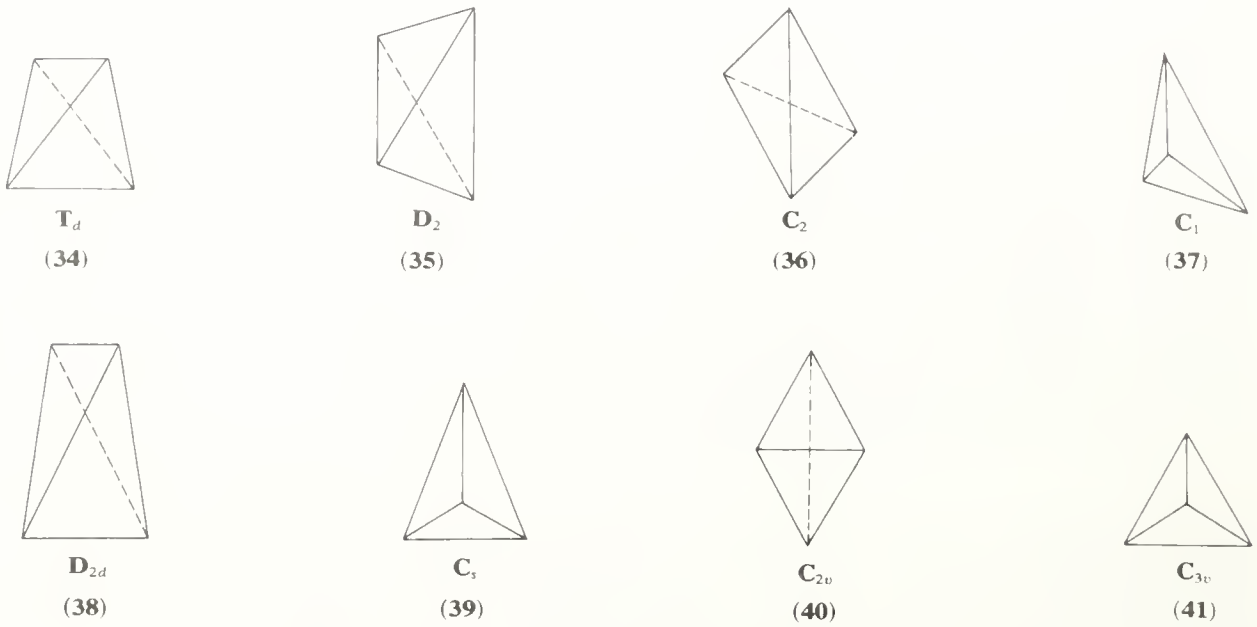


Figure 4 The eight point-group symmetries of the tetrahedron

(**35**), $\mathbf{C}_2$ (**36**), and $\mathbf{C}_1$ (**37**) symmetry can, in principle, incorporate a centre of chirality as well. Figure 5 shows that the regular $\mathbf{T}_d$ tetrahedron (**34**) can also be considered as the simplex for centres of prochirality, *e.g.* (**43**), pseudoasymmetry (or pseudochirality),[42,43] *e.g.* (**44**) and (**45**), and propseudoasymmetry (or propseudochirality), *e.g.* (**46**). The $\mathbf{D}_{2d}$ tetrahedron (**38**) in Figure 4 is the simplex for axial chirality, prochirality, and pseudoasymmetry (pseudochirality), while the $\mathbf{C}_s$ tetrahedron (**39**) in Figure 4 is the simplex for planar chirality, prochirality, and pseudoasymmetry (pseudochirality). For examples of axial and planar prochirality and pseudoasymmetry (pseudochirality), the reader is referred to the original literature.[26–29,32] Although chiral centres, axes, and

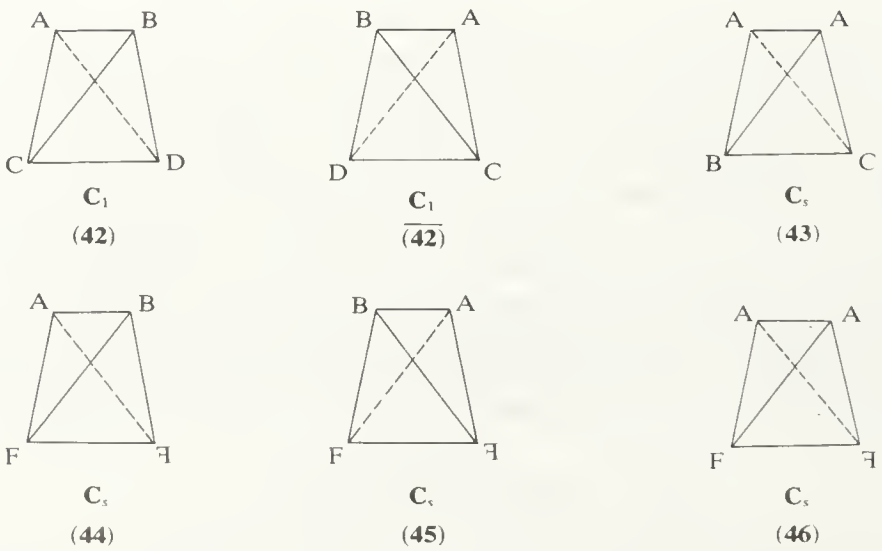
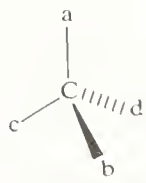
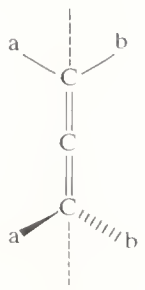


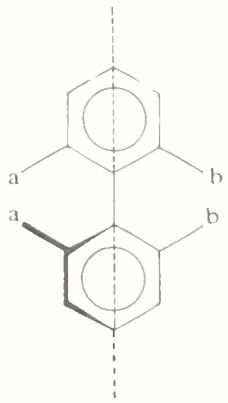
Figure 5 The regular $\mathbf{T}_d$ tetrahedron (**34**) as a simplex for chirality, prochirality, pseudoasymmetry, and propseudoasymmetry



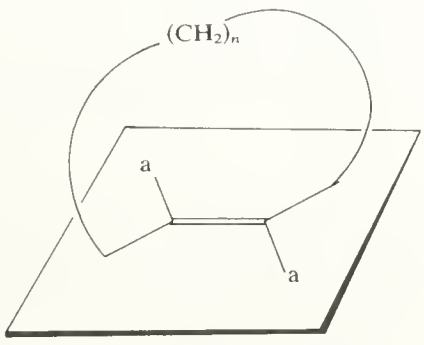
(47)



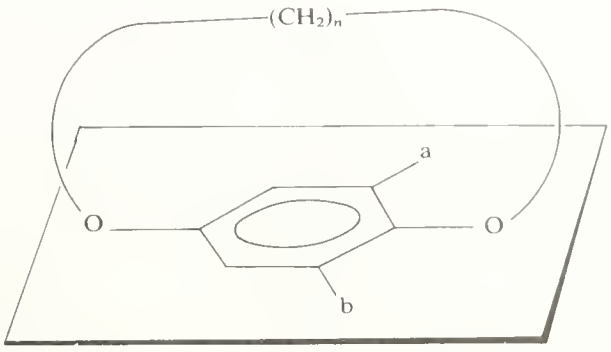
(48)



(49)



(50)



(51)

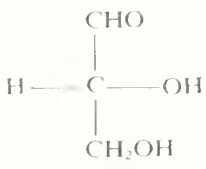
planes will be discussed in more detail in Section 1.4, it might be instructive to relate these to the general molecular phenomena at this juncture. Compounds of the type Cabcd (**47**) contain the familiar chiral centre, whereas in appropriately substituted allenes (**48**) and biphenyls (**49**) the element of chirality is an axis. A plane of chirality is present in *trans*-cycloalkanes (**50**) and in appropriately substituted paracyclophanes (**51**).

1.4 ISOMERISM

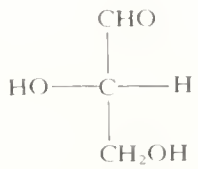
1.4.1 Some definitions

Although the concept of isomerism has been around in chemistry for more than 150 years, an element of vagueness and mystery still surrounds its usage by chemists. The IUPAC Commission on Nomenclature of Organic Compounds in their rules[32] on stereochemistry carefully avoid the problems by merely stating that compounds with identical molecular formulae but differing in the nature or sequence of bonding of their atoms in space are termed isomers. The rules proceed to identify the two major classifications of isomers: (i) those that differ in their constitution and (ii) stereoisomers which are inherent in the above definition of isomers. The constitution defines the nature and sequence of the bonding between atoms in molecules. Isomers differing in constitution are called constitutional isomers, *e.g.* butane ($MeCH_2CH_2Me$) and 2-methylpropane ($MeCHMe_2$), dimethyl ether (MeOMe) and ethanol ($MeCH_2OH$), and the keto ($MeCOCH_2CO_2Et$) and enol ($MeC(OH)=CHCO_2Et$) forms of acetoacetic ester. Isomers are called stereoisomers when they differ only in the arrangement of their atoms in space, *e.g.* D- and L-glyceraldehyde (**52**), *cis*- (**53**) and *trans*-but-2-ene (**16**), *gauche*- (**54**) and *anti*-butane (**55**), and the biphenyls, (*R*)-(**56**) and (*S*)-(**56**). Stereoisomers may be configurational or conformational in type. The term configuration relates to the particular spatial arrangement of atoms in molecules of defined constitution without regard to those

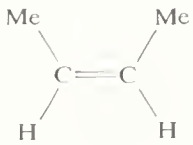
arrangements which differ only in torsion about single bonds. Isomers differing in configuration are called configurational isomers, *e.g.* D- and L-glyceraldehyde (**52**), *cis*-(**53**) and *trans*-but-2-ene (**16**), and (*Z*)- and (*E*)-*N*-methylformamide (**57**). The term conformation relates to the different spatial arrangements of atoms in molecules of defined configuration obtained on torsion about one or more single bonds, *e.g.* *gauche*-(**54**) and *anti*-butane (**55**), and the biphenyls (*R*)-(**56**) and (*S*)-(**56**). For most organic molecules, our knowledge of molecular shape—or structure—is only complete when the constitution, configuration, and conformation are known.



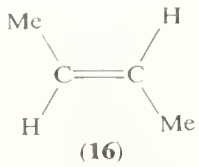
D-(+)-(**52**)



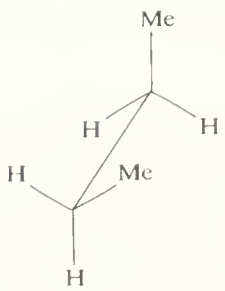
L-(−)-(**52**)



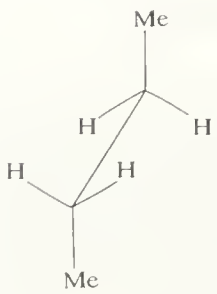
(**53**)



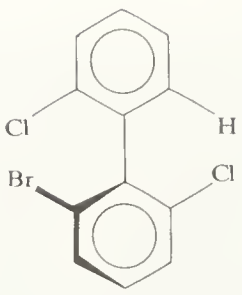
(**16**)



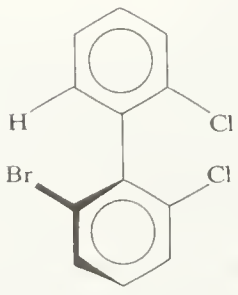
(**54**)



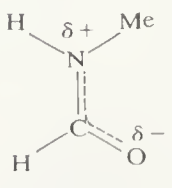
(**55**)



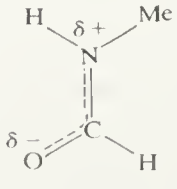
(*R*)-(**56**)



(*S*)-(**56**)

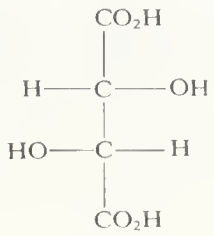


(*Z*)-(**57**)

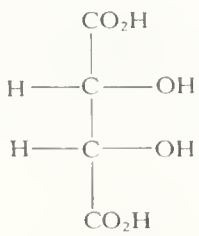


(*E*)-(**57**)

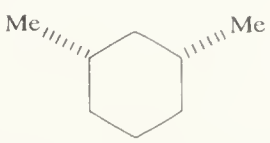
Stereoisomers (both configurational and conformational) are either enantiomers or diastereoisomers. Enantiomerism has already been discussed in conjunction with chirality in Sections 1.2 and 1.3. Suffice it to state here that molecules which are related as object is to mirror image and yet non-superimposable upon one another are enantiomers. Diastereoisomers are any stereoisomers which are not enantiomers of each other. This dichotomous subdivision first suggested by Wheland[44] has now gained general acceptance,[32] although it produces some surprises for those versed in the old definition. For example, it means that not only are stereoisomers such as L-(**5**) and *meso*-tartaric acid (**58**), and *cis*- (**59**) and *trans*-1,3-dimethylcyclohexane (**60**), which contain chiral centres, classified as diastereoisomers, but so are *cis*- (**61**) and *trans*-1,4-dimethylcyclohexane (**62**), and *cis*- (**53**) and *trans*-but-2-ene (**16**), which are devoid of chirality. Although the term *cis–trans* isomerism remains acceptable[32] as a sub-class of diastereoisomerism, it is to be hoped[30] that terms such as optical and geometrical isomers will soon disappear from the scene. Prelog[26–28,45] has drawn attention to a rather novel example of stereoisomerism amongst some cyclopeptides and has coined the terms cycloenantiomer and cyclodiastereoisomer to describe this rather specialized phenomenon. In addition, cyclic molecules are capable of another type of structural isomerism which has been referred to as topological isomerism.[6] This is exhibited by, for example, catenanes,[46] which are formed by the interlocking of cyclic atomic arrays.



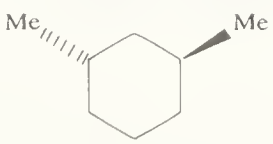
L-(**5**)



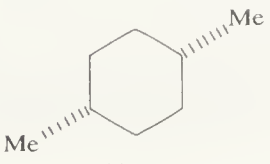
(**58**)



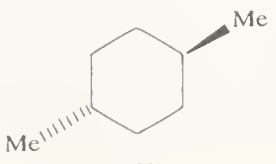
(**59**)



(**60**)



(**61**)



(**62**)

Finally, the situation governing synthetic and natural polymers requires some comment. The term primary structure defines the constitution of a polymer as well as the configuration of all the chiral centres along the chain and in the side chains. The secondary structure is known when the conformation of the chain is defined. In the case of polymers—some proteins, nucleic acids, and polysaccharides in particular—ordering of the structure by a multitude of many weak non-covalent interactions between two or more chains in the same or separate molecules can occur. The term tertiary structure can be employed to describe molecules of known primary and secondary structure which interact intermolecularly, *e.g.* to form double or triple helices.

1.4.2 Designation of constitution

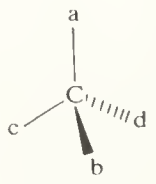
The designation of the constitution of an organic molecule is perhaps most readily communicated by means of a formula presented in two-dimensional space. However, this form of presentation, whilst highly precise, is demanding on space and so the need for names and a system of nomenclature arises. The literature in this area is vast and IUPAC has attempted over the years to introduce some rhyme and reason into chemical nomenclature. The reader is referred to the literature[47,48] on IUPAC nomenclature of organic chemistry but is reminded of the need to come to terms with reality and trivial nomenclature, *e.g.* 'glucose' is going to be 'glucose' for a long time to come!

1.4.3 Designation of absolute configuration

The term absolute configuration is used[32] to describe the known three-dimensional arrangement of ligands around a chiral element. It became possible after 1951 by the use of a technique[49] based on X-ray fluorescence to determine the absolute stereochemistry of a chiral molecule. In a particular case, the absolute configuration of a molecule can be represented on two-dimensional paper using the familiar 'wedge' and 'dash' notation or some suitably defined projection formula, *e.g.* the Fischer projection formula. Once again, however, there is a need to designate absolute configuration by means of a symbolism which can be coupled to the name of a compound. In recent years, the (*RS*) convention introduced by Cahn, Ingold, and Prelog[50] in 1951 and modified subsequently in 1956[51] and 1966[29] has tended to replace[32,52] the older DL convention in many areas of organic chemistry.

1.4.3.1 *The* (RS) *convention*

The Cahn–Ingold–Prelog system[29] for assigning absolute configuration depends upon a sequence rule procedure to specify the chirality of each chiral element (centre or axis) in a configurationally-chiral molecule.



(**47**)

In its most familiar form, the system has been employed with the chiral carbon (Cabcd) atom (**47**), although it can equally well be applied to other atoms (N, S, P *etc.*) carrying four different ligands (abcd); even lone pairs of electrons can be accommodated! A sequence rule (see below) is employed in order to arrange the ligands a, b, c, and d with the priority: a > b > c > d. The chiral centre is then viewed (Figure 6) from the side remote

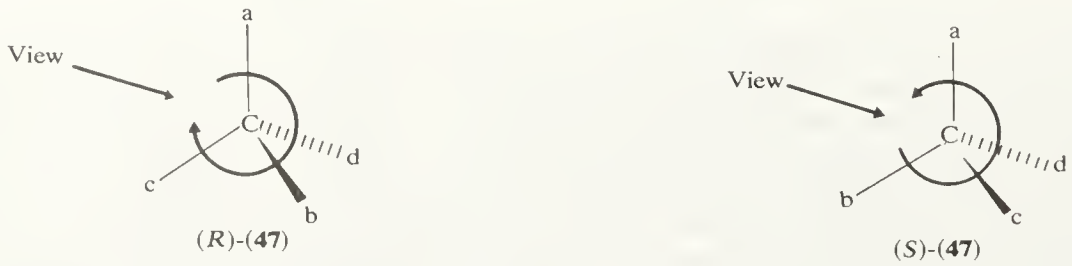
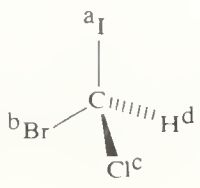
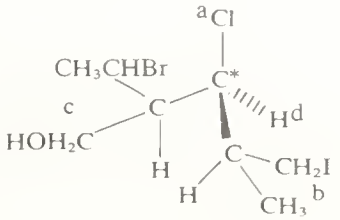


Figure 6 The designation of the absolute configuration of a chiral centre using the (*RS*) convention

from ligand d of lowest priority. If the ligands a, b, and c describe a clockwise array, the descriptor (*R*) (Latin, *rectus* ≡ right) is used and if they describe an anticlockwise array the descriptor (*S*) (Latin, *sinister* ≡ left) is used. In order to deduce the priority a > b > c > d, the sequence rule is invoked according to the following simplified procedure. First of all, ligands are arranged in order of decreasing atomic number so that, in bromochloroiodomethane (**63**), for example, a > b > c > d corresponds to I > Br > Cl > H and hence it has the (*S*) configuration. If the atoms in two or more of the ligands attached to the chiral centre are the same, then decisions regarding their priorities are reached by working outwards concurrently atom by atom until the first point of difference is reached. The procedure is illustrated by considering the priority a > b > c > d assigned to the ligands in (**64**), which is $Cl > CH(CH_2I)CH_3 > CH(CHBrCH_3)CH_2OH > H$ and hence the chiral



(*S*)-(**63**)



(**64**)

centre C* in (**64**) has the (*R*) configuration. Note that as soon as the atom—iodine, in this case—of highest atomic number in the two ligands under comparison is reached, it claims precedence for its ligand over the other ligand where there might be an accumulation of atoms—in this case, bromine and oxygen—with smaller atomic numbers. Multiple-bonded atoms in double or triple bonds are split formalistically into two and three bonds, respectively. The examples given in Figure 7 illustrate the practice of denoting the

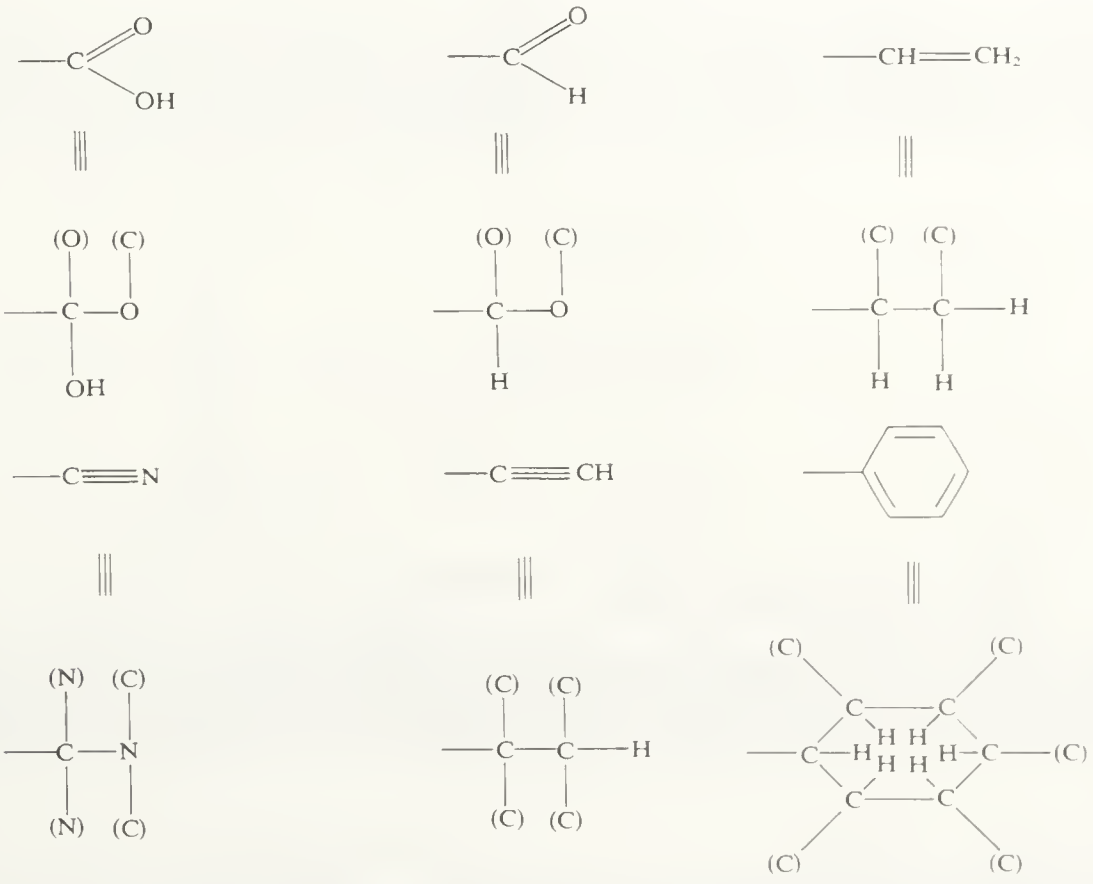
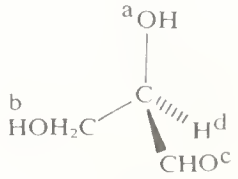


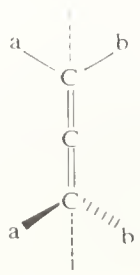
Figure 7 The representation of multiple bonded atoms in the Cahn–Ingold–Prelog system of nomenclature

duplicated or triplicated atoms in parenthesis. In D-glycraldehyde, D-(**52**), the priority a>b>c>d assigned to the ligands is OH>CHO>CH_2OH>H and so it has the (*R*) configuration. Finally, when isotopes are present, the atom of higher mass number takes priority, *e.g.* D>H (see Section 1.5.2). Compounds can, of course, contain more than one chiral centre. In these cases, the descriptors (*R*) and (*S*) are associated with their IUPAC locants, *e.g.* the enantiomeric pentane-2,4-diols $CH_3CH(OH)CH_2CH(OH)CH_3$ (**65**) are differentiated as (2*R*,4*R*) and (2*S*,4*S*).



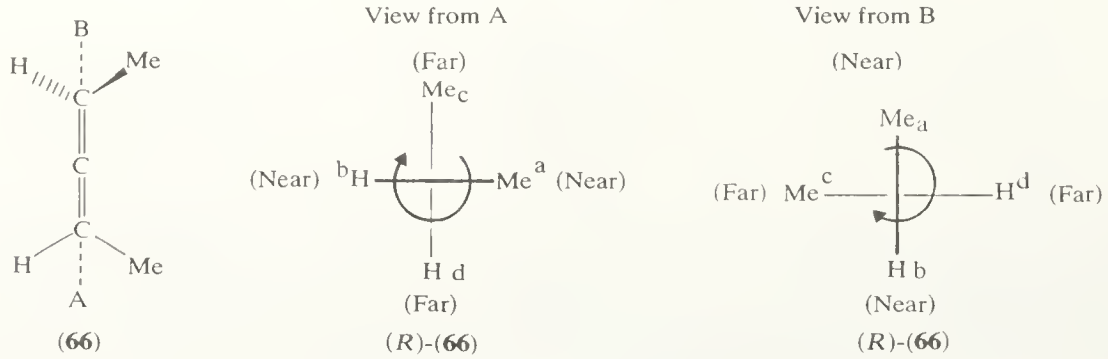
(*R*)-(**52**)

Appropriately substituted allenes, *e.g.* (**48**), are configurationally chiral and the element of chirality is an axis based on the $\mathbf{D}_{2d}$ simplex (**38**). A comparison of (**47**) with (**48**) (p. 13) indicates that fewer ligand differences are required to produce chirality around an



(**48**)

axis than are necessary to produce a chiral centre. The chiral allene can be viewed along its chiral axis in either direction, and, in assigning the priority a>b>c>d to the four ligands, it is assumed that near ligands precede far ligands. Thus, applying the sequence rules to the dimethylallene (**66**) in Figure 8 establishes that it has the (*R*) configuration.



(**66**) (*R*)-(**66**) (*R*)-(**66**)

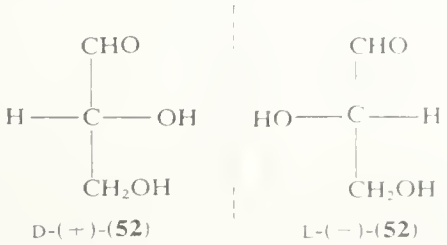
Figure 8 The designation of the absolute configuration of the chiral axis of the dimethylallene (**66**) using the (*RS*) convention

Other examples of axial chirality are found[32] amongst alkylidenecycloalkanes, spiro compounds, and adamantoids. Also, the allenic fragment can be part of a cyclic system as in (+)-cyclonona-1,2-diene, which is shown in Section 2.2.1 to have the (*R*) configuration.

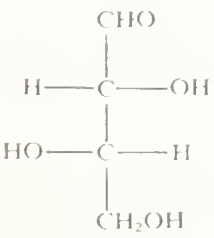
1.4.3.2 The DL *convention*

This much older convention is still used with α-amino acids,[53] cyclitols,[54] and carbohydrates.[55] It can be applied to molecules of the type R^1CHXR^2 which can be oriented in a

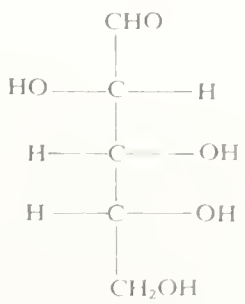
Fischer projection formula such that the most highly oxidized carbon-containing ligand is at the top. Then, if X is on the right, the configuration is D, whereas if X is on the left the configuration is L. Thus, (+)-glyceraldehyde, (+)-(**52**), has the D configuration and (−)-glyceraldehyde, (−)-(**52**), the L configuration. Difficulties can arise in applying this convention when more than one chiral centre is present. In such cases, it is conventional to number the carbon chain of the Fischer projection from top to bottom and allow the absolute configuration of the highest-numbered chiral carbon atom to determine the nature of the configurational descriptor. Thus, (−)-threose, (−)-(**67**), has the L configuration and (−)-arabinose, (−)-(**68**), the D configuration. The relative configurations at the other chiral centres in L-(**67**) and D-(**68**) are defined by the generic prefixes *threo* and *arabino*, respectively. It is probably desirable[29,32] that these 'local' systems of nomenclature be retained since the adoption of the (*RS*) convention would be both confusing and cumbersome. However, there is no reason[29,32] why the (*RS*) cannot be 'mixed' with the DL convention when the need arises.



D-(+)-(**52**) L-(−)-(**52**)



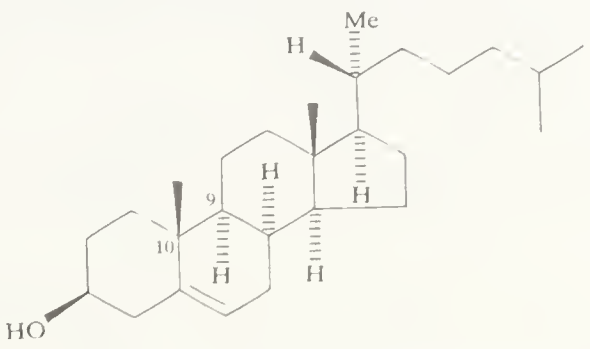
L-(−)-(**67**)



D-(−)-(**68**)

1.4.3.3 The αβ convention

The only other convention of major importance nowadays is the αβ system, employed[56] with a series of trivial names for steroids and related compounds. When the rings of a steroid are denoted as projections on to the plane of the paper, the formula is oriented as in cholesterol (**8**), for example. A ligand attached to a ring is termed alpha (α) if it lies below the plane of the paper, *e.g.* the H atoms at C-9, and beta (β) if it lies above the plane of the paper, *e.g.* the Me group at C-10.



(**8**)

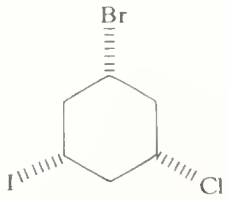
1.4.4 Designation of relative configuration

The term relative configuration is used[32] to describe the relative positions of ligands on different atoms in a molecule. Relative configurational differences can occur in both chiral and achiral molecules.

1.4.4.1 In molecules with chiral centres

When only the relative configurations of a number of chiral centres in a molecule are known, the (*RS*) convention is used on the arbitrary assumption that the chiral centre with

the lowest locant according to the IUPAC nomenclature rules has chirality (*R*). In the case of a racemic modification, the prefix *rel* is also used, *e.g.* the racemic cyclohexane derivative (±)-(**69**) is *rel*-(1*R*,3*S*,5*S*)-1-bromo-3-chloro-5-iodocyclohexane, and racemic $CH_3CH(OH)CH_2CH(OH)CH_3$ (**65**) is designated *rel*-(2*R*,4*R*)-pentane-2,4-diol. In optically active or *meso* compounds, the prefix *rel* is also employed, *e.g.* the *cis*-isomer (**59**) of 1,3-dimethycyclohexane becomes *rel*-(1*R*,3*S*)-1,3-dimethylcyclohexane and *meso*-$CH_3CH(OH)CH_2CH(OH)CH_3$ (**65**) is called *rel*-(2*R*,4*S*)-pentane-2,4-diol.

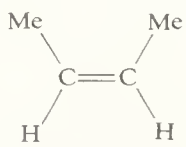


(±)-(**69**)

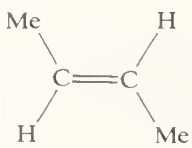
(Only one enantiomer shown)

1.4.4.2 The (EZ) *convention*

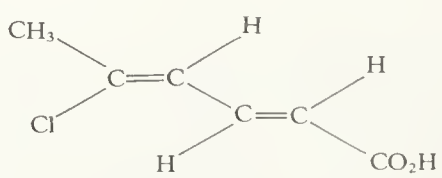
Although the terms *cis* and *trans* are adequately well defined in the case of disubstituted olefins, their use becomes[30,32] ambiguous with trisubstituted olefins and impracticable with tetrasubstituted olefins. It is better to adopt a system of nomenclature[30,32,57] based on the sequence rules for structures of the type abC=Ccd. If the priorities are a>b and c>d and a and c are *cis* to each other, then the configuration is *seqcis* and the descriptor (*Z*) (German, *zusammen* ≡ together) is used in naming the compound. If the priorities are the same and a and c are *trans* to each other, then the configuration is *seqtrans* and the descriptor (*E*) (German, *entgegen* ≡ opposite) is used in naming the compound. Thus, *cis*-but-2-ene (**53**) has the (*Z*) configuration and *trans*-but-2-ene (**16**) has the (*E*) configuration. The convention can be applied to other double bonds, *e.g.* C=N and N=N bonds, and, in relation to the stereochemistry of oximes, the use of the terms *syn* and *anti* should now be discontinued. Finally, if a molecule contains several double bonds then the necessary prefix is associated with the relevant locant prescribed by the IUPAC nomenclature rules, *e.g.* compound (**70**) is (2*E*,4*Z*)-5-chloro-2,4-hexadienoic acid.



(**53**)



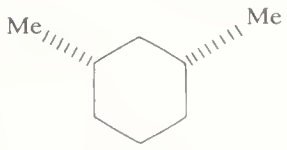
(**16**)



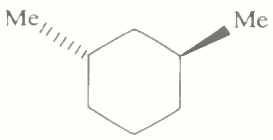
(**70**)

1.4.4.3 In monocyclic systems with substituents

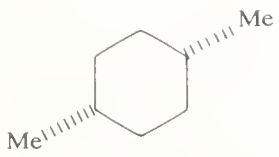
In compounds such as *cis*- (**59**) and *trans*-1,3-dimethylcyclohexane (**60**), the prefixes define their diastereoisomeric relationship unequivocally. The (*RS*) convention can be employed to define absolutely the configuration of a particular enantiomer of *trans*-1,3-dimethylcyclohexane (**60**). However, the (*RS*) convention when applied to racemic modifications is cumbersome (see Section 1.4.4.1) and it is often more convenient to apply the prefixes *cis* and *trans*, *e.g.* for the 1,4-dimethylcyclohexanes (**61**) and (**62**), respectively. Unfortunately, in more highly substituted examples, the *cis–trans* nomenclature becomes equivocal, *e.g.* in the dimethylcyclohexanol derivative (**71**), is the 4-methyl substituent considered to be *trans* to the hydroxyl group at C-1 or *cis* to the methyl group at C-1? In ambiguous situations such as this, the relative configurations of the substituents



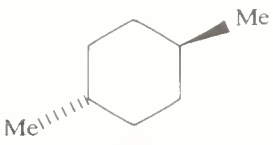
(**59**)



(**60**)

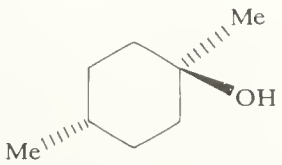


(**61**)

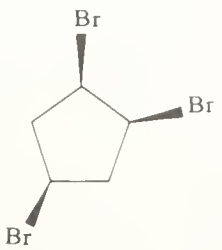


(**62**)

are expressed[30,32] by adding *r* (for reference ligand) before the locant of the lowest-numbered of these substituents according to the IUPAC nomenclature rules of numbering, *e.g.* the tribromocyclopentane derivative (**72**) becomes *r*-1,*cis*-2,*cis*-4-tribromocyclopentane. When two different substituents are attached to the lowest-numbered ring atom, then the ligand with preference under the IUPAC nomenclature system is designated as the reference ligand, *e.g.* the dimethylcyclohexanol derivative (**71**) becomes 1,*trans*-4-dimethylcyclohexan-*r*-1-ol.



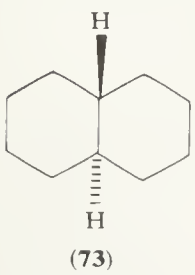
(**71**)



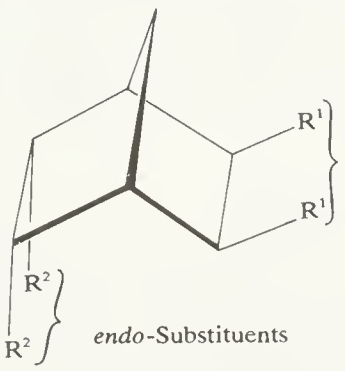
(**72**)

1.4.4.4 In fused-ring systems

Bicyclic systems can be treated as examples of *cis–trans* isomerism just like disubstituted monocyclic systems, *e.g.* *trans*-decalin (**73**). The use of the prefixes *exo* and *endo* to indicate relative stereochemistry in bicyclic systems such as bicyclo[2,2,1]heptane (norbornane) (**74**) is well established by contemporary usage. When the relative configuration at more than one bridgehead has to be specified, the descriptors *cisoid* and *transoid* are employed, *e.g.* the tricyclic hydrocarbon (**75**) is referred to as *cis-transoid-cis*-perhydroanthracene. See also Section 4.4.5.2 for a discussion of the relative stereochemistry of the seven configurational isomers of dicyclohexyl-18-crown-6.



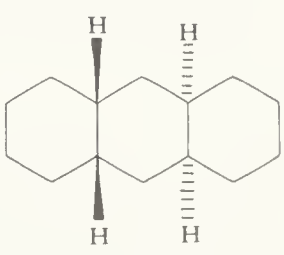
(**73**)



exo-Substituents

endo-Substituents

(**74**)



(**75**)

1.4.5 Designation of conformation

The designation of the conformation of a molecule is potentially even more hazardous and challenging to the chemist than is the designation of its constitution or configuration.

As conformational considerations represent the most recent level of structure to have been considered stereochemically, the nomenclature system is still at an embryonic stage.

Appropriately substituted biphenyls, *e.g.* (**49**), have been treated as examples of axially chiral systems and the (*RS*) convention has been employed[29,30,32] to designate their chirality as (*R*) or (*S*). The need for their absolute conformational properties to be defined has arisen out of the fact that many biphenyls containing bulky *ortho* substituents have been resolved[3,6] into their enantiomeric pairs, *e.g.* 6,6′-dinitrodiphenic acid. It will be recalled that the $\mathbf{D}_{2d}$ simplex in Figure 4 forms the basis for designating axial chirality. In tetra-*ortho*-substituted biphenyls the apices of this elongated tetrahedron correspond with C-2, C-6, C-2′, and C-6′. The chiral biphenyl can be viewed along its axis in either direction and, in assigning the priority a > b > c > d to the four ligands, it is assumed—as with chiral allenes (see Section 1.4.3.1)—that near ligands precede far ligands. Thus, applying the sequence rules to the 6,6′-dinitrodiphenic acid (**76**) in Figure 9 establishes that (**76**) has chirality (*R*). Occasionally, this kind of axial chirality is found in biphenyls which also have chiral centres associated with them (see Section 4.2.3.2).

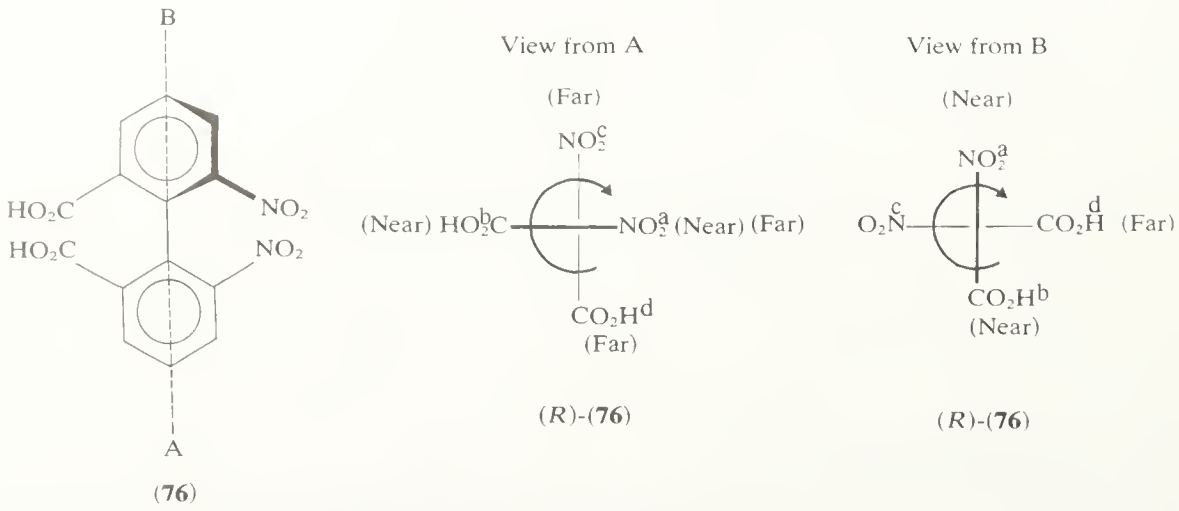
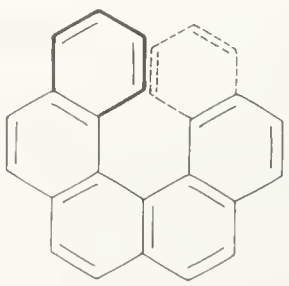


Figure 9 The designation of axial chirality in 6,6′-dinitrodiphenic acid (**76**) using the (*RS*) convention

For the few specialized cases in which planar chirality has to be specified using the (*RS*) convention, the reader is referred to the original literature.[29,32]

A number of molecules are conformationally chiral on account of their helicity, *e.g.* the propeller conformation (**9**) of tri-*o*-thymotide and hexahelicene (**77**). In such situations, according as the identified helix is left-handed or right-handed, it is designated (*M*) (for minus) and (*P*) (for plus), respectively. It has been shown[35] by circular dichroism that (+)-tri-*o*-thymotide has the (*M*)-propeller conformation (**9**). Nucleic acids, proteins, and polysaccharides also exhibit helicity (see Ref. 29) in their tertiary structure.



(**77**)

In 1,2-disubstituted ethanes (XCH_2CH_2X), conformations are described[32,58] (see Figure 10) as synperiplanar (*sp*), synclinal (*sc*), anticlinal (*ac*) , or antiperiplanar (*ap*) according as

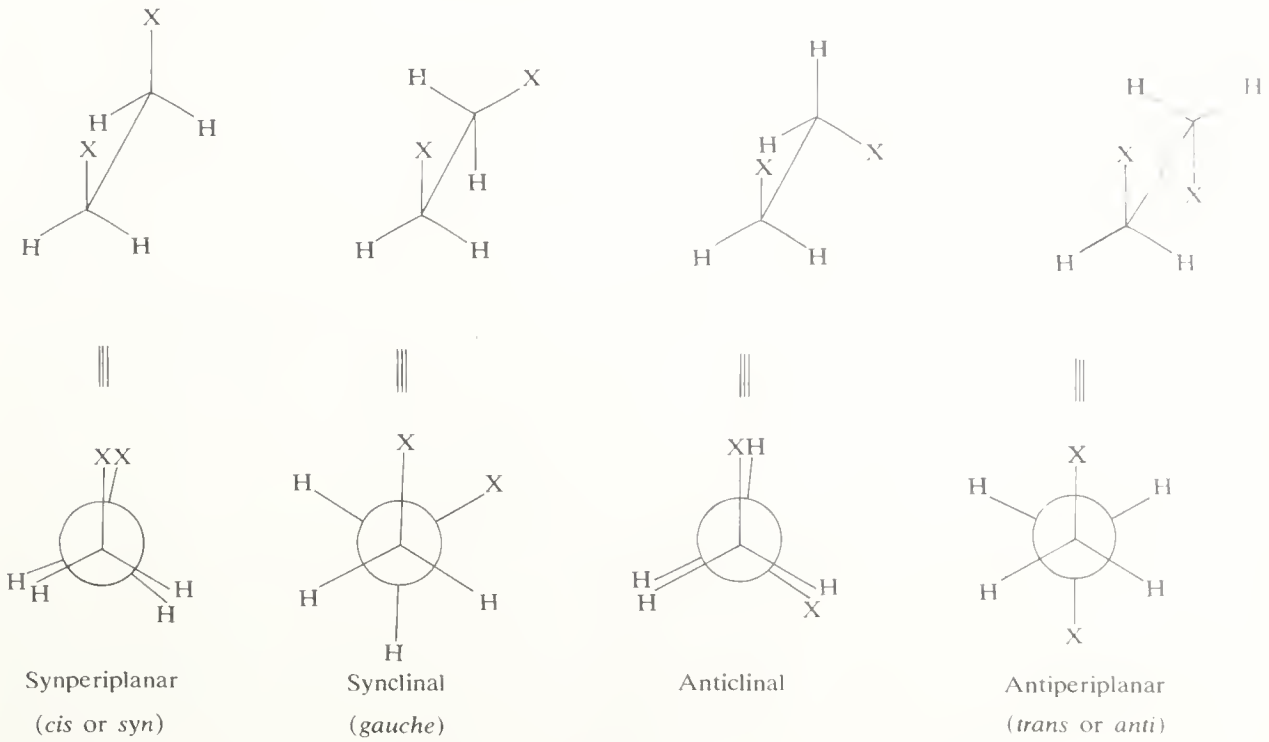


Figure 10 The terminology for describing conformations of 1,2-disubstituted ethanes. Older terms which are still in use are shown in brackets

the torsional angle is within ±30° of 0°, ±60°, ±120°, or ±180°, respectively. In more complicated situations, the ligands which define the torsional angle are selected[32] on the following basis: (i) when all three ligands on a carbon atom are different, that given priority by the sequence rule is chosen; (ii) when one ligand out of the three is unique, it is chosen; and (iii) when all three ligands are the same, the one which provides the smallest torsional angle is chosen. It should be noted that, whereas synclinal and antiperiplanar conformations can correspond to ground-state conformations (*i.e.* isomers), synperiplanar and anticlinal conformations correspond to transition-state conformations, at least in $C(sp^3)—C(sp^3)$ bonding situations. This system of designating relative conformation can be extended to $C(sp^3)—C(sp^2)$ bonding situations. Examples of both kinds are given in Figure 11. The absolute conformation of a particular torsional angle can be analysed[32] through its helicity. The smaller rotation required to eclipse the front ligand with the back ligand is noted as shown in Figure 12. If the rotation is right handed, the conformation is described as (*P*); if the rotation is left-handed, the conformation is described as (*M*).

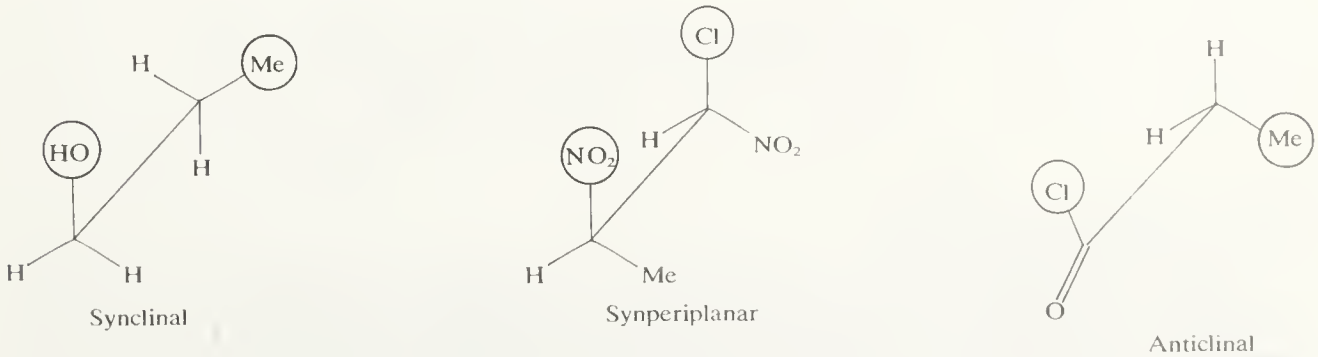


Figure 11 The designation of relative conformation. The circled ligands are the reference ligands

A flexible ring system will seek its minimum-energy conformation where the sum of the classical components (bond deformation strain, torsional strain, non-bonded interactional

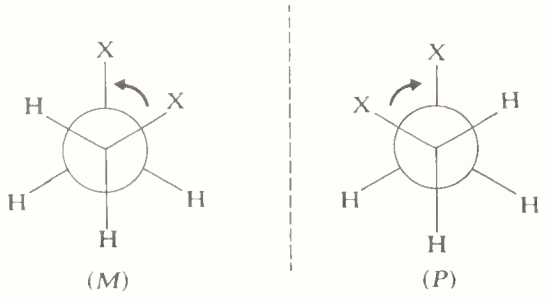
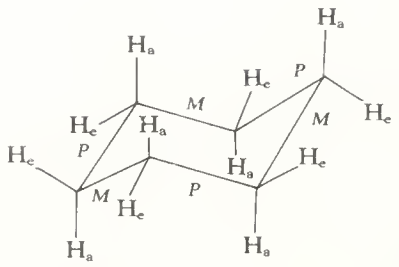


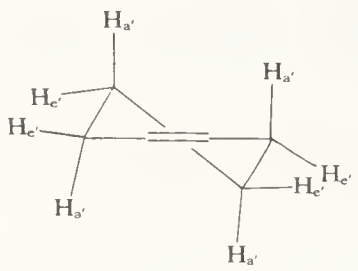
Figure 12 The designation of the absolute conformation of synclinal 1,2-disubstituted ethanes



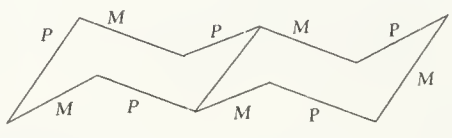
$\mathbf{D}_{3d}$

(**22**)

strain, and electronic interactional strain) of strain energy are minimized with respect to the molecular geometry (see Section 2.1.7). For six-membered saturated ring compounds, the rigid chair conformation is the most stable conformational isomer, *e.g.* the chair conformation (**22**) of cyclohexane which has $\mathbf{D}_{3d}$ symmetry. If the chair conformation is assumed to have idealized tetrahedral geometry (which it does not[59] quite have!) then the bonds that are parallel to the principal C_3 axis are termed axial (a) and those which, on projection towards this axis, define tetrahedral angles with it are termed equatorial (e). In less-symmetrical ring systems, *e.g.* the half-chair conformation (**78**) of cyclohexene, the terms pseudoaxial (a′) and pseudoequatorial (e′) are often employed. When it is necessary to define the absolute conformation of ring compounds, then the (*MP*) convention can be applied to the synclinal ring bonds, *e.g.* the chair conformation (**22**) of cyclohexane has alternate (*M*) and (*P*) synclinal ring bonds, as has *trans*-decalin (**79**).



(**78**)



(**79**)

1.4.6 Concept of isomerism

It has been pointed out[6] that the concept of isomerism only takes on practical significance when there is some means of distinguishing between isomers. However, the time scale of observation is often important in this connection. If isomers can be isolated physically, they can usually be distinguished by spectroscopic and/or diffraction methods. Even when they are too unstable to be isolated, they can sometimes be observed by, say, n.m.r. spectroscopy (see Figure 1). Chlorocyclohexane exhibits[60] both axial and equatorial C—Cl stretching frequencies in its infrared spectrum at room temperature, although the

^{1}H n.m.r. spectrum shows no indications of the presence of diastereoisomeric conformations until the temperature is lowered to −100 °C. Finally, at −150 °C, it is possible to separate the axial and equatorial conformations into non-crystalline and crystalline samples, respectively.

Recently, Eliel[61] has recommended that isomers should be defined independently of the conditions of their observation. In order to do this, it must be agreed that only molecules in their lowest electronic, vibrational, and torsional states qualify to be isomers (*cf.* Section 1.4.5), *i.e.* they must correspond to a minimum on a potential energy hypersurface. Two species with the same molecular formula are considered to be isomeric if the energy barrier separating them is higher than RT mol^{-1} (2.47 kJ mol^{-1} at 25 °C). When the energy barrier is smaller than RT mol^{-1}, they are identical. For example, the barrier to inversion in cyclobutane is approximately 5.9 kJ mol^{-1} and so it is capable of conformational isomerism. By contrast, the barrier to inversion in oxetan is approximately 0.17 kJ mol^{-1} and so it exists as one species at room temperature (see Section 4.4.2). Acceptance of this definition of isomerism would remove many of the inconsistencies and some of the terminology of the past. An arbitrary distinction has been drawn between conformational isomers (called atropisomers) which are separated by sufficiently high torsional energy barriers to permit their isolation, *e.g.* the enantiomers of 6,6′-dinitrodiphenic acid (**76**) (in Figure 9), and those which are rapidly inverting or interconverting at room temperature. Also, a qualitative distinction is often drawn between constitutional isomers such as n-butane and isobutane and the readily interconvertible constitutional isomers known as tautomers, *e.g.* the keto and enol forms of acetoacetic ester. Although it is probably desirable from the point of view of teaching that redundant imprecise terminology of this kind be discontinued for the sake of clarity and simplification, it seems likely that its use will persist for some time to come.

It often transpires that the number of isomers that can be observed by a particular means of detection falls short of the number of isomers expected on the basis of the above definition. The number of observable isomers or species corresponds to[61,62] the so-called residual isomers or species. Examples of both residual constitutional isomerism, *e.g.* the valence bond isomerization between 7-cyano-7-trifluoromethylcycloheptatriene (**80**) and 7-cyano-7-trifluoromethylnorcaradiene (**81**) (see Figure 13), and residual stereoisomerism, *e.g.* the conformational isomerization of 1,2-dichloroethane (see Figure 13), are known. Molecular propellers of the triarylmethane type, for example, 1-(2-methoxynaphthyl)-1-(2-methylnaphthyl)-1-(3-methyl-2,4,6-trimethoxyphenyl)methane (**82**), which is a 32-isomer system with three different aryl groups lacking local C_2 symmetry, can exhibit[62,63] residual diastereoisomerism. Two diastereoisomers of (**82**) have been separated[63] by fractional crystallization; they are interconvertible but the energy barrier is high (128 kJ mol^{-1}).

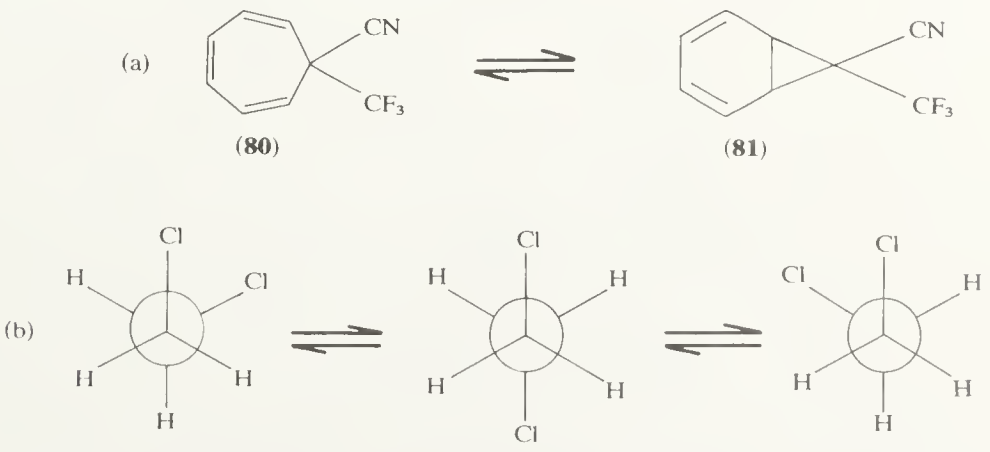
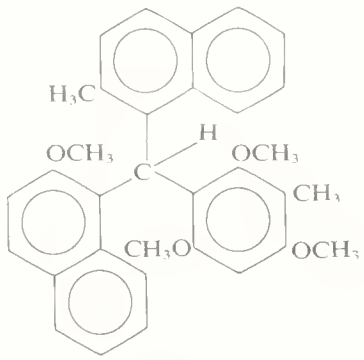


Figure 13 Examples of residual constitutional isomerism (a) and residual stereoisomerism (b)



(82)

1.5 TOPISM

1.5.1 Some terminology

Just as isomerism is concerned with comparisons between molecules, so a whole branch of stereochemistry can be built around[6] internal comparisons of ligands within molecules. However, it is only in comparatively recent times that this aspect of stereochemistry concerned with so-called topic relationships[7,20,30,64,65] has received adequate expression, although the concept has been illustrated in the glorious multitude of reactions catalysed by enzymes since time immemorial. Topism, which is derived from the Greek word *topos* meaning place, relates to a form of analysis which compares ligands in relation to their environment. Thus, two ligands in a molecule are said to be homotopic if their superimposition can be achieved[65] by (i) rotation about a C_n axis, *e.g.* the two hydrogen atoms (and the two chlorine atoms) in dichloromethane (**1**) are homotopic on account of C_2 symmetry, (ii) rapid changes in configuration or conformation, *e.g.* the methyl hydrogen atoms in toluene are homotopic as a result of rapid torsional changes about the C(sp^3)—C(sp^2) bond, or (iii) translational motion in the case of infinite polymers. Ligands which are not homotopic by any of these criteria are said to be heterotopic. If heterotopic

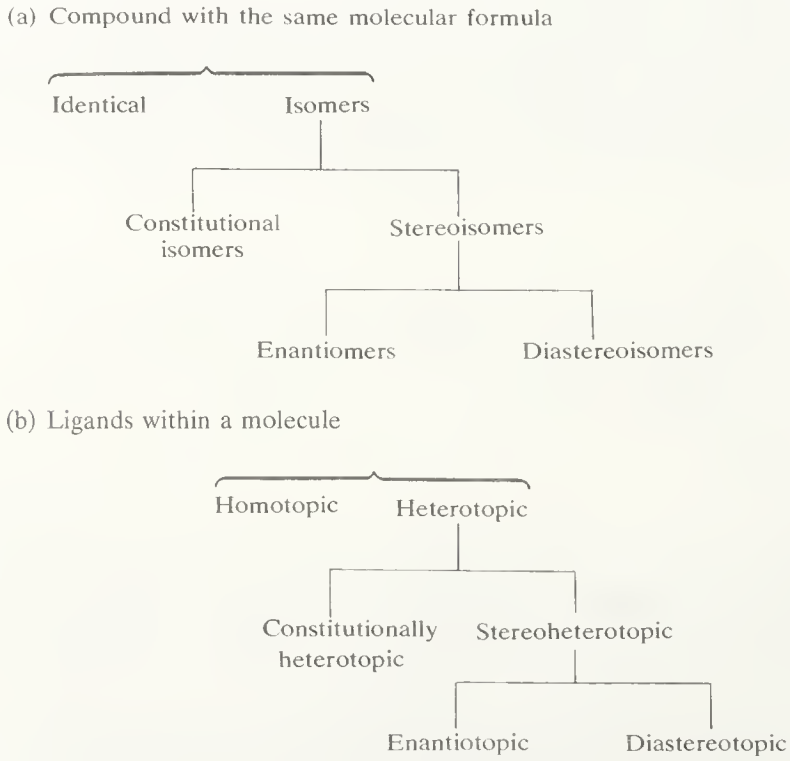


Figure 14 The conceptual correspondence between isomerism and topism

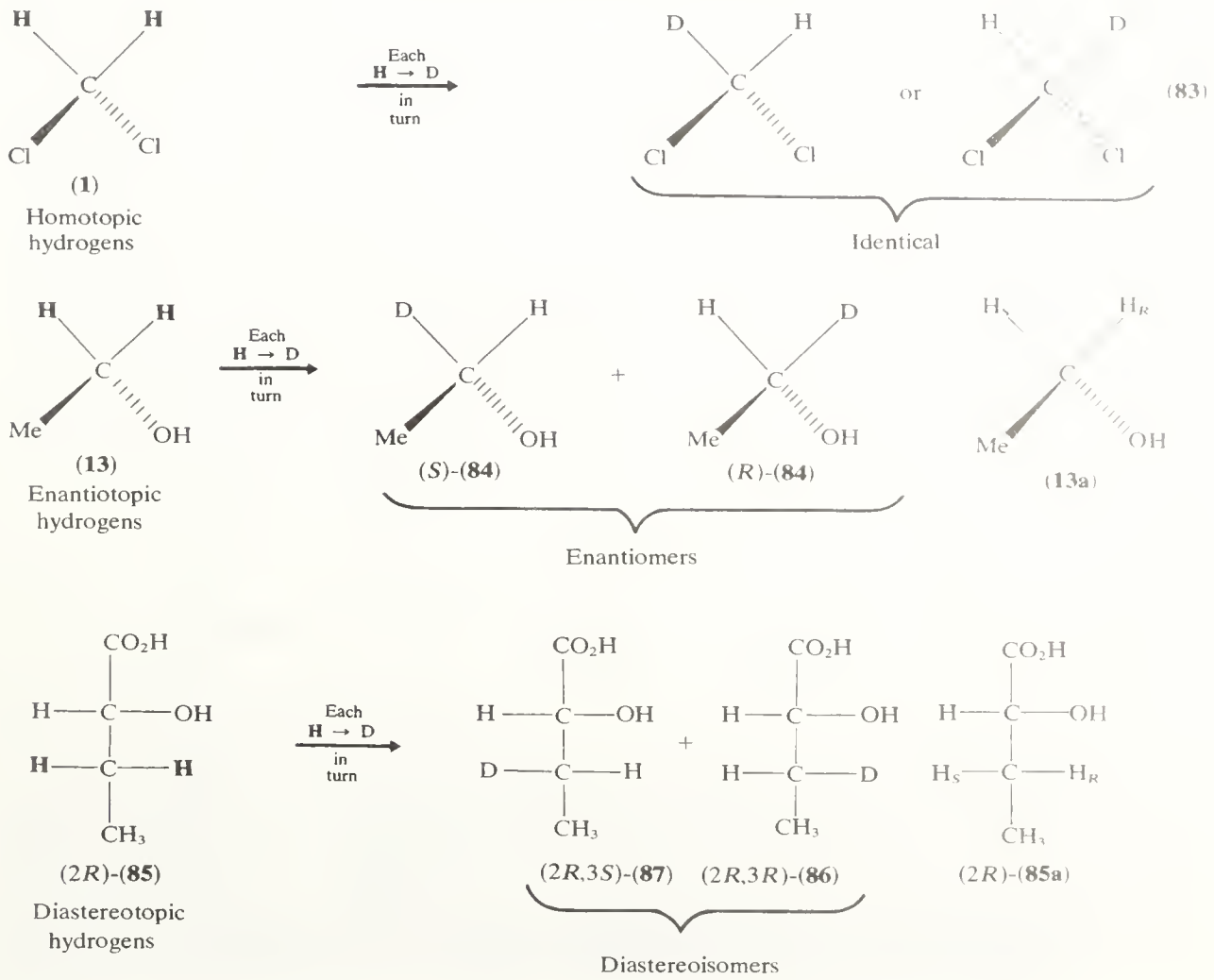


Figure 15 The use of the substitution criterion to establish topic relationships between ligands. The designation of *pro-R* and *pro-S* ligands

ligands are in constitutionally different environments they are said to be constitutionally heterotopic, *e.g.* the methylene protons (**H**) at C-1 and C-2 in propan-1-ol, $CH_3C\mathbf{H}_2C\mathbf{H}_2OH$, whereas heterotopic ligands in stereoisomerically different environments are said to be stereoheterotopic. Finally, the class of stereoheterotopic ligands can be divided into (i) enantiotopic and (ii) diastereotopic ligands depending on (i) whether the ligands can be exchanged by an S_n symmetry operation, *e.g.* the methylene hydrogens in ethanol (**13**) are enantiotopic, or (ii) whether the ligands cannot be exchanged by any symmetry operation on the molecule at all, *e.g.* the methyl groups on C-6 of α-pinene (**7**) are diastereotopic. Figure 14 illustrates clearly the close conceptual correspondence between isomerism and topism. A substitution criterion (see Figure 15) can be used[20] to establish or confirm the nature of the topic relationship between stereoheterotopic ligands. Consecutive replacement of the homotopic hydrogens in dichloromethane (**1**) by deuterium gives only one deuterated compound (**83**). Consecutive replacement of the enantiotopic ligands in ethanol (**13**) by deuterium leads to the enantiomers (*R*)-(**84**) and (*S*)-(**84**). Consecutive replacement of the diastereotopic hydrogens in (*R*)-malic acid, (2*R*)-(**85**), by deuterium leads to the diastereoisomers (2*R*,3*R*)-(**86**) and (2*R*,3*S*)-(**87**).

An understanding of topic relationships between ligands in molecules is useful when interpreting n.m.r. spectra. Under all circumstances, homotopic nuclei exhibit the same chemical shifts and the signals are said to be isochronous. However, diastereotopic nuclei can exhibit different chemical shifts and if they do the signals are said to be anisochronous. Enantiotopic nuclei exhibit isochronous behaviour in achiral solvents but in the

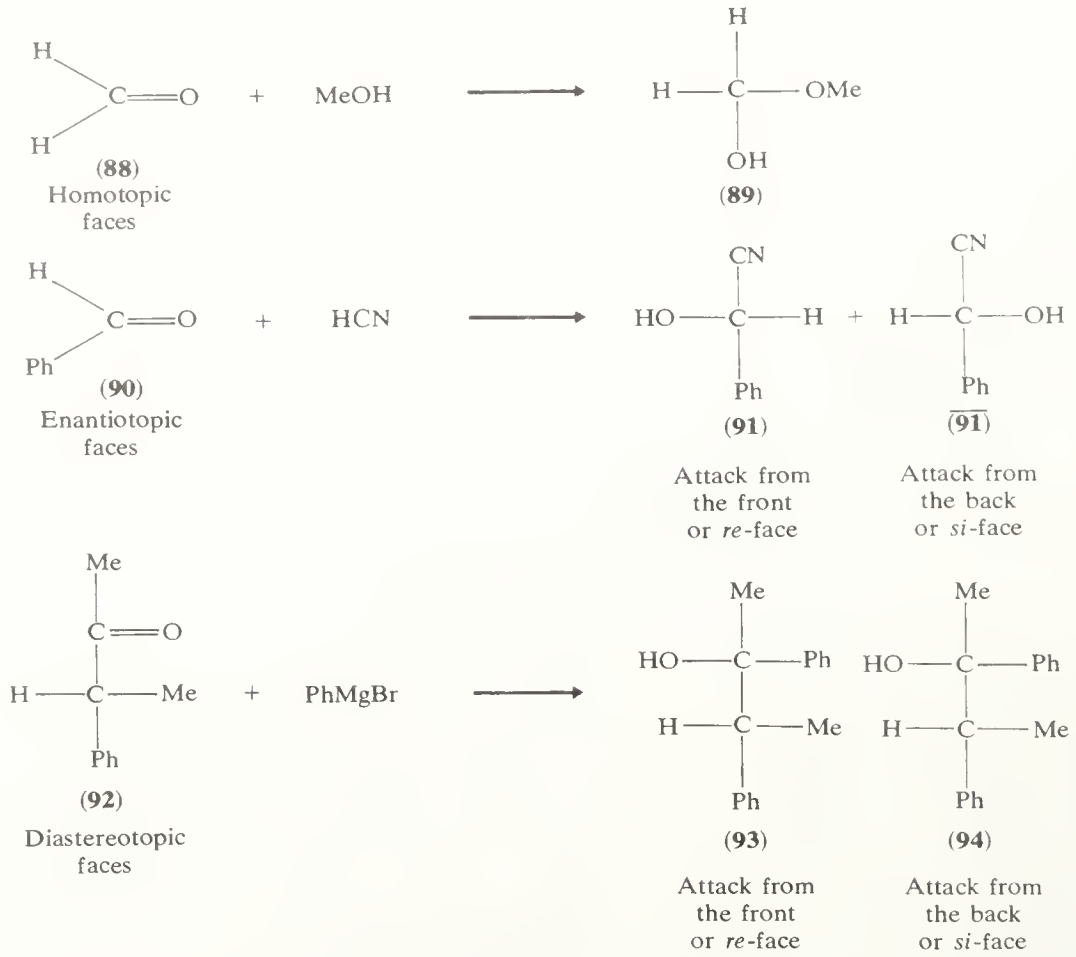


Figure 16 The use of nucleophilic additions to carbonyl groups in establishing topic relationships between faces. The designation of *re*- and *si*-faces

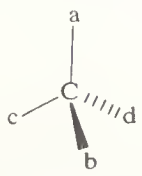
presence of chiral solvents[66] or complexing agents,[67] including enzymes which may be regarded as chiral reagents, enantiotopic ligands can be distinguished. Thus, enantiotopic nuclei may exhibit anisochronous behaviour in a chiral environment.

Topic relationships are also useful for describing regions of space around atoms and bonds in molecules. In particular, the faces of double bonds associated with sp^2 hybridized carbon atoms can be homotopic or stereoheterotopic. As illustrated in Figure 16, the faces of carbonyl groups can be homotopic, enantiotopic, or diastereotopic. Formaldehyde (**88**) only forms one hemiacetal (**89**) because its two faces are equivalent or homotopic. However, in benzaldehyde (**90**) the two faces are enantiotopic and so addition of cyanide ion to either face is equally probable and gives rise to two enantiomeric mandelonitriles (**91**) and (**$\bar{91}$**). In the presence of emulsion, only one of these enantiomers is formed, *i.e.* enzymes can distinguish between enantiotopic faces. Finally, the two faces of 3-phenylbutan-2-one (**92**) are diastereotopic and hence it gives rise to two diastereoisomeric alcohols in unequal proportions on addition of phenyl Grignard reagent to the carbonyl group. Many years ago, Cram[68] formulated his well-known rule which allows predictions of the preferentially formed product to be made in these situations of so-called asymmetric induction. More recently, this kind of stereoselectivity has been subjected to detailed mathematical treatment.[69]

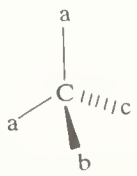
1.5.2 Prochirality

Just as compounds which contain chiral centres of the type Cabcd (**47**) can display enantiomerism and diastereoisomerism, so those which contain a centre of the type Caabc

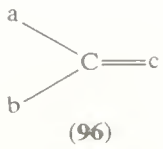
(**95**), where the ligands a are either enantiotopic or diastereotopic, are said[70,71] to contain a prochiral centre. In addition to centres of prochirality, axes and planes may also constitute prochiral elements (*cf.* chiral elements). Thus, a general definition of prochirality can be given. If a chiral assembly is obtained when a ligand in an assembly of ligands is replaced by a different ligand, then the original assembly is prochiral. Hence, centres of prochirality Caabc (**95**) in molecules can carry either enantiotopic or diastereotopic ligands, and since these stereoheterotopic ligands can be distinguished by chiral reagents, *e.g.* enzymes, it is useful to have symbols based on the Cahn–Ingold–Prelog sequence rule[29] to differentiate between heterotopic ligands (see Section 1.5.2.1). However, we have seen that faces in molecules containing double bonds, for example, can also be stereoheterotopic. Consequently, a kind of prochirality also exists for assemblies of the type abC=c (**96**). Since stereoheterotopic faces can be distinguished by enzymes, it is also useful to have a system of nomenclature based on the Cahn–Ingold–Prelog sequence rule[29] (see Section 1.5.2.2).



(**47**)



(**95**)



(**96**)

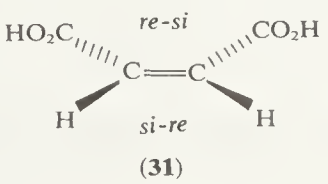
1.5.2.1 The pro-R/pro-S *convention*

The relationship between prochirality and chirality is well-defined and hence the sequence rule[29] can be used[70] to specify the paired stereoheterotopic ligands associated with prochiral elements. If replacement of one of the paired ligands by a ligand of higher priority leads to (*R*) chirality, then the ligand is designated *pro-R* and given the descriptor L_R (L for ligand). If (*S*) chirality results from this test, then the ligand is designated *pro-S* and given the descriptor L_S. The notation is illustrated for ethanol (**13a**) and (2*R*)-malic acid, (2*R*)-(**85a**), in Figure 15.

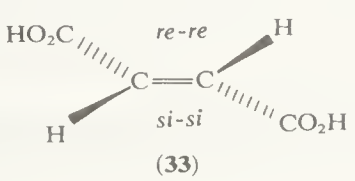
1.5.2.2 The re/si *convention*

Stereoheterotopic faces may be specified[70] by using the Cahn–Ingold–Prelog sequence rule in two dimensions (see Figure 17). If the arrangement of the ligands according to the priority a>b>c is clockwise, the face is designated a *re*-face, whereas an anticlockwise arrangement defines a *si*-face. The use of the convention is illustrated with benzaldehyde (**90**) and 3-phenylbutan-2-one (**92**) in Figure 16 (see also Section 5.1.5). It can also be employed with carbon–carbon double bonds where the arrangement of ligands about both carbon atoms is specified. Thus, maleic acid (**31**) has *re-si*- and *si-re*-faces and fumaric acid (**33**) has *re-re*- and *si-si*-faces.

Figure 17 The designation of stereoheterotopic faces using the *re/si* convention



(**31**)



(**33**)

1.5.3 Pseudoasymmetry (pseudochirality)

Centres of the type Caabc (**95**) are not always prochiral. If the paired ligands a each contain a source of chirality and are enantiomerically related by internal comparison, then a molecule containing such a centre is said to have[29,32] a centre of pseudoasymmetry (or pseudochirality[42,43]). For example, the alditols ribitol (**97**) and xylitol (**98**) shown in Figure 18 both have pseudoasymmetric centres at C-3. Although they are examples of achiral molecules since ligands b and c are devoid of chirality, compounds containing a centre of pseudoasymmetry can be chiral if either or both of these ligands contains a source of

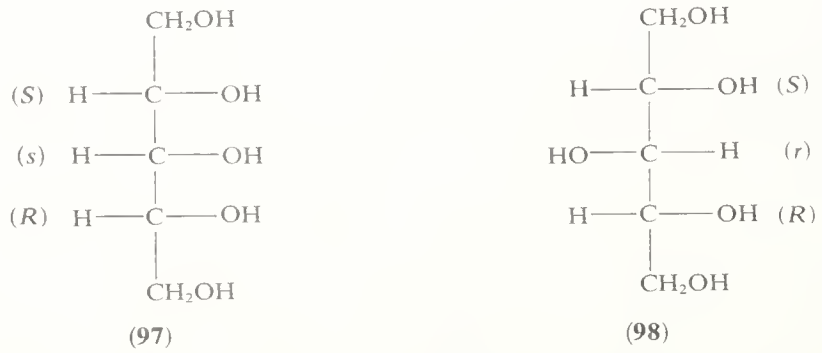


Figure 18 Examples of compounds containing pseudoasymmetric centres. The designation of intramolecular relative configurations using the (*rs*) convention

chirality. In common with the elements of chirality and prochirality, the phenomenon of pseudoasymmetry manifests itself in axes and planes of pseudoasymmetry as well (see Refs. 26–29 and 72 for a discussion of these rather specialized situations). In order to specify the intramolecular relative configurations about a centre of pseudoasymmetry using the Cahn–Ingold–Prelog convention, a sub-rule[29,32] to the sequence rule, which states that for the paired chiral ligands L_R precedes L_S, is employed. The intramolecular relative configurations of pseudoasymmetric elements are then specified by the descriptors (*r*) and (*s*) in a manner similar to that used in the specification of absolute configurations at chiral elements by the descriptors (*R*) and (*S*). Figure 18 illustrates the use of the descriptors (*r*) and (*s*) to specify the intramolecular relative configurations at C-3 of xylitol (**98**) and ribitol (**97**), respectively.

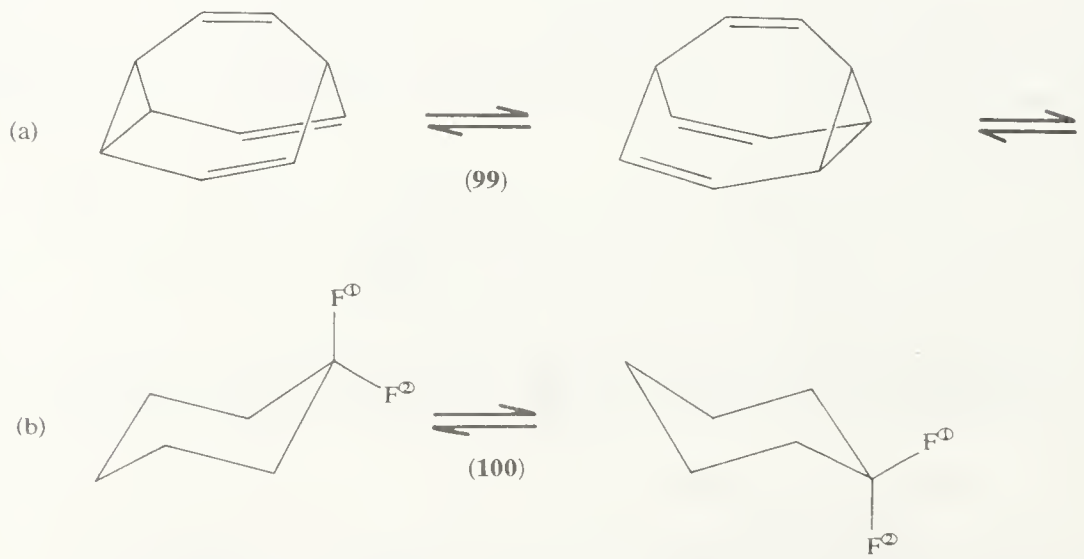


Figure 19 Examples of constitutional topomerization (a) and diastereotopomerization (b)

1.6 TOPOMERISM

Following on the conceptual advances described in the previous section, a nomenclature system has been proposed[73] for intramolecular exchange processes which do not involve any change in structure and can frequently be followed by dynamic n.m.r. spectroscopy.[74] The system identifies a process which leads to interchange of identical ligands between distinguishable chemical or magnetic environments as a topomerization. It is suggested that the indistinguishable species involved in the exchange are called topomers. The most common type of topomerizations which can occur are illustrated in Figure 19. Bullvalene (**99**) represents an example of valence bond or constitutional topomerization in which one and the same ligand (carbon or hydrogen) visits four constitutionally different positions (allylic, two kinds of vinylic, and cyclopropanoid) during equilibration. Diastereotopomerizations are also well known, *e.g.* the ring inversion of 1,1-difluorocyclohexane (**100**), and examples of enantiotopomerizations and homotopomerizations, although much less common, are known.

1.7 DYNAMIC STEREOCHEMISTRY: A BRIEF COMMENT

The dynamic aspects of stereochemistry are concerned with how reactions depend upon configurational and conformational properties of reactants and products and the transition states separating them. There is little doubt that stereoelectronic effects in substitutions, additions, eliminations, and rearrangements are best discussed within the context of reaction mechanisms and no attempt has been made in this introductory chapter to cover this vast and growing field of stereochemistry. Indeed, the stage of development in dynamic stereochemistry is such that inconsistencies abound in the use of terminology and nomenclature. It will be obvious to the reader of this work that different authors attach different meanings to terms such as stereoselectivity and stereospecificity, although attempts[3,75] have been made to restrict their use to the description of particular phenomena. At the constitutional level of structure, terms such as chemoselectivity and regioselectivity have been widely adopted by many authors. Suggestions for the designations of reaction mechanisms have also been made.[76]

Dynamic stereochemistry has, of course, impinged upon developments in synthesis, particularly chiral or asymmetric synthesis.[12] During the last 25 years,[77] conformational analysis has had much influence in this field. Most recently the high stereoselectivity exhibited by most so-called pericyclic reactions has been interpreted[78,79] in a number of ways. At the constitutional level of structure, computer assisted synthesis[80,81] promises much for the future.

References

1. D. H. R. Barton, *Experientia*, 1950, **6,** 316; *cf. Topics Stereochem.*, 1971, **6,** 1.
2. Numerous articles in 'Steric Effects in Organic Chemistry,' ed. M. S. Newman, Wiley, New York, 1956.
3. E. L. Eliel, 'Stereochemistry of Carbon Compounds', McGraw Hill, New York, 1962.
4. E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, 'Conformational Analysis', Wiley, New York, 1965.
5. M. Hanack, 'Conformational Theory', Academic. New York, 1965.
6. K. Mislow, 'Introduction to Stereochemistry', Benjamin, New York, 1965.
7. E. L. Eliel, 'Elements of Stereochemistry', Wiley, New York, 1969.
8. R. Bentley, 'Molecular Asymmetry in Biology', Academic, New York, 1969, vol. I.
9. R. Bentley, 'Molecular Asymmetry in Biology', Academic, New York, 1970, vol. II.
10. J. F. Stoddart, 'Stereochemistry of Carbohydrates', Wiley, New York, 1971.
11. W. L. Alworth, 'Stereochemistry and its Application in Biochemistry', Wiley, New York, 1972.
12. J. D. Morrison and H. S. Mosher, 'Asymmetric Organic Reactions', Prentice-Hall, New Jersey, 1971.
13. J. McKenna, 'Conformational Analysis of Organic Compounds', in 'The Royal Institute of Chemistry Lecture Series', London 1966, No. 1.
14. Numerous articles in *Progr. Stereochem.*, 1954, **1,** ed. W. Klyne; 1958, **2,** ed. W. Klyne and P. B. D. de la Mare; 1962, **3,** ed. W. Klyne and P. B. D. de la Mare; 1969, **4,** ed. B. J. Aylett and M. M. Harris, Butterworths, London.

15. Numerous articles in *Topics Stereochem.*, 1967, **1;** 1967, **2;** 1968, **3;** 1969, **4;** 1970, **5;** 1971, **6;** 1973, **7;** 1974, **8;** 1976, **9,** ed. N. L. Allinger and E. L. Eliel, Wiley, New York.
16. Numerous articles in 'Conformational Analysis. Scope and Present Limitations', ed. G. Chiurdoglu, Academic, New York, 1971.
17. Numerous articles in *Pure Appl. Chem.*, 1971, **25,** 465–666.
18. Numerous articles in *Tetrahedron*, 1974, **30,** 1473–2007.
19. Numerous articles on 'Chirality and Chiral Structures' in *Israel J. Chem.*, 1976/77, **15,** 1–130.
20. K. Mislow and M. Raban, *Topics Stereochem.*, 1967, **1,** 1.
21. H. H. Jaffé, and M. Orchin, 'Symmetry in Chemistry', Wiley, New York, 1965.
22. F. A. Cotton, 'Chemical Applications of Group Theory', 2nd edn., Wiley, New York, 1971.
23. J. D. Donaldson and S. D. Ross, 'Symmetry and Stereochemistry', Wiley, New York, 1972.
24. A. V. Shubnikov and V. A. Koptsik, 'Symmetry in Science and Art', Plenum, New York, 1974.
25. K. Mislow and P. Bickart, *Israel J. Chem.*, 1976/77, **15,** 1.
26. V. Prelog, *Proc., k. ned. Akad. Wetchschap.* (*B*), 1968, **71,** 108.
27. V. Prelog, *Chem. Britain*, 1968, **4,** 382.
28. V. Prelog, *Science*, 1976, **193,** 17.
29. R. S. Cahn, C. K. Ingold, and V. Prelog, *Angew. Chem. Internat. Edn.*, 1966, **5,** 385.
30. E. L. Eliel, *J. Chem. Educ.*, 1971, **48,** 163.
31. W. K. Noyce, *J. Chem. Educ.*, 1961, **38,** 23.
32. IUPAC 1974 Recommendations for Section E, 'Fundamental Stereochemistry', *Pure Appl. Chem.*, 1976, **45,** 13. Also see K. Mislow, *Bull. Soc. chim. belges*, 1977, **86,** 595, for the view of an iconoclast.
33. Lord Kelvin, 'Baltimore Lectures', Clay, London, 1904, pp. 436, 619.
34. L. L. Whyte, *Nature*, 1957, **180,** 513; 1958, **182,** 198.
35. A. P. Downing, W. D. Ollis, and I. O. Sutherland, *J. Chem. Soc.* (*B*), 1970, 24.
36. J. F. Stoddart, W. A. Szarek, and J. K. N. Jones, *Canad. J. Chem.*, 1969, **47,** 3213.
37. F. de Jong, M. G. Siegel, and D. J. Cram, *J.C.S. Chem. Comm.*, 1975, 551.
38. D. J. Williams and D. Lawton, *Tetrahedron Letters*, 1975, 111.
39. E. Ruch, *Accounts Chem. Res.*, 1972, **5,** 49.
40. J. E. Leonard, G. S. Hammond, and H. E. Simmons, *J. Amer. Chem. Soc.*, 1975, **97,** 5052.
41. H. O. L. Fischer and E. Baer, *Chem. Rev.*, 1941, **29,** 287.
42. S. I. Goldberg and W. D. Bailey, *J. Amer. Chem. Soc.*, 1971, **93,** 1046.
43. J. G. Nourse, *J. Amer. Chem. Soc.*, 1975, **97,** 4594.
44. G. W. Wheland, 'Advanced Organic Chemistry', 3rd edn., Wiley, New York, 1960.
45. V. Prelog and H. Gerlach, *Helv. Chim. Acta*, 1964, **47,** 2288; H. Gerlach, J. A. Owtschinnikow, and V. Prelog, *Helv. Chim. Acta*, 1964, **47,** 2294.
46. G. Schill, 'Catenanes, Rotoxanes, and Knots', Academic, New York, 1971.
47. R. S. Cahn, 'Introduction to Chemical Nomenclature', 4th edn., Butterworths, London, 1974.
48. IUPAC Nomenclature of Organic Chemistry. 1969 Definitive Rules for: Section A, Hydrocarbons; Section B, Fundamental Heterocyclic Systems; Section C, Characteristic Groups containing Carbon, Hydrogen, Oxygen, Nitrogen, Halogen, Sulfur, Selenium and/or Tellurium, Butterworths, London, 1971.
49. J. M. Bijvoet, A. F. Peerdeman, and A. J. van Bommel, *Nature*, 1951, **168,** 271.
50. R. S. Cahn and C. K. Ingold, *J. Chem. Soc.*, 1951, 612.
51. R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, 1956, **12,** 81.
52. R. S. Cahn, *J. Chem. Educ.*, 1964, **41,** 116.
53. IUPAC/IUB Nomenclautre of α-Amino-acids, *IUPAC Information Bull.*, Appendix No. 46, 1975.
54. IUPAC/IUB 1973 Recommendation for the Nomenclature of Cyclitols, *Pure Appl. Chem.*, 1974, **37,** 285.
55. IUPAC/IUB Tentative Rules for Carbohydrate Nomenclature, *IUPAC Information Bull.*, Appendix No. 7, 1970.
56. IUPAC/IUB 1971 Recommendations for the Nomenclature of Steroids, *Pure Appl. Chem.*, 1972, **31,** 283.
57. J. E. Blackwood, C. L. Gladys, K. L. Loening, A. E. Petrarca, and J. E. Rush, *J. Amer. Chem. Soc.*, 1968, **90,** 509; J. E. Blackwood, C. L. Gladys, A. E. Petrarca, W. H. Powell, and J. E. Rush, *J. Chem. Documentation*, 1968, **8,** 30.
58. W. Klyne and V. Prelog, *Experientia*, 1960, **16,** 521.
59. C. Romers, C. Altona, H. R. Buys, and E. Havinga, *Topics Stereochem.*, 1969, **4,** 39.
60. F. R. Jensen and C. H. Bushweller, *J. Amer. Chem. Soc.*, 1966, **88,** 4279.
61. E. L. Eliel, *Israel J. Chem.*, 1976/77, **15,** 7.
62. K. Mislow, *Accounts Chem. Res.*, 1976, **9,** 26.
63. P. Finocchiaro, D. Gust, and K. Mislow, *J. Amer. Chem. Soc.*, 1974, **96,** 3198.
64. D. Arigoni and E. L. Eliel, *Topics Stereochem.*, 1969, **4,** 127.
65. H. Hirschmann and K. R. Hanson, *European J. Biochem.*, 1971, **22,** 301.
66. W. H. Pirkle, *J. Amer. Chem. Soc.*, 1966, **88,** 1837; W. H. Pirkle and S. D. Beare, *ibid.*, 1969, **91,** 5150.
67. D. A. Laidler and J. F. Stoddart, *J.C.S. Chem. Comm.*, 1976, 979.
68. D. J. Cram and F. A. Abd Elhafez, *J. Amer. Chem. Soc.*, 1952, **74,** 5828; D. J. Cram and K. R. Kopecky, *J. Amer. Chem. Soc.*, 1959, **81,** 2748.
69. E. Ruch and I. Ugi, *Topics Stereochem.*, 1969, **4,** 99.
70. K. R. Hanson, *J. Amer. Chem. Soc.*, 1966, **88,** 2731.
71. H. Hirschmann and K. R. Hanson, *J. Org. Chem.*, 1971, **36,** 3293.

72. V. Prelog and G. Helmchen, *Helv. Chim. Acta*, 1972, **55,** 2581, 2599, 2612; G. Helmchen, G. Haas, and V. Prelog, *ibid.*, 1973, **56,** 2255.
73. G. Binsch, E. L. Eliel, and H. Kessler, *Angew. Chem. Internat. Edn.*, 1971, **10,** 570.
74. G. Binsch, *Topics Stereochem.*, 1968, **3,** 146; I. O. Sutherland, *Ann. Rev. NMR Spectroscopy*, 1971, **4,** 71.
75. E. L. Eliel, *J. Chem. Educ.*, 1964, **41,** 73.
76. R. D. Guthrie, *J. Org. Chem.*, 1975, **40,** 402.
77. E. L. Eliel, *J. Chem. Educ.*, 1975, **52,** 762.
78. R. B. Woodward and R. Hoffmann, *J. Amer. Chem. Soc.*, 1965, **87,** 395; *Angew. Chem. Internat. Edn.*, 1969, **8,** 781.
79. M. J. S. Dewar, *Angew. Chem. Internat. Edn.*, 1971, **10,** 761.
80. E. J. Corey, *Quart. Rev.*, 1971, **25,** 455; E. J. Corey and W. L. Jorgensen, *J. Amer. Chem. Soc.*, 1976, **98,** 189, 203; E. J. Corey, H. W. Orf, and D. A. Pensak, *ibid.*, 1976, **98,** 210.
81. J. B. Hendrickson, *J. Amer. Chem. Soc.*, 1977, **99,** 5439.

PART 2

HYDROCARBONS

2.1

Saturated Hydrocarbons

T. CLARK
Universität Erlangen-Nürnberg
and
M. A. McKERVEY
University College, Cork

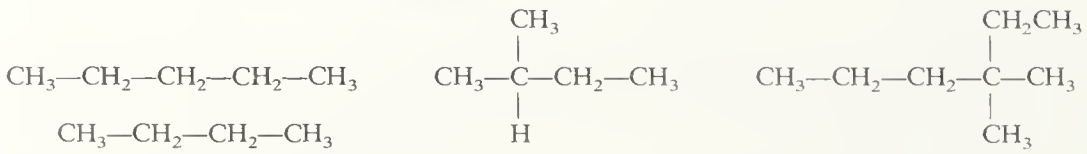
2.1.1 INTRODUCTION 38
2.1.2 CONSTITUTION AND NOMENCLATURE 40
2.1.2.1 IUPAC nomenclature 40
2.1.2.2 Alicyclic alkanes 41
2.1.2.3 Polycycloalkanes 42
2.1.3 SOURCES OF SATURATED HYDROCARBONS 46
2.1.4 PHYSICAL PROPERTIES 49
2.1.4.1 Acyclic alkanes 49
2.1.4.2 Monocyclic and polycyclic alkanes 50
2.1.5 STEREOCHEMISTRY AND CONFORMATIONAL ANALYSIS 52
2.1.5.1 Bond angles and lengths 52
2.1.5.2 Alkyl- and polyalkyl-cyclohexanes 60
2.1.5.3 Conformations of carbocyclic rings larger than cyclohexane 64
2.1.6 THERMOCHEMICAL PROPERTIES 66
2.1.6.1 Combustion: alkanes and cycloalkanes as fuels 66
2.1.6.2 Thermochemical properties from combustion measurements 68
2.1.6.3 Empirical methods for estimating heats of formation of alkanes 70
2.1.6.4 Bond-energy terms 72
2.1.6.5 The group increment approach 73
2.1.6.6 Cyclic, polycyclic, and bridged-ring alkanes 'skew separate' and 'single conformation' group increments 78
2.1.6.7 Heats of formation and strain energies from molecular mechanics calculations 79
2.1.6.8 Cycloalkanes and polycycloalkanes 80
2.1.7 PREPARATION OF ACYCLIC ALKANES 91
2.1.7.1 Alkanes from olefins by reduction 91
2.1.7.2 Alkanes from aldehydes and ketones 92
2.1.7.3 Alkanes from alcohols and alkyl halides 93
2.1.7.4 Alkanes from carboxylic acids 96
2.1.8 SYNTHESIS OF CYCLIC AND POLYCYCLIC ALKANES 96
2.1.9 REACTIONS OF ACYCLIC ALKANES 105
2.1.9.1 Halogenation 105
2.1.9.2 Nitration 108
2.1.9.3 Oxidation 109
2.1.9.4 Catalytic isomerization of alkanes 110
2.1.9.5 Catalytic alkylation of alkanes 111

2.1.9.6 *Alkane cracking reactions* 111
2.1.9.7 *Thermal cracking* 112
2.1.9.8 *Catalytic cracking* 112
2.1.9.9 *Catalytic reforming and dehydrocyclization of alkanes* 112
2.1.10 REACTIONS OF CYCLOALKANES AND POLYCYCLOALKANES 112

2.1.1 INTRODUCTION

Carbon is unique among the elements in the number of compounds which it can form, and the chemistry of carbon compounds, historically referred to as organic chemistry, owes its wonderful unity and variety to the remarkable stability of the carbon–carbon single bond. Saturated hydrocarbons, composed only of carbon and hydrogen atoms bound together by single covalent bonds, form the structural backbone of many organic compounds, and carbon chains and rings can be constructed in a seemingly infinite variety of lengths and patterns. The generic name of acyclic saturated hydrocarbons, linear or branched, is alkane, and that of cyclic saturated hydrocarbons, in which the carbon atoms are linked in one or more rings, is cycloalkane.

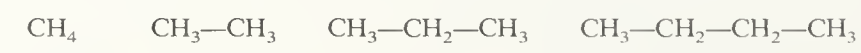
The simplest alkane, methane, has been known for a long time in the form of 'marsh gas' which is produced by the bacterial decomposition of organic matter under anaerobic conditions. Methane is also present in coal seams; when released during mining operations, it can accumulate in sufficient amount to form an explosive mixture with air ('fire damp'). The hydrogen atoms in methane, CH_4, are arranged about the carbon atom in a tetrahedral fashion. The alkanes are all derivable from methane by the successive replacement of hydrogen atoms by methyl groups; they are thus all built on a skeleton in which the valence angles are near to the tetrahedral value of 109.5° and the distances between two linked carbon atoms are 154 pm. The homologous series has the general formula C_nH_{2n+2}, each member differing from the next by a CH_2 unit. Alkanes are classified as 'continuous chain' (*i.e.* unbranched) if all the carbon atoms in the chain are linked to no more than two other carbon atoms, or 'branched chain' if one or more carbon atoms are linked to more than two other carbon atoms:



continuous-chain, or normal alkanes

branched-chain alkanes

The first four continuous-chain alkanes have non-systematic names:



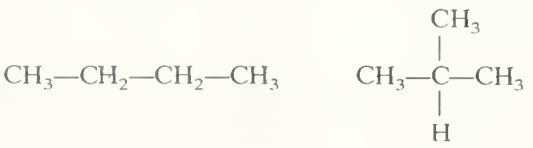
The higher members, beginning with pentane, are named systematically with a numerical prefix (pent-, hex-, hept-, *etc.*) indicating the number of carbon atoms and the ending '-ane' classifying the compound as a saturated hydrocarbon. Examples are listed in Table 1. The prefix n (for normal) is often used to specify a continuous-chain alkane. However, in the absence of any qualifying prefix the alkane is considered to be 'normal' or unbranched.

The names in Table 1 are common to both branched and unbranched alkanes. The possibility of branched-chain alkanes begins with butane, in which case two constitutions

TABLE 1
Acyclic Alkanes, C_nH_{2n+2}

n	*Name*	*n*	*Name*	*n*	*Name*
1	Methane	13	Tridecane	30	Triacontane
2	Ethane	14	Tetradecane	31	Hentriacontane
3	Propane	15	Pentadecane	32	Dotriacontane
4	Butane	16	Hexadecane	33	Tritriacontane
5	Pentane	17	Heptadecane	40	Tetracontane
6	Hexane	18	Octadecane	50	Pentacontane
7	Heptane	19	Nonadecane	60	Hexacontane
8	Octane	20	Eicosane	70	Heptacontane
9	Nonane	21	Heneicosane	80	Octacontane
10	Decane	22	Docosane	90	Nonacontane
11	Undecane	23	Tricosane	100	Hectane
12	Dodecane	24	Tetracosane	132	Dotriacontahectane

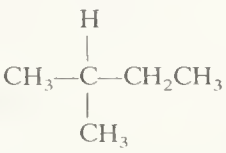
can be written, both of which are derived from the formula C_4H_{10}:



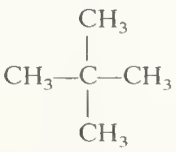
n-butane or butane

isobutane or 2-methylpropane (systematic)

Butane and isobutane are said to be constitutional isomers, the term referring to compounds of the same molecular formula but with different atom-to-atom bonding sequences. Isobutane has a 'branched chain' constitution whereas butane (or n-butane) has a 'continuous-chain' constitution. More constitutional isomers are possible when additional carbon and hydrogen atoms are present in an alkane. Thus, there are three isomeric pentanes, those additional to n-pentane being:



isopentane or 2-methylbutane (systematic)



neopentane or 2,2-dimethylpropane (systematic)

The number of theoretically possible constitutional isomers increases sharply as the homologous series expands. Table 2 reveals that there are 5, 9, and 18 isomers of C_6H_{14}, C_7H_{16}, and C_8H_{18}, respectively, and a collossal 4.11×10^9 $C_{30}H_{62}$ isomers. All alkanes up to and including the 75 decanes have been synthesized, but beyond C_{10} only a minute fraction of the total represented by Table 2 are known substances.

TABLE 2
Constitutional Isomers for C_nH_{2n+2}

n	*Isomer numbers*
5	3
6	5
7	9
8	18
9	35
10	75
20	366 319
30	4.11×10^9

2.1.2 CONSTITUTION AND NOMENCLATURE

A systematic nomenclature for saturated hydrocarbons (and their functionalized derivatives) has been evolved by the International Union of Pure and Applied Chemistry (IUPAC). This system began only after a number of the simpler alkanes had received trivial or non-systematic names. For example, the name butane was derived from the C_4 compound butyric acid, which was first isolated from rancid butter. Several of these trivial names are still universally accepted and are incorporated in the IUPAC nomenclature (see Table 3). However, trivial names for alkanes containing multiple branching can become cumbersome or ambigious, and considering the numbers of isomers with which chemists may have to contend, a systematic nomenclature became an obvious necessity.

TABLE 3
Alkyl Groups and Simple Alkanes

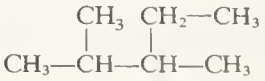
Constitution	*Substitutient name*	*Common name of alkane*
$-CH_3$	methyl[a]	methane[a]
$-CH_2CH_3$	ethyl[a]	ethane[a]
$-CH_2CH_2CH_3$	n-propyl[b]	propane[a]
$-CH(CH_3)_2$	isopropyl[a]	propane[a]
$-CH_2CH_2CH_2CH_3$	n-butyl[b]	n-butane[b]
$-CH_2CH(CH_3)_2$	isobutyl[a]	isobutane[a]
$-CH(CH_3)-CH_2CH_3$	sec-butyl[a,c] (s-butyl)	n-butane[b]
$-C(CH_3)_2-CH_3$	tert-butyl[a,d] (t-butyl)	isobutane[a]
$-CH_2CH_2CH_2CH_2CH_3$	n-pentyl[b] (n-amyl)	n-pentane[b]
$-CH_2CH_2-CH(CH_3)-CH_3$	isopentyl[a] (isoamyl)	isopentane[a]
$-CH_2-C(CH_3)_2-CH_3$	neopentyl[a]	neopentane[a]
$-C(CH_3)_2-CH_2CH_3$	tert-pentyl[a,d] (tert-amyl) (t-pentyl) (t-amyl)	isopentane[a]

[a] Name accepted by IUPAC.[1] [b] Prefix n must be dropped when using this to designate a side chain in the IUPAC system. [c] sec = secondary; often abbreviated s. [d] tert = tertiary; often abbreviated t.

2.1.2.1 IUPAC nomenclature[1]

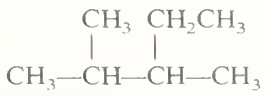
The current rules for naming alkanes are:

1. The names of the unbranched acyclic alkanes are those in Table 1.
2. The longest continuous chain of carbon atoms is taken as the backbone on which the various substituents are considered to be attached. The name of this continuous chain forms the root of the IUPAC name of the molecule. Thus, the molecule below is a



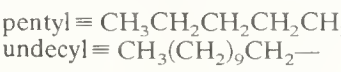
pentane rather than a butane derivative since the longest continuous chain contains five carbon atoms. If a molecule contains two or more continuous chains of equal length, the more highly substituted one is taken as the backbone.

3. The backbone carbon atoms are then numbered sequentially starting from the end of the chain and the substituent groups are assigned numbers corresponding to their positions on the backbone. The direction of numbering is chosen so as to give the lowest sum for the numbers of the side-chain substituents. Thus:

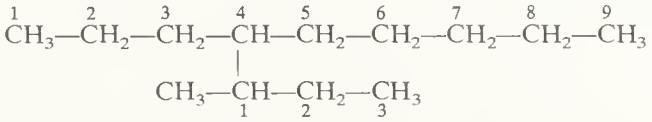


is 2,3-dimethylpentane (not 3,4-dimethylpentane).

4. Substituent groups derived from the unbranched acyclic alkanes by removal of a hydrogen atom from a terminal carbon atom are named by replacing the ending '-ane' of the name by '-yl'. The carbon atom with the free valence is numbered as 1. These substituents are called normal, or straight-chain, alkyls. For example:



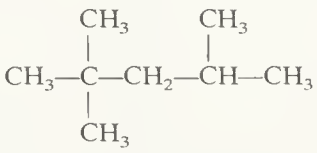
Branched-chain substituent groups are given names by a simple extension of this system. The longest chain of the substituent is numbered starting with the carbon atom attached directly to the parent continuous chain. Parentheses are then used to separate the numbering of the substituent and that of the main continuous chain:



4-(1-methylpropyl)nonane

The IUPAC rules also permit the use of some non-systematic substituent group names. These are summarized in Table 3.

5. When there are two identical substituents at the same position, numbers are supplied for each:



2,2,4-trimethylpentane

6. When there are two or more different substituents present, the problem arises as to what preference they should be given in the systematic name. Two systems are acceptable which cite the substituents (i) in order of increasing complexity or (ii) in alphabetical order. The latter system is used in *Chemical Abstracts*. Substituents are not listed numerically unless this happens to conform to (i) or (ii).

2.1.2.2 Alicyclic alkanes

The group alicyclic alkanes comprises those substances containing one or more closed rings of carbon atoms (carbocyclic rings). As with acyclic alkanes, alicyclic structures can be constructed in a seemingly infinite variety of patterns and shapes. There are too many types of alicyclic alkanes known to discuss them all individually, so we shall concentrate on the constitution and nomenclature of representative types of the more important monocyclic, bicyclic, and polycyclic systems.

The names of the monocyclic alkanes (carbocyclic rings with no side chains) are obtained by attaching the prefix 'cyclo' to the name of the acyclic unbranched alkane with

the same number of carbon atoms. The generic name of monocyclic alkanes (with or without side chains) is 'cycloalkane', *e.g.* cyclopropane, cyclobutane. The monocycloalkanes fall conveniently into groups with well-recognized structural and chemical characteristics, and are frequently classified in the following way:

3- and 4-membered: small rings
5-, 6-, and 7-membered: common rings
8- to 11-membered: medium rings
12-membered and larger: large rings.

Substituent groups derived from cycloalkanes (with no side chains) are named by replacing the ending '-ane' of the hydrocarbon name by '-yl', the carbon atom with the free valence being numbered as 1. The generic name of these substituents is 'cycloalkyl'. Substituents on cycloalkanes are assigned numbers consistent with their positions in such a way as to keep the sum of the numbers to a minimum. Thus, 1,4-dimethylcyclohexane is preferred to either 2,5- or 3,6-dimethylcyclohexane. The use of the non-systematic substituent group names listed in Table 3 is permitted, *e.g.* t-butylcyclohexane.

2.1.2.3 Polycycloalkanes

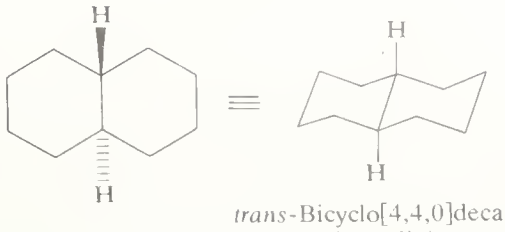
The use of non-systematic or trivial names for polycycloalkanes is widespread. This is simply a matter of convenience; systematic names for compounds containing several rings can be cumbersome and lengthy. It is, for example, easier to cope with a name like triamantane than with its systematic counterpart, heptacyclo[7,7,1,$1^{3,15}$,$0^{1,12}$,$0^{2,7}$,$0^{4,13}$,$0^{6,11}$]-octadecane! Trivial names are usually chosen so as to convey a prominent feature of the structure in question, *e.g.* cubane, propellane, peristylane, dodecahedrane, tetrahedrane.

Systematically, saturated alicyclic systems containing more than one ring are named on the basis of the total number of carbon atoms present and the manner in which the rings are joined together. A system containing two rings only having two or more atoms in common takes the name of the acyclic hydrocarbon containing the same number of carbon atoms, preceded by the prefix 'bicyclo-'. The two rings are joined by a 'bridge' which is defined as a bond or an atom or an unbranched chain of atoms connecting two different parts of the molecule. When the bridge consists of a bond only, the system is often referred to as a 'fused-ring' system; when the bridge consists of one or more atoms, it is said to be a 'bridged-ring' system. The two tertiary carbon atoms connected through the bridge are termed 'bridgeheads'. The number of carbon atoms in each of the three bridges connecting the two tertiary carbon atoms is indicated in brackets in descending order. The numbering commences with one of the bridgeheads, proceeds by the longest path to the second bridgehead, continues from the latter atom by the longest unnumbered path back to the first bridgehead, and is completed by the shortest path. Applications of this system to some simple bicycloalkanes are shown in Figure 1; where trivial names are also available, these are shown in parentheses. Three-dimensional perspectives are included.

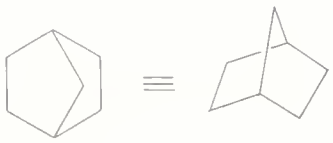
Saturated bridged ring alicyclic systems of three or more rings may be named in accordance with the principles outlined above. The appropriate prefix 'tricyclo-', 'tetracyclo-', *etc.*, is substituted for 'bicyclo-' before the name of the open-chain alkane containing the same total number of carbon atoms, the number of rings being regarded as equal to the number of scissions required to convert the polycycle into an open-chain structure. The prefix is then followed by brackets containing, in decreasing order, numbers indicating the carbon atoms in the two branches of the main ring, the main ring, and the secondary bridges. The main ring and the main bridge form a bicyclic system which is numbered accordingly. The location of the secondary bridges is indicated by superscripts after the number indicating the number of carbon atoms comprising the bridges. For the purpose of numbering, the secondary bridges are taken in decreasing order, and the numbering of any bridge follows from the part already numbered, proceeding from the highest numbered bridgehead. Examples illustrating the method are given in Figure 2.

Bicyclo[3,2,1]octane

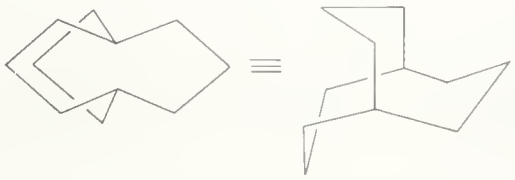
Note: longest path = 1,2,3,4,5; next longest = 5,6,7,7; shortest = 1,8,5.



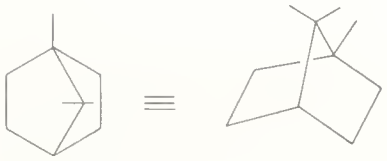
trans-Bicyclo[4,4,0]decane
(Decalin)



Bicyclo[2,2,1]heptane
(Norbornane)



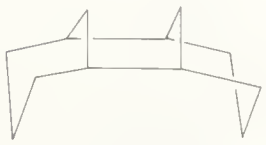
Bicyclo[3,3,3]undecane
(Manxane)



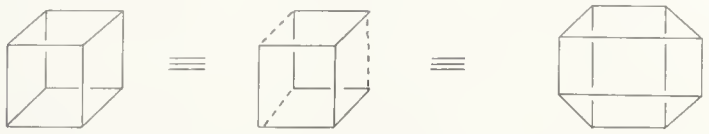
1,7,7-Trimethylbicyclo[2,2,1]heptane
(Camphane)

Figure 1 Nomenclature of some bicycloalkanes

Tricyclo[2,2,1,$0^{2,6}$]heptane

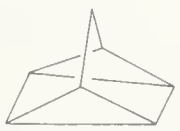


Tricyclo[5,3,1,$1^{1,6}$]dodecane

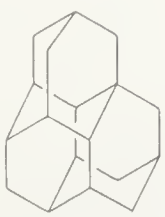


Pentacyclo[4,2,0,$0^{2,5}$,$0^{3,8}$,$0^{4,7}$]octane (Cubane)

Tricyclo[3,3,1,$1^{3,7}$]decane
(Adamantane)



Tetracyclo[3,2,0,$0^{2,7}$,$0^{4,6}$]heptane
(Quadricyclane)



Heptacyclo[7,7,1,$1^{3,15}$,$0^{1,12}$,$0^{2,7}$,$0^{4,13}$,$0^{6,11}$]octadecane
(Triamantane)

Figure 2 Nomenclature of some polycycloalkanes

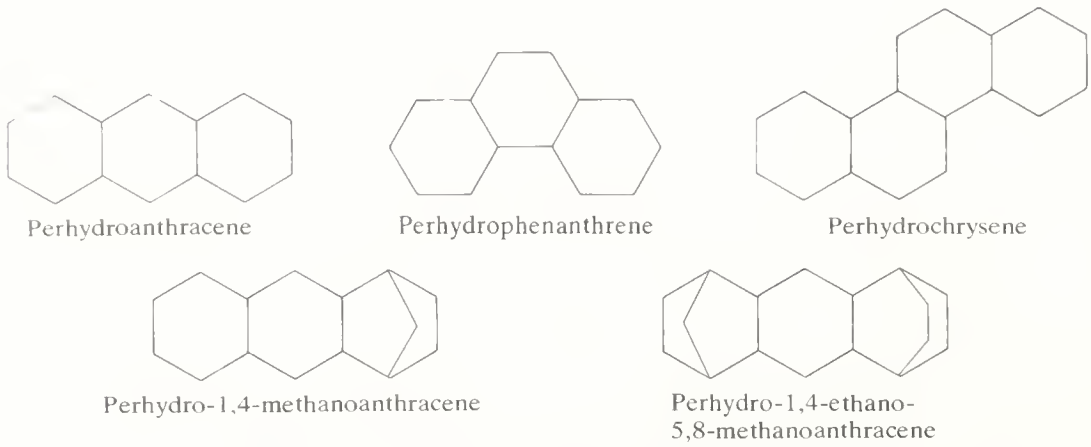


Figure 3 Nomenclature of perhydroaromatic systems

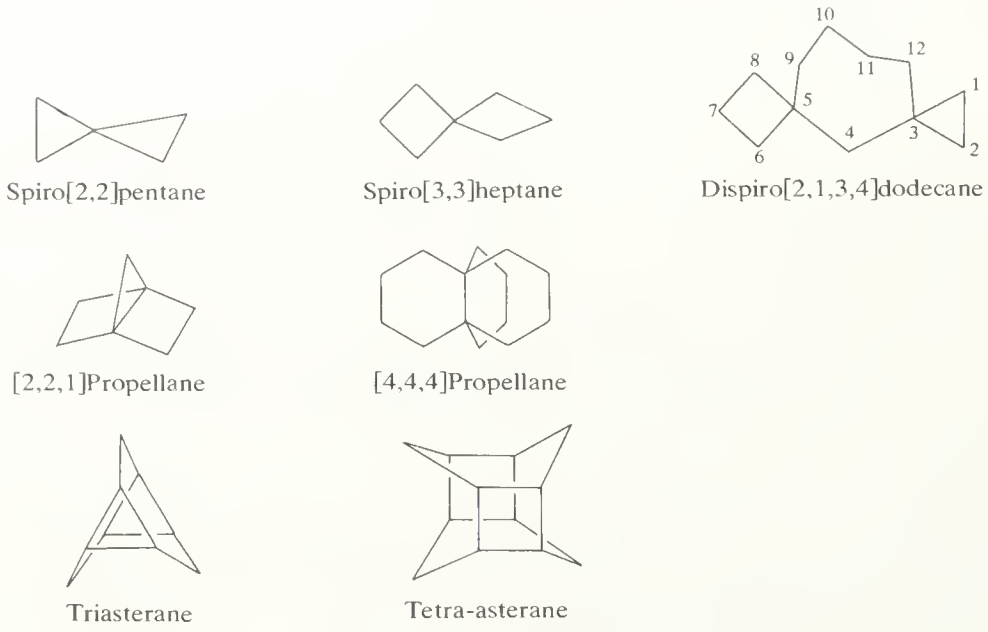


Figure 4 Nomenclature of some spiranes, propellanes, and asteranes

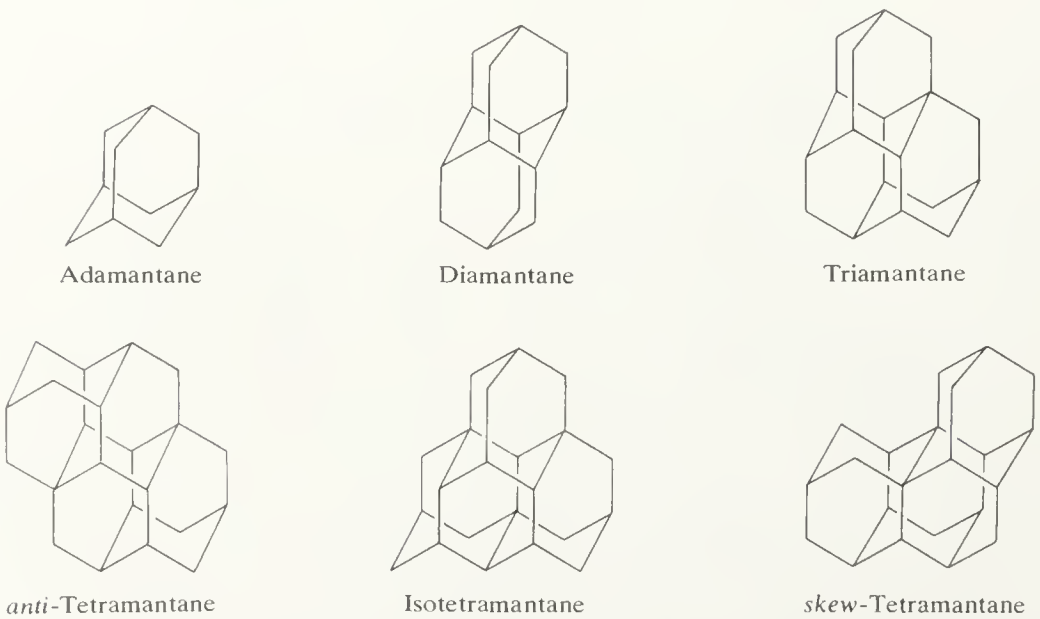


Figure 5 The adamantanes

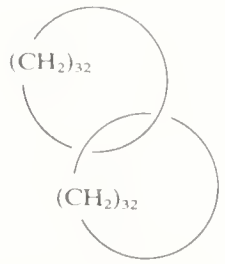


Figure 6 A catenane

The above rules do not apply to all classes of polycyclic alkanes. Saturated cyclic systems having the same carbon skeleton as aromatic hydrocarbons are termed '*ortho*-fused' or '*ortho*- and *peri*-fused'. The prefix 'perhydro' is added to indicate full hydrogenation. Thus, the full hydrogenation product of anthracene is perhydroanthracene and that of phenanthrene, perhydrophenanthrene. This rule does not apply to mono- and bi-cyclic systems (the names perhydrobenzene and perhydronaphthalene are not used, cyclohexane and bicyclo[4,4,0]decane being preferred). Perhydro systems containing other bridges are named by adding a prefix derived from the hydrocarbon having the same number of carbon atoms as the bridge, followed by numbers indicating the points of attachment to the perhydro system. Some examples of these systems are shown in Figure 3. Stereochemical aspects of these systems are discussed in Section 2.1.5.

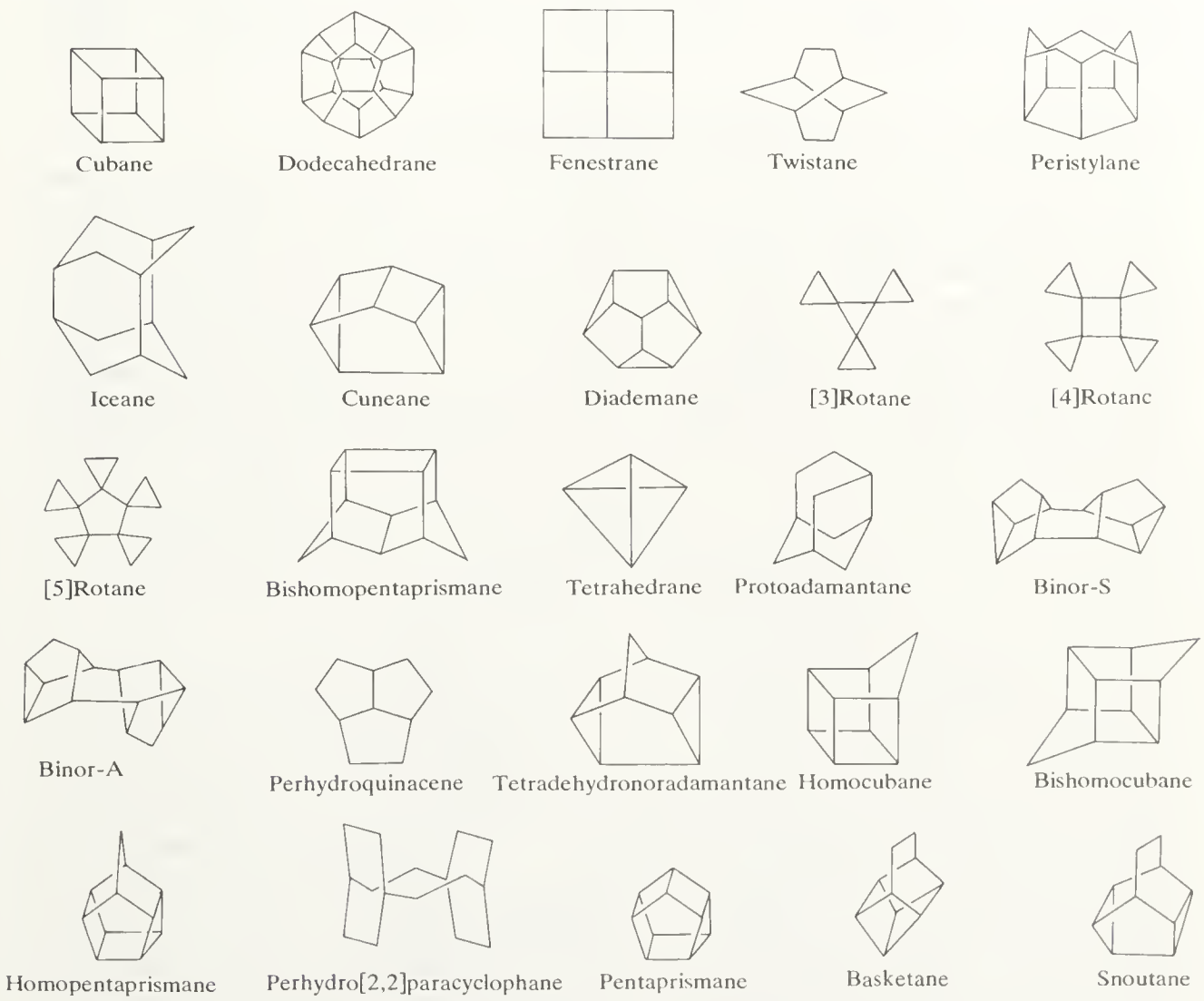


Figure 7 Some polycyclic alkanes, known and unknown

Another class of compound whose names differ from those derived above are the so-called 'spiro' alkanes. A spiro compound is one in which a single atom is the only common member of two rings. Monospiro compounds having just two carbocyclic rings are named by placing the prefix 'spiro' before the name of the normal acyclic alkane containing the same total number of carbon atoms. The number of carbon atoms linked through the spiro atom in each ring is then indicated in ascending order in brackets The carbon atoms are numbered consecutively starting with a ring atom next to the spiro atom, first through the smaller ring (if the rings are of unequal size), then through the spiro atom around the second ring. Polyspiro compounds containing three or more rings are accommodated by placing 'dispiro-', 'trispiro-', *etc.* before the alkane name. Some examples are given in Figure 4. Several other groups of polycyclic alkanes have acquired characteristic names which, though not systematic, facilitate chemical communication. Ginsburg has urged that tricyclic compounds with the general shape of a propeller be called propellanes.[2] Another group with a star-like appearance are called asteranes.[3] Some members of both these groups are included in Figure 4. The diamondoid series of polycyclic hydrocarbons represents another group whose structure is based on the regular, repititious array of carbon atoms found in diamond. This series, of which the first members are known, are universally known by the trivial name adamantanes (Figure 5).

A particularly interesting series of bicyclic alkanes is found in the catenanes.[4] Catenanes differ from other bicyclic alkanes in one important respect: the rings are not held together by any valence forces but are loosely associated as in the links of a chain (Figure 6). Numerous other polycyclic alkanes are known or have been dreamt of. A random selection is given in Figure 7. Perhaps they reflect the exuberance of organic chemists.

2.1.3 SOURCES OF SATURATED HYDROCARBONS

The principal source of saturated hydrocarbons is petroleum [L. *petra*, a rock, and *oleum*, oil] which includes natural gas and oil. Biological processes lasting millions of years transform animal and plant materials into complex mixtures of hydrocarbons ranging in size from methane to about $C_{70}H_{142}$. It is impossible to say when petroleum was first discovered. In some form it seems to have been applied to the uses of man in the earliest periods recorded in history. The ruins of Nineveh and Babylon suggest that the asphalt mortar used in walls and buildings was obtained from evaporated petroleum probably from the springs of Is on the Euphrates. Herodotus refers to pitch drawn from the springs on the island of Zante; Pliny, Plutarch, Aristotle, and Josephus mention deposits in Albania and on the Caspian Sea. The first commercial well was drilled in Titusville, Pennsylvania, in 1859. This well, 23 m deep, produced 25 barrels a day of a dark, viscous liquid that brought to an end the era of candles and whale-oil lamps.[5] Large reservoirs of petroleum have been since discovered in North and South America, in the coastal waters of Western Europe, in Eastern Europe, in the Sahara Desert, in and around the Persian Gulf, and in the Pacific Ocean.

Natural gas and oil occur together, the former consisting of the more volatile, low molecular weight alkanes, mostly methane with progressively smaller amounts of ethane, propane, and butane. North Sea gas, for instance, contains about 94% methane. The composition of crude oil varies from source to source; generally, however, the chief constituents are the higher straight-chain and branched-chain alkanes. Cycloalkanes, especially the methyl and ethyl derivatives of cyclopentane and cyclohexane, are often present, and some wells produce substantial amounts of aromatic hydrocarbons, *e.g.* toluene. The crude oil of Hodonin in Czechoslovakia is unusual in that it contains the novel caged hydrocarbons adamantane and diamantane (Figure 5). Petroleum refining[6,7] refers to the combination of physical and chemical processes whereby crude oil is converted into various grades of fuels, the first operation being fractional distillation. Because of the approximate relationship between boiling point and molecular weight (see Table 6), fractional distillation amounts to a rough separation according to carbon number

TABLE 4

Petroleum Constituents

Fraction	*Distillation range* (°C)	*Carbon number*
Gas	below 20	C_1,C_2,C_3,C_4
Light petroleum	20–90	C_5,C_6
Ligroin (light naphtha)	90–120	C_6,C_7
Petrol (gasoline)	100–200	C_7–C_{10} and cycloalkanes
Paraffin (kerosene)	200–300	C_{12}–C_{18} and aromatics
Gas oil	above 300	higher alkanes
Lubricating oil	above 300	higher alkanes
Residue (asphalt and bitumen)	non-volatile	polycyclic structures

(Table 4).[8] Each fraction may still be a very complicated mixture, however, since it may contain alkanes of a range of carbon numbers, each of which may be represented by numerous isomers. Further stages in refining depend on the chemical composition and volatility of the various fractions, and on their ultimate uses. For some uses it matters little that the fractions are complex mixtures. However, for petrol (gasoline), the structures of the components and their ratio are important. The chief uses are as fuels and as raw materials for the manufacture of organic chemicals. Vast quantities of petroleum are used daily for the production of heat and power by combustion (oxidation) and fluctuations in supplies are a major source of economic and political instability. The propane–butane fractions are frequently separated from the more volatile components by liquefaction, compressed into cylinders, and sold as bottled gas. The petrol fractions obtained directly by distillation often contain a large proportion of straight-chain alkanes which are not suitable as fuels in modern high-compression motor engines. It is important that petrol should burn smoothly in the engine and should not detonate or 'knock', since knocking reduces engine power. The tendency of a fuel to cause knocking is expressed as the 'octane number' which is thus a measure of the performance of the fuel. Most modern car engines require a fuel with an octane number between 90 and 100. The octane numbers of some individual members of the petrol fractions are given in Table 5.[9] The data show that straight-chain alkanes have the lowest performance as fuels and that branched-chain alkanes and aromatics have high octane number ratings. Thus, the major chemical processes carried out in modern refineries are designed to convert the naturally occurring straight-chain or low-performance fuels into branched-chain and aromatic structures.[6,7]. These processes are: (i) Catalytic alkylation, which produces high-octane fuels from the

TABLE 5

Octane Numbers of Some Hydrocarbons

Hydrocarbon	*Octane number*
n-Pentane	62
2-Methylbutane	90
Cyclopentane	85
n-Hexane	26
2-Methylpentane	73
2,2-Dimethylbutane	93
Benzene	>100
Cyclohexane	77
n-Heptane	0
n-Octane	0
2,2,4-Trimethylpentane	100
1,2-Dimethylcyclohexane	79
Ethylbenzene	98
Xylenes	>100

low-molecular weight gaseous products of the refining operation; it involves the acid-catalyzed addition of alkenes such as propene or butene to isobutane. (ii) Catalytic isomerization in which n-alkanes undergo thermodynamically controlled skeletal change into branched-chain isomers. The main use is the conversion of n-butane into isobutane which is then used in process (i). (iii) Catalytic reforming, which includes dehydrogenation of cyclohexanes to aromatics, dehydroisomerization of alkylcyclopentanes to aromatics, isomerizations of type (ii), and dehydrocyclization of n-alkanes to aromatics. (iv) Catalytic cracking in which the high-boiling gas oil fractions are broken down to smaller alkanes with high octane numbers. The chemical basis of these processes is discussed in more detail in Section 2.1.9 on reactions of alkanes.

In addition to its use as fuels, petroleum is the chief raw material in the petrochemical industry.[7] The flow chart in Figure 8 gives a brief summary of some of the numerous products obtained in this way. Although the chemistry involved in some of these routes is discussed (see Section 2.1.9) under reactions of alkanes, they are summarized here to provide a coherent overall picture. It should be noted that the needs of the petrochemical and refining industries often coincide in as much as many of the products required in refining to upgrade octane ratings are also important raw materials in organic chemical manufacture. In general, the most important processes in petrochemical production are: (i) Cracking for alkenes. In this process, low-boiling petroleum fractions are taken to high temperatures in steam, and ethylene, propene, butenes, and butadiene are the chief products. A wide range of substances, including polymers, are obtained from these alkenes. (ii) Cracking for acetylene. The preparation of acetylene from the lower alkanes is thermodynamically feasible at temperatures above about 900 °C. (iii) Catalytic reforming. This process provides the major source of benzene, toluene, and the xylenes (see process (ii) under refining above). (iv) Direct oxidation. Low-boiling petroleum fractions can be oxidized directly to acetic acid. A further oxidative conversion of n-alkanes, now in commercial application, is microbiological oxidation to protein-containing materials.

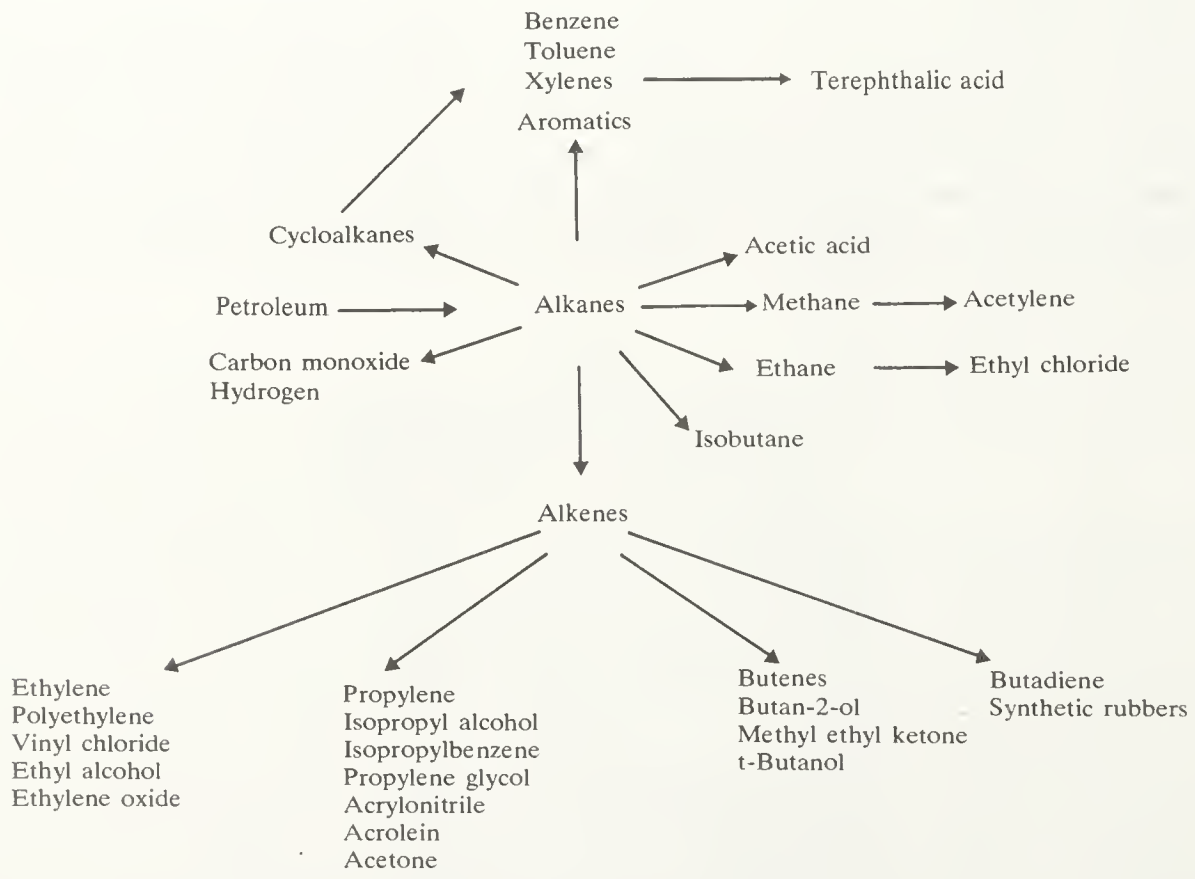


Figure 8 Some petroleum products

(v) Steam reforming. In this process, low-boiling alkane fractions react with steam at about 800 °C over a nickel catalyst, giving a mixture of carbon monoxide and hydrogen, known as 'synthesis gas'. This mixture is used in the manufacture of ammonia and methanol. (vi) Chlorination. The chlorination of methane is discussed in Section 2.1.9.

Other natural sources of saturated hydrocarbons exist, although none compares in importance with petroleum. Coal provides some alkanes *via* the Fischer–Tropsch process.[7] In this process a mixture of carbon monoxide and hydrogen, obtained from hot coke and steam, is passed over an iron or cobalt catalyst at high temperatures to give a mixture of alkanes and alkenes with a range of molecular weights. At the present time, the Fischer–Tropsch process is not economically viable in most countries. Plants are a source of both acyclic and cyclic hydrocarbons, and many polycyclic structures are found among the terpenes. The essential oils of *Cannabis sativa* contain n-alkanes from C_9 to C_{39} together with their 2-methyl, 3-methyl and 2,2-dimethyl derivatives, as do the leaves of some citrus trees.[10] The chief alkanes in the latter are C_{27}, C_{31}, and C_{33}. The alkanes vary in size with the age of the fruit. Mature fruit contains largely C_{27}–C_{33} alkanes whereas immature fruit contains mostly C_{20}–C_{25} alkanes.[11]

2.1.4 PHYSICAL PROPERTIES

2.1.4.1 Acyclic alkanes

The homologous series of straight-chain alkanes shows a smooth gradation in physical properties (see Table 6 and Figure 9).[12] Methane, ethane, propane, and butane are gases in their standard states; the C_5 to C_{17} members are liquids; and the higher members are solids. All members are insoluble in, and lighter than, water. The density of liquid methane is less than half that of water. With succeeding members the density increases rapidly for a time and then levels off at about 0.77 g cm^{-3}. Boiling points increase with molecular weight, the increase for every additional CH_2 group decreasing progressively. Methane and ethane differ in boiling point by 73 °C, but the C_9 and C_{10} members differ by only 24 °C. For the series butane to dodecane, the average increase is about 30 °C; from tridecane to eicosane the average increase for each CH_2 group is near to 16 °C. This trend means that lower alkanes are more easily separable by fractional distillation than are higher members. After an initial slight irregularity (propane is lower melting than methane) the melting points of the straight-chain alkanes increase with molecular weight. From C_9 to C_{25} the increments in the melting points from one homologue to the next are alternately higher and lower than a mean extrapolated value, and a similar alternation in transition temperatures between two crystalline forms is observed with homologues containing more than 20 carbon atoms.

Branched-chain alkanes do not reveal the same smooth gradation in physical properties as do the straight-chain homologues; possibly, there is too great a variation in molecular shape and volume for regularities to be apparent. Generally, however, branching lowers the melting point (eicosane and its isomer, 5-(1-butyl)hexadecane, melt at 36.4 and −11.6 °C, respectively). Volatility increases with increasing branching, as the following data show:

Isomer	*M.p.* (°C)	*B.p.* (°C)
Hexane	−94	68.7
3-Methylpentane	−118	63.3
2-Methylpentane	−154	60.3
2,3-Dimethylpentane	−129	58.0
2,2-Dimethylbutane	−98	49.7

TABLE 6

Physical Constants of Normal Paraffins

Name	*Formula*	*M.p.* (°C)	*B.p.*(°C/760 mmHg)	d_4^{20} (g cm $^{-3}$)	n_D^{20}
Methane	CH_4	−182.6	−161.6	0.4240 (at b.p.)	—
Ethane	C_2H_6	−183.3	−88.5	0.5462 (at b.p.)	—
Propane	C_3H_8	−187.1	−42.2	0.5824 (at b.p.)	1.3397 (at b.p.)
Butane	C_4H_{10}	−138.4	−0.50	0.6011 (at 0 °C)	1.3562 (at −15 °C)
Pentane	C_5H_{12}	−129.7	36.1	0.6263	1.3577
Hexane	C_6H_{14}	−94.0	68.7	0.6594	1.3749
Heptane	C_7H_{16}	−90.5	98.4	0.6838	1.3876
Octane	C_8H_{18}	−56.8	125.7	0.7026	1.3974
Nonane	C_9H_{20}	−53.7	150.8	0.7177	1.4054
Decane	$C_{10}H_{22}$	−29.7	174.1	0.7301	1.4119
Undecane	$C_{11}H_{24}$	−25.6	195.9	0.7402	1.4172
Dodecane	$C_{12}H_{26}$	−9.7	216.3	0.7487	1.4216
Tridecane	$C_{13}H_{28}$	−6.0	235.5	0.7563	1.4256
Tetradecane	$C_{14}H_{30}$	5.5	253.6	0.7627	1.4290
Pentadecane	$C_{15}H_{32}$	10.0	270.7	0.7684	1.4319
Hexadecane	$C_{16}H_{34}$	18.1	287.1	0.7733	1.4345
Heptadecane	$C_{17}H_{36}$	22.0	302.6	0.7767 (at m.p.)	1.4360 (at 25 °C)
Octadecane	$C_{18}H_{38}$	28.0	317.4	0.7767	1.4367 (at 28 °C)
Nonadecane	$C_{19}H_{40}$	32.0	331.6	0.7776	1.4335 (at 38 °C)
Eicosane	$C_{20}H_{42}$	36.4	345.1 (at 15 mm Hg)	0.7777	1.4346 (at 40 °C)
Heneicosane	$C_{21}H_{44}$	40.4	215	0.7782	1.4240 (at 70 °C)
Docosane	$C_{22}H_{46}$	44.4	224–225	0.7782	1.4358 (at 45 °C)
Tricosane	$C_{23}H_{48}$	47.4	234	0.7797	1.4270 (at 70 °C)
Tetracosane	$C_{24}H_{50}$	51.1	243	0.7786	1.4283 (at 70 °C)
Pentacosane	$C_{25}H_{52}$	53.3	259	0.7785	1.4380 (at 60 °C)
Hexacosane	$C_{26}H_{54}$	57.0	262	0.7587 (at 90 °C)	—
Heptacosane	$C_{27}H_{56}$	60.0	270	0.7788 (at 60 °C)	—
Octacosane	$C_{28}H_{58}$	61.6	279–281	0.7792	—
Nonacosane	$C_{29}H_{60}$	64.0	286	0.7797	—
Triacontane	$C_{30}H_{62}$	66.0	304	0.7795 (at 70 °C)	—
Tetracontane	$C_{40}H_{82}$	81.4	—	—	—
Pentacontane	$C_{50}H_{102}$	91.9–92.3	420–422	—	—
Hexacontane	$C_{60}H_{122}$	98.5–99.3	—	—	—
Heptacontane	$C_{70}H_{142}$	105–105.5	—	—	—
Hectane	$C_{100}H_{202}$	115.1–115.4	—	—	—

2.1.4.2 Monocyclic and polycyclic alkanes

The melting points and boiling points (Table 7) of the monocycloalkanes are somewhat higher than for their open-chain counterparts. The general floppiness of acyclic alkanes and their conformational heterogeneity render them more difficult to fit into a crystalline lattice and less likely to attract neighbouring molecules of the same type than the more rigid cyclic structures; hence they have lower melting points. The melting point curve for the homologous series of monocycloalkanes, in contrast to the acyclic series, does not show a continuous rise with increasing molecular weight. Thus, cyclododecane has a higher melting point than cyclotridecane.[13,14] Some members of the series (cyclododecane, for example) undergo phase transitions at temperatures below their melting points. Rather large positive entropy changes are associated with these transitions and the solid which exists between the transition temperature and the melting point can be looked on as a mesophase in which orientational disorder exists. These mesophases are frequently referred to as plastic crystals. For a discussion of empirical relationships between physical properties of cyclic hydrocarbons such as boiling point, density, and refractive index and molecular volume, see the article by van Bekkum *et al.*[15]

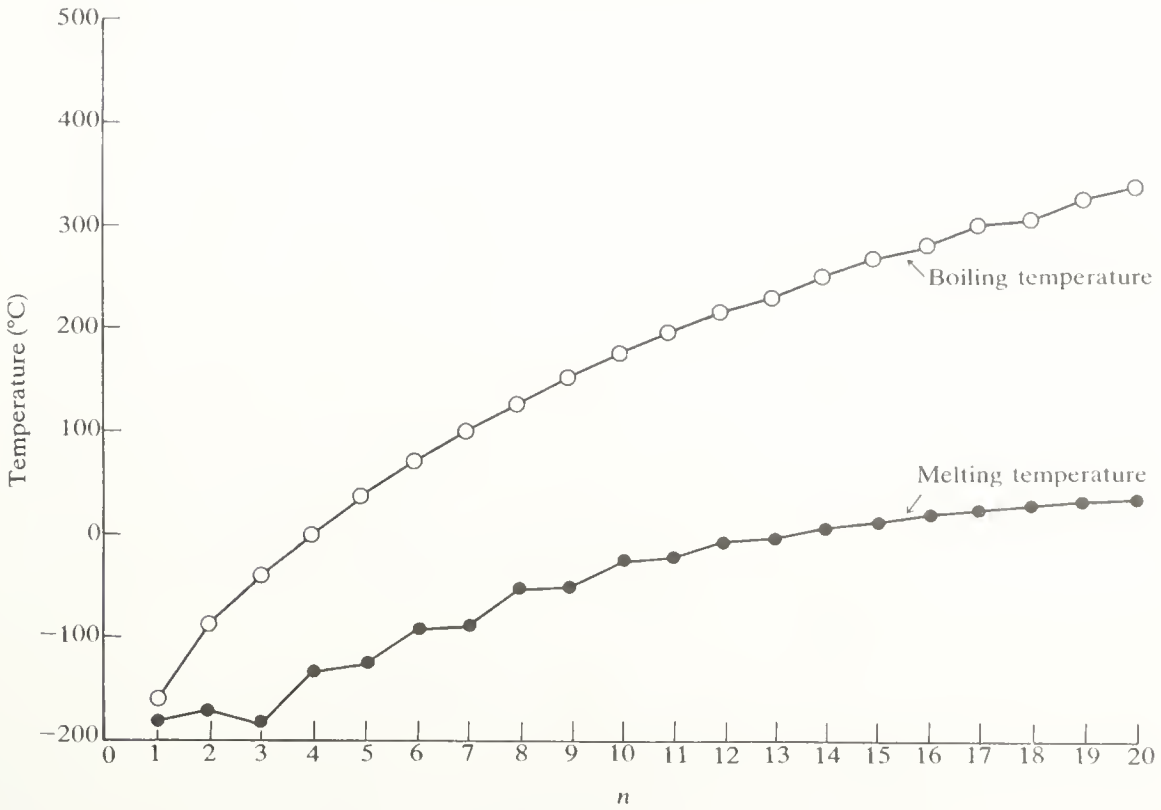


Figure 9 Melting and boiling point curves for n-alkanes

Relationships between the physical properties (excluding thermochemical) of polycyclic alkanes and molecular shape and volume are exceedingly difficult to discern.[16] With solid compounds, crystal packing factors are of obvious importance and these can vary widely from structure to structure. The diamondoid hydrocarbon series, illustrated in Figure 5, reveals a decreasing melting point pattern as the cage gets larger: *anti*-tetramantane melts at 174 °C whereas triamantane melts at 221° C; substitution of a methyl group at the

TABLE 7

Physical Constants of Cycloalkanes

Name	*M.p.* (°C)	*B.p.* (°C/mmHg)	d_4^{20} (g cm^{-3})	n_D^{20}
Cyclopropane	−127	−34.5 (760)	0.688 (−40 °C)	1.377 (−40 °C)
Cyclobutane	−90	−12.5 (760)	0.7038 (0 °C)	1.3752 (0 °C)
Cyclopentane	−93	49.5 (760)	0.7510 (15 °C)	1.4094
Cyclohexane	6.5	80 (760)	0.7753	1.4268
Cycloheptane	8	119 (760)	0.8275	1.4449
Cyclo-octane	4	148 (749)	0.8362	1.4581
Cyclononane	10	69 (14)	0.8534	1.4328
Cyclodecane	9.5	69 (12)	0.8575	1.4714
Cycloundecane	−7	91 (12)	0.8591	—
Cyclododecane	61	—	0.861	—
Cyclotridecane	23.5	128 (20)	0.861	—
Cyclotetradecane	54	131 (11)	0.863	—
Cyclopentadecane	61	147 (12)	0.860	—
Cyclohexadecane	57	170 (20)	0.854	—
Cycloheptadecane	65	—	0.853	—
Cyclo-octadecane	72	—	0.853	—
Cyclononadecane	80	—	—	—
Cycloeicosane	61	—	—	—
Cyclotriacontane	56	—	0.855	—
Cyclotetracontane	76	—	—	—

2-position of triamantane raises the melting point to 315 °C; 2-methyltriamantane may well be the alkane with the highest-known melting point.[17]

2.1.5 STEREOCHEMISTRY AND CONFORMATIONAL ANALYSIS

2.1.5.1 Bond angles and lengths

Much structural and stereochemical information on acyclic and alicyclic alkanes has been obtained by spectroscopic methods. The X-ray diffraction technique has been extended to quite small alkanes by making measurements at very low temperatures. Molecular conformations in the crystalline state are obtained by the X-ray method, but these may not necessarily be the conformations existing in solution or in the gas phase. Electron diffraction is applicable to relatively small, or highly symmetrical, alkanes in the gas phase. It has the advantage that additional information about higher-energy conformations can be obtained from variable-temperature studies. Microwave spectroscopy provides valuable information on gas-phase conformation, especially when isotopically substituted alkanes are available.

Alkane conformations are determined by bond lengths and angles and a striking feature of the former is their relative invariability. C—H bond lengths are approximately 110 pm and C—C bond lengths approximately 154 pm. The C—C bond lengths in such diverse structures as ethane and diamond vary by less than 1%. A selection of C—C bond lengths in alkanes is shown in Table 8. For acyclic structures, the C—C bond length becomes slightly longer as the carbon atoms are more highly substituted with alkyl groups, but the effect is not large except with highly crowded structures such as tri-t-butylmethane. The short C—C bond length in cyclopropane is a consequence of bond 'bending' in which some of the electron density is situated outside the C—C axis, effectively decreasing the covalent radius of the carbon atoms. The C—C bond lengths in cyclobutane, cyclopentane, and cyclohexane are much closer to the acyclic value. For polycycloalkanes not possessing unusual features, the C—C bond lengths are generally close to those found in the monocycloalkanes, those in adamantane, for example (Table 9, f) being comparable with that in cyclohexane.[18] Only when small rings are fused into rigid systems do large deviations occur. Thus, the C—C bond lengths in bicyclo[1,1,0]butane (Table 9, a)[19] are

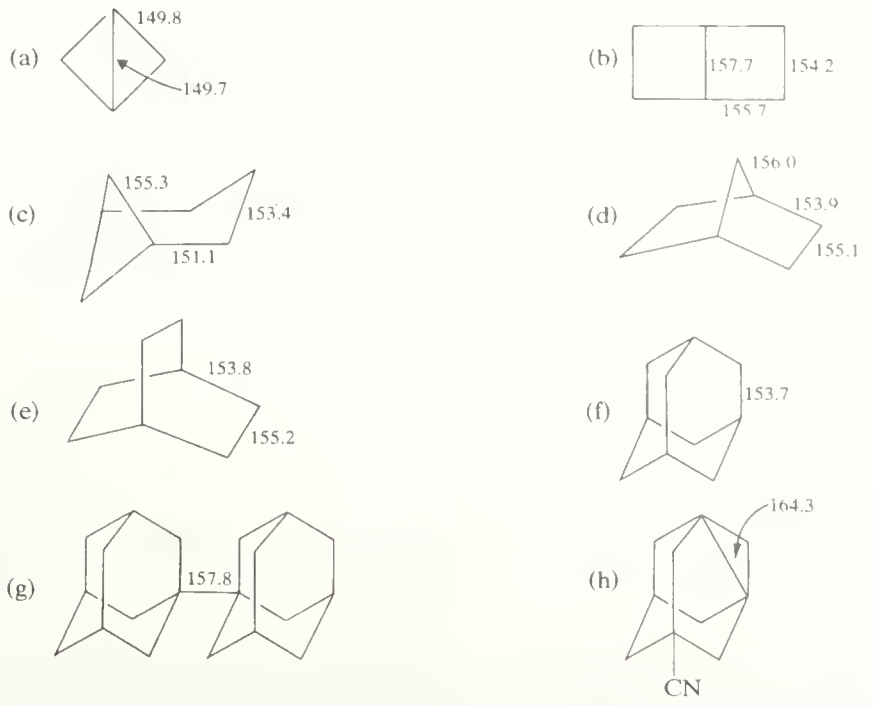
TABLE 8
C—C Bond Lengths in Some Saturated Hydrocarbons (pm)

Diamond	154.4
Ethane	153.4[a]
Propane	153.2[b]
2-Methylpropane	153.5[c]
2,2-Dimethylpropane	154.1[d]
Tri-t-butylmethane	161.1[e] (C_t—C_q)
	154.8 (C_q—C_p)
Cyclopropane	151.0[f]
Cyclobutane	154.8[g]
Cyclopentane	153.9[g]
Cyclohexane	153.6[h]

[a] L. S. Bartell and H. K. Higginbotham, *J. Chem. Phys.*, 1965, **42,** 851. [b] T. Iijima, *Bull. Chem. Soc. Japan*, 1972, **45,** 1291. [c] R. L. Hilderbrandt and J. D. Wieser, *J. Mol. Structure*, 1973, **15,** 27. [d] B. Beagley, D. P. Brown, and J. J. Monaghan, *J. Mol. Structure*, 1969, **4**, 233. [e] L. S. Bartell and H. B. Burgi, *J. Amer. Chem. Soc.*, 1972, **94,** 5236, 5239. [f] O. Bastiansen, F. N. Fritsch, and K. Hedberg, *Acta Cryst.*, 1964, **17,** 538. [g] A. Almenningen, O. Bastiansen, and P. N. Stancke, *Acta Chem. Scand.*, 1961, **15,** 711. [h] See Ref. 31.

TABLE 9

Some C—C Bond Lengths (pm) in Polycycloalkanes



[a] Ref. 19. [b] B. Andersen and R. Srinivasan, *Acta Chem. Scand.*, 1972, **26**, 3468. [c] G. Dallinga and L. H. Toneman, *Rec. Trav. chim.*, 1969, **88**, 185. [d] A. Yokozeki and K. Kuchitsu, *Bull. Chem. Soc. Japan*, 1971, **44**, 2356. [e] A. Yokozeki, K. Kuchitsu, and Y. Morino, *Bull. Chem. Soc. Japan*, 1970, **43**, 2017. [f] Ref. 18. [g] R. A. Alden, J. Kraut, and T. G. Traylor, *J. Amer. Chem. Soc.*, 1968, **90**, 74. [h] Ref. 20.

even shorter than those in cyclopropane, and the dehydroadamantyl system (h in Table 9) has an unusually long internal C—C bond.[20] Additional C—C bond lengths are given in Table 9.

According to valence bond theory, the bond angles in alkanes should be 109.47°. In fact, this is only the case for a symmetrically substituted alkane, *e.g.* methane or neopentane. The CCC angles in n-alkanes are typically of the order of 112.5°, and for most acyclic alkanes the values lie between 111° and 113°. This opening of the CCC angles is a consequence of non-bonded repulsion of hydrogen atoms. Gross deformation of CCC angles is found in small ring cycloalkanes, giving rise to high strain and enhanced reactivity.

Molecular mechanics calculations represent, at present, the most generally applicable method for the prediction of alkane structures. Excellent agreement with experimental data is obtained for all but the most highly strained alkanes. The application of molecular mechanics calculations to structure–energy relationships is discussed later in this section. Molecular orbital methods, both semi-empirical and *ab initio*, have not yet reached the point of routine applicability to alkanes and cycloalkanes, except for the smaller members of the series.

Methane has a well-defined configuration but lacks conformational isomers. Ethane is the simplest alkane capable of conformational isomerism: the two carbon atoms are linked by a single carbon–carbon bond about which rotation can and does occur; the recognition in the 1930s that this rotation is not free and unhindered marks a highlight in the development of conformational analysis of acyclic and alicyclic molecules.[21] Rotation in ethane produces conformational change and a view along the carbon–carbon axis in the Newman projections in Figure 10 clearly reveals the different conformations.

In one symmetrical form the hydrogen atoms are eclipsed, whereas in another symmetrical form the hydrogen atoms have moved into a staggered arrangement about the central

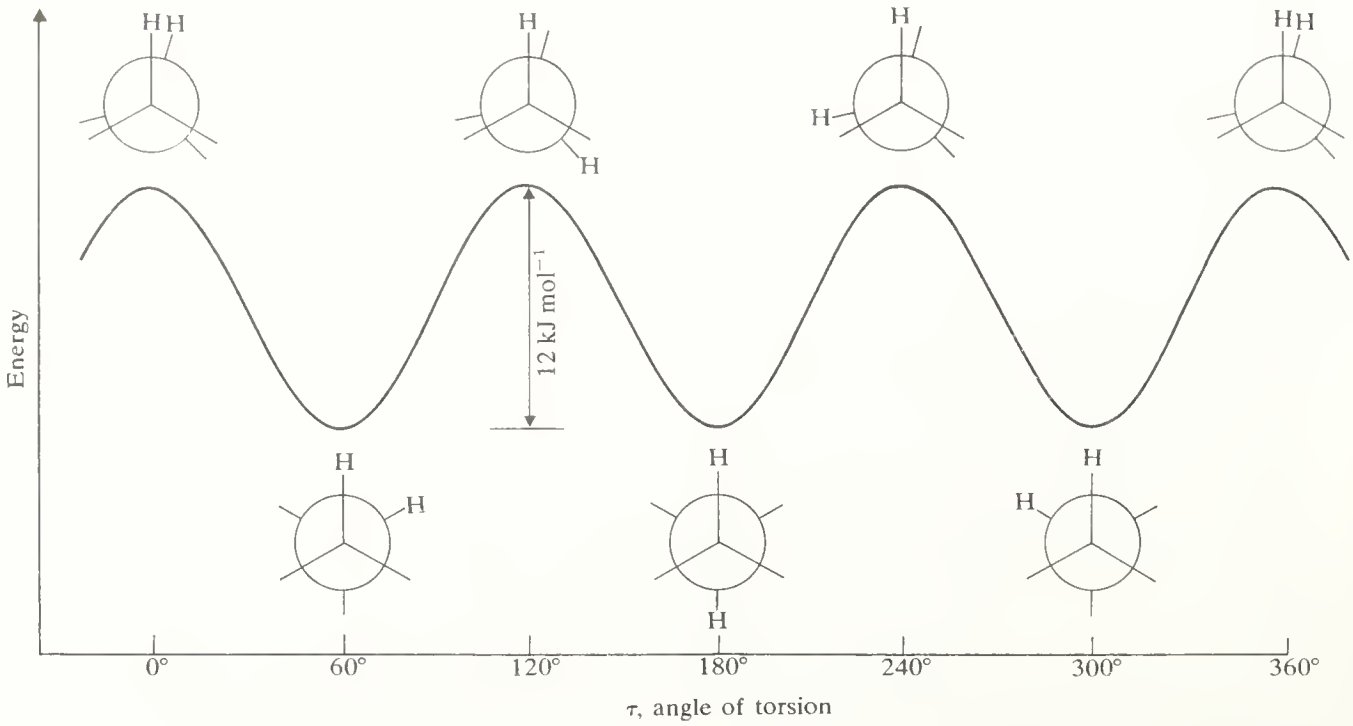


Figure 10 Energy profile for C—C bond rotation in ethane. Rotation of the back carbon is described by the changing torsional angle between the two hydrogens that are shown. The remaining hydrogens have been deleted for clarity. The upper figures are eclipsed conformations, while the lower figures are staggered conformations

bond. The rotational barrier in ethane, which is rather low (*ca.* 12 kJ mol^{-1}), can be described in terms of the change in the potential energy of the molecule as a function of the change in the torsional, or dihedral, angle.[22] Figure 10 also shows the effect that one complete rotation about the central bond has on the potential energy. The low-energy conformations, whose torsional angles are 60°, are called staggered forms. These staggered forms are separated by higher-energy forms recognizable as the eclipsed forms in which the torsional angles are 0°. Since a given hydrogen atom must pass three opposing hydrogen atoms in making a full 360° revolution, the energy barrier is said to be threefold; it follows that there are three distinct but energetically identical conformations, since any hydrogen atom can be staggered between three different pairs of opposing hydrogen atoms. While the origins of the energy barrier in ethane, which is easily surmounted at room temperature, is still a matter for discussion, it seems likely that it is not due to direct steric interference between vicinal hydrogen atoms in the eclipsed form.[23] Such steric interactions are very small because vicinal hydrogen atoms are far apart, relative to the sum of the van der Waals radii, even in the eclipsed form. The situation arising from rotation about a C—C single bond in propane is rather similar to that in ethane.

Unlike ethane and propane, not all staggered conformations of n-butane are equivalent nor are all eclipsed conformations alike. The Newman projections and torsional angle–energy profile in Figure 11 show that rotation about the central CH_2—CH_2 single bond produces different sets of conformations. Forms A, C, and E are all staggered conformations, but they are not alike. Conformation A, in which the methyl groups are 180° apart, is called the *anti* conformation, while C and E, in which the methyl groups are staggered 60° apart, are called *gauche* conformations. The eclipsed conformations are distinguished by the presence of either methyl–methyl eclipsing (D) or methyl–hydrogen eclipsing (B or F). The conformation of highest energy (D) results when the two methyl groups eclipse each other, and the most stable arrangement (A) when they are 180° apart, the energy

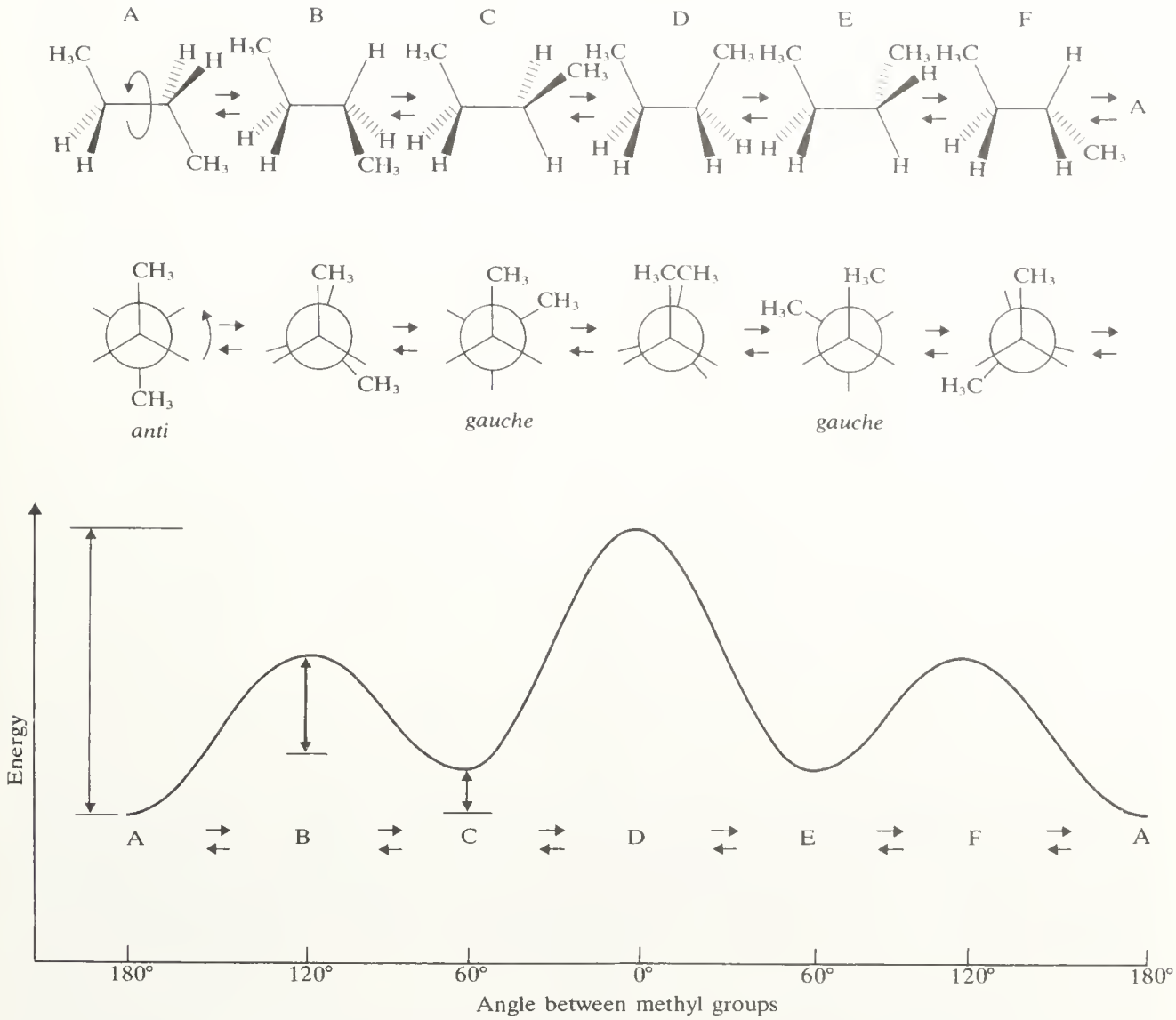


Figure 11 Conformational distribution in n-butane. Interconversion is accomplished by rotation in the direction of the curved arrow. Conformations A, C, and E are staggered conformers, while B, D, and F are eclipsed conformations

difference being about 20 kJ mol^{-1}. This difference is significantly larger than the rotational barrier in ethane, suggesting that there is some direct interaction involving the methyl groups in conformation D. When the methyl groups are staggered 60° apart, the energy minimum corresponds to the *gauche* form; the energy difference between forms A and C of about 3.5 kJ mol^{-1} is often referred to as being equivalent to the *gauche* (or *skew*) butane interaction. The barrier between *anti*- and *gauche*-butane is so small that the two forms interconvert at room temperature, producing an equilibrium mixture in which the *anti* form predominates. Simple hydrocarbons represent rather well-behaved extensions of the conformational analysis presented above for ethane and butane. The magnitudes of the barriers to rotation in many small molecules have been reviewed by Lowe.[24]

Substitution of methyl groups for hydrogen atoms on one of the carbon atoms produces a regular increase of about 2.5 kJ mol^{-1} in the height of the rotational energy barrier. The barrier in ethane is about 12 kJ mol^{-1}. In propane, the barrier is about 14 kJ mol^{-1}, corresponding to an increase of about 2 kJ mol^{-1} for methyl–hydrogen eclipsing. When two methyl–hydrogen eclipsing interactions occur, as in 2-methylpropane, the barrier

increases to 16 kJ mol^{-1}. The increase in going to 2,2-dimethylpropane, in which the barrier is 19 kJ mol^{-1}, is about 7 kJ mol^{-1} for the total of three methyl–hydrogen eclipsing interactions.

Let us now consider how these principles can be used when a carbon chain is formed into a ring, bearing in mind that many cyclic alkanes exhibit large valence angle deviations from the normal tetrahedral value. von Baeyer was the first to suggest that there should be a relationship between the strain in a cyclic hydrocarbon and the extent to which bond angles are distorted from the normal tetrahedral value.[25] According to this theory, the cyclic skeleton was assumed to have the shape of a planar polygon, and the strain was then expressed in terms of the angle of distortion of the bonds. On this basis, von Baeyer predicted that the strain in a cycloalkane should decrease from that in cyclopropane to a mimimum in cyclopentane and then increase again for cyclohexane and larger rings. The theory was incorrect in its proposal that cycloalkane rings are planar.[21] In fact, the simplest carbocycle, cyclopropane, in which three carbon atoms form the corners of an equilateral triangle, is the only planar member of the series. The angles between carbon atoms in cyclopropane are far removed from the preferred tetrahedral angle and the molecule suffers severe angle strain. The vicinal hydrogen atoms in cyclopropane are all eclipsed and, despite the strain in the system, it is so rigid that conformational isomers caused by twisting of the methylene groups cannot exist. Substituted cyclopropanes can exhibit both enantiomerism (*e.g. trans*-1,2-dimethylcyclopropane) and diastereoisomerism (*e.g. cis*- and *trans*-1,2-dimethylcyclopropanes).

The four-membered carbocycle cyclobutane has a lesser amount of 'Baeyer strain' between adjacent carbon atoms because they form 90° angles. Planar cyclobutane has all its vicinal hydrogen atoms eclipsed, but the additional strain arising from these interactions can be relieved somewhat by deformation of the ring. In fact, cyclobutane has been shown by electron diffraction to have a slightly puckered shape; in the most stable arrangement, opposite pairs of carbon atoms lie either above or below a plane containing the other pair. Between these stable extremes there is a continuum of unstable conformations. The relief of torsional strain which results from a slight amount of puckering is sufficient to allow the necessary additional bond angle distortion into the system. The experimental values for the pucker angle in cyclobutane derivatives are generally in the range 20–35°, the latter being found for the parent system. The energy difference between puckered and planar conformations in cyclobutanes appears to be small. Many substituted cyclobutanes exhibiting enantiomerism and diastereoisomerism are known. Models show that whereas planar cyclobutane has only one type of hydrogen atom, the puckered conformation has two kinds of hydrogen atom, corresponding somewhat to the axial and equatorial hydrogen atoms of cyclohexane (*vide infra*). For example, replacement of a hydrogen atom on carbons 1 and 3 by a methyl group (Figure 12) gives a *trans* isomer with an equatorial–axial type of relationship or a *cis* isomer which may be either diaxial or diequatorial. The *cis-trans* relationships of representative hydrogen atoms on cyclobutane are given in Figure 12. These relationships are independent of the shape (planar *vs.* puckered) of the ring.[21]

Unlike cyclopropane and cyclobutane, cyclopentane is nearly free of angle distortion.[21] Planar cyclopentane should have an angle of 108° at each corner, which is very close to the tetrahedral value. Thus, almost no Baeyer strain should exist in the planar form. However, planar cyclopentane would have no less than five eclipsed ethane interactions. In fact, the molecule is definitely not planar, the increase in angle strain in the non-planar form being more than compensated for by the reduction in strain associated with a smaller number of eclipsed interactions. The two most easily described conformations of cyclopentane are the envelope ($\mathbf{C}_s$ symmetry) and the half-chair ($\mathbf{C}_2$ symmetry). In the envelope conformation (Figure 13), one carbon atom is displaced from a plane containing the other four carbon atoms, whereas in the half-chair conformation, the plane containing three contiguous carbon atoms has the fourth and fifth carbon atoms displaced an equal distance above and below this plane. The energy differences between the conformations are small, and rapid conformational interconversion occurs. In effect, all the carbon atoms

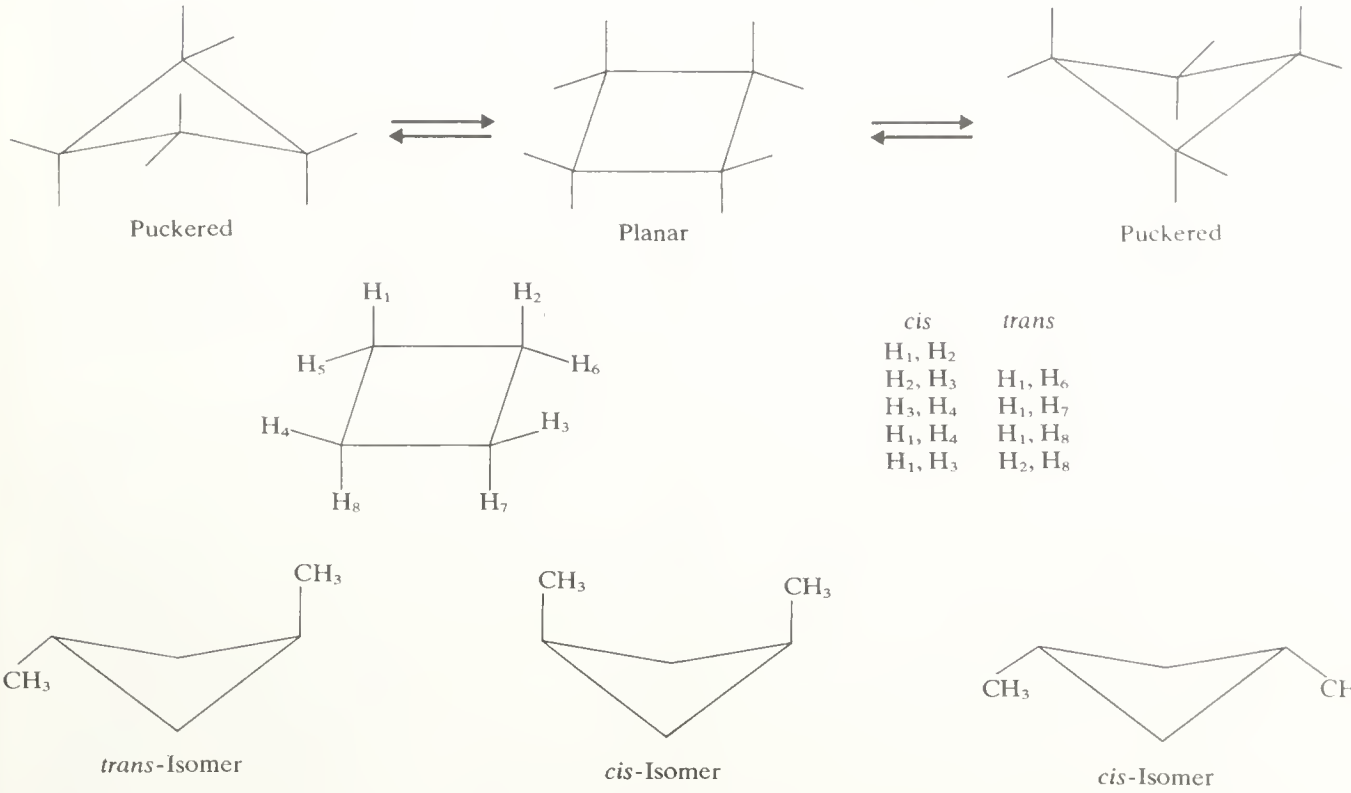
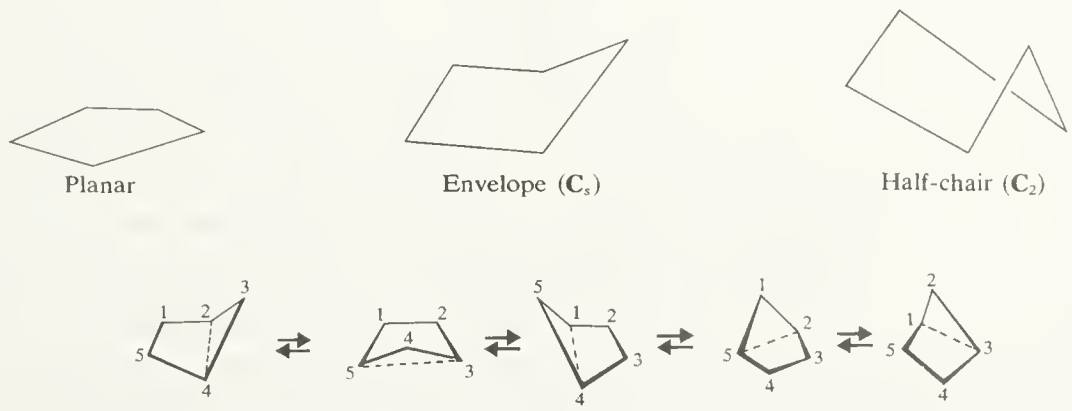


Figure 12

in cyclopentane take turns at being the out-of-plane atom in the envelope form and the two out-of-plane atoms in the half-chair form, and the low-energy motion by which the puckering travels around the ring by a series of rotations (equivalent to one atom going 'up' and an adjoining atom going 'down') is called 'pseudorotation' (Figure 13).[26]

The pseudorotation travels around the ring like a wave in the course of which the



Pseudorotation in a five-membered ring. The structure in the upper left is planar, while all others exist in the 'envelope' form. The dashed line represents a fold, *i.e.* it marks the intersection of two planes

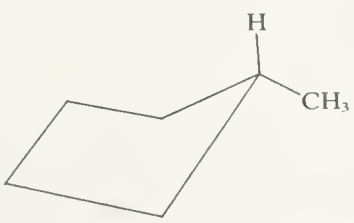


Figure 13

internal energy of the molecule varies little so that no well-defined energy minima or maxima occur. The same kind of motion interconverts the various half-chair conformations. Substituted cyclopentanes may also adopt puckered conformations, which may be either envelope or half-chair depending on the nature and degree of substitution. It appears, for example, that the most stable conformation of methylcyclopentane is one in which the ring adopts the envelope form with the methyl group in an equatorial type location at the lip of the envelope, as in Figure 13. The envelope form is also believed to be important in *cis*- and *trans*-1,3-dimethylcyclopentane, of which the former is the more thermochemically stable: the *cis* isomer can accommodate the methyl groups in equatorial-like arrangements in an envelope conformation whereas the *trans* form would resemble more closely an equatorial–axial arrangement; the stability order of *cis*- and *trans*-1,3-dimethylcyclopentane is not consistent with a planar ring.

We now turn to the important six-membered ring system, cyclohexane, and its derivatives. The conformational behaviour and stereochemistry of such compounds have been studied in great detail and many more facts are available than on any other cyclic system.[21] Apart from the importance of cyclohexyl structures in many classes of natural products, the analysis of this system has led to the development of important structure–energy relationships in organic chemistry. Cyclohexane and its derivatives are particularly well suited to detailed conformational analysis; they are usually characterized by a small number of energy minima, and the most stable conformations are separated by energy barriers that are higher, and more easily measured, than the energy barriers in other ring systems.

Shortly after von Baeyer published his strain theory, Sachse realized that the cyclohexane ring may be constructed in puckered shapes in which all the valence angles were tetrahedral[27] or nearly so. If the carbon atoms of cyclohexane were forced to lie in one plane, they would form a simple hexagon with 120° bond angles, resulting in considerable Baeyer strain. Furthermore, a planar form should also have severe eclipsing interactions between vicinal hydrogen atoms. Sachse pointed out that strainless bond angles of 109.5° would result if the carbon atoms were in alternate positions above and below the general plane of the ring. In such an arrangement the vicinal hydrogen atoms become staggered and unfavourable eclipsing interactions are thus removed. The puckered highly symmetrical form of cyclohexane, first recognized by Sachse, is now universally referred to as the chair conformation (Figure 14). Sachse also envisaged an alternative, less-rigid arrangement for non-planar cyclohexane which he called the flexible form. Although additional aspects of Sachse's analysis were later discounted by Mohr,[28] it does represent the first insight on the conformational properties of cyclic molecules. There is now much evidence in support of the view that the most stable arrangement for cyclohexane and many of its derivatives is the chair conformation shown in Figure 14; a Newman projection of the molecule is included which emphasizes the staggered nature of the hydrogen atoms around the ring. An important consequence of this conformation is the existence of two kinds of carbon–hydrogen bond. The chair conformation has a three-fold simple axis of symmetry. Six C—H bonds are approximately parallel to this axis, three pointing 'up' and three pointing 'down'. These are called 'axial' bonds. The remaining six C—H bonds are nearly perpendicular to the symmetry axis, and are called 'equatorial' bonds. Thus, a given carbon atom bears an axial hydrogen atom and an equatorial hydrogen atom. That cyclohexane possesses axial and equatorial C—H bonds was first demonstrated by Kohlrausch and his co-workers and later confirmed by Hassel and by Pitzer.[29] The real impact of this discovery on structure–reactivity relationships in organic chemistry was pointed out by Barton in a seminal paper published in 1950.[30] The cyclohexane ring does not in fact exist in a perfect chair conformation. Recent electron diffraction studies in the gas phase reveal a slight flattening of the ring compared with that expected from a molecular model with perfect tetrahedral geometry. The observed torsional angles are 55.9°, compared with 60° for a perfect chair conformation, and the axial C—H bonds are not perfectly parallel but are orientated outwards by about 7°. The C—C and C—H bond lengths are 152.8 and 111.9 pm, respectively, and the CCC angles are 111.08°.[31]

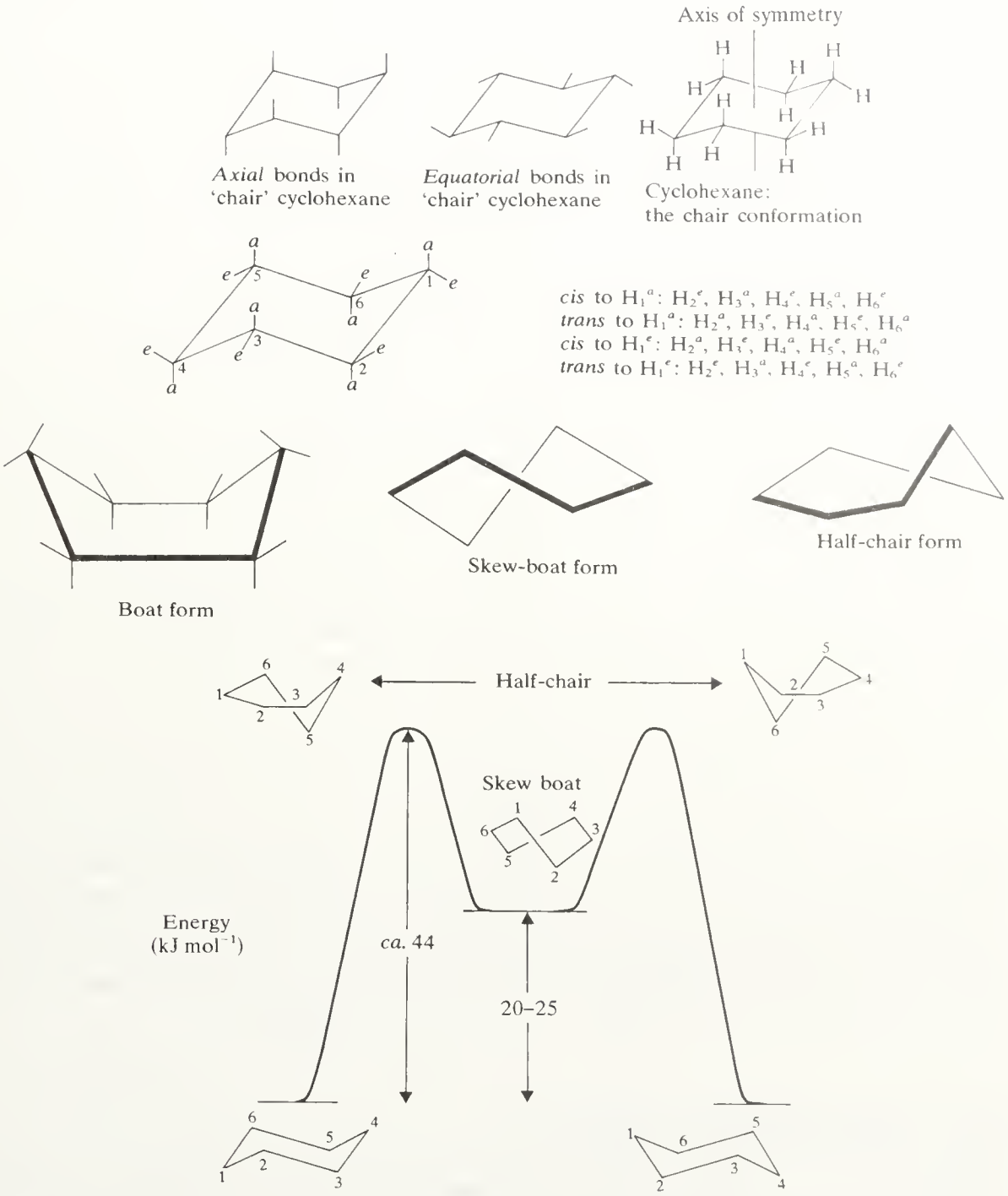


Figure 14 Conformations and conformational changes in cyclohexane

Let us now consider conformational changes in the chair form of cyclohexane, keeping bond angles and lengths close to their normal values. These changes are easily followed with the aid of a molecular model capable of C—C bond rotation and the concomitant potential energy changes are conveniently expressed in the form of a plot of energy as a function of torsional angle, in a manner similar to that shown earlier for ethane and n-butane. Figure 14 emphasizes that the chair form with no angle strain and a minimum of eclipsing strain does represent an energy minimum. A model reveals that although the chair form is quite rigid it can readily be manipulated by torsional changes into non-chair conformations which have greater flexibility. One of these is the so-called 'boat' conformation.[32] The model reveals that although angle strain is absent from the boat form, there is considerable eclipsing among the hydrogen atoms on each side of the boat. In addition,

the boat form experiences van der Waals repulsion between the 'bowsprit' hydrogen atoms located at opposite ends of the ring. These bowsprit hydrogen atoms are separated from each other by a distance of 183 pm, which is considerably less than the sum of the van der Waals radii. The sum total of these unfavourable interactions renders the boat form 24–28 kJ mol ^{1} less stable than the chair form (Figure 14). In going to the boat form, the bottom part of the chair is rotated upwards or the back part rotated downwards. Either way, bond angle distortion is required and, accordingly, the potential energy passes through a maximum value. The form corresponding to the transition state is often called the 'half-chair' (or 'half-twist') and the height of the barrier has been estimated by n.m.r. spectroscopic methods and calculation to be 40–44 kJ mol^{-1}. Further examination of the model reveals, however, that the boat form itself does not represent a conformation of minimum potential energy. In manipulating the model so as to pass from one boat form to another, a second flexible form is observed in which eclipsing of vicinal hydrogen atoms is relieved somewhat and the bowsprit interactions are less severe. This form, which represents a genuine energy minimum relative to the boat form, is called a skew-boat (or twist) form (Figure 14). Thus, the boat form represents the transition between various skew-boat forms and the half-chair form represents the transition between the chair and skew-boat forms (Figure 14). A number of attempts have been made to quantify the energy differences involved.[21] Strain energy calculations indicate that the skew-boat conformation is about 20–25 kJ mol^{-1}, and the boat conformation about 28 kJ mol^{-1}, higher in energy than the chair conformation.[33,34] A direct measurement of the chair–skew-boat energy difference has recently been made using high-vacuum deposition techniques coupled with low-temperature infrared spectroscopy.[35] For measurements of heats of combustion and equilibrium constants with systems constrained in a non-chair conformation, see Refs. 21a and 21c.

Just as ethane can exist in three degenerate staggered conformations, interconvertible by C—C bond rotation, cyclohexane can exist in two chair conformations. Interconversion of the chair forms is known as conformational inversion: in passing from one to the other, the chair is first transformed into the flexible form which, in turn, is converted into the other chair, as shown in Figure 14. Conformational inversion in cyclohexane occurs rapidly, the first-order rate constant being 10^4–10^5 s^{-1} at 300 K.[36] When cyclohexane is cooled, the rate of chair–chair interconversion is reduced and at low temperatures (< -100 °C) it is possible to identify two sets of signals in the ^{1}H n.m.r. spectrum, corresponding to the axial and equatorial hydrogen atoms. As the temperature is raised the two sets of signals merge, producing a single sharp signal at room temperature. This behaviour suggests that the two chair forms are in rapid equilibrium.

2.1.5.2 Alkyl- and polyalkyl-cyclohexanes

In the process of ring inversion in cyclohexane (Figure 15), all equatorial C—H bonds become axial and all axial C—H bonds become equatorial. In the parent system this change is degenerate, but in substituted cyclohexanes it has important conformational consequences. Substitution on a cyclohexane ring does not significantly affect the rate of conformational inversion, but it does affect the equilibrium distribution between alternative chair forms which are no longer identical. Energy differences between conformations of substituted cyclohexanes can be measured by a variety of physical methods, as can the kinetics of ring inversion.[21c] N.m.r. spectroscopy has been especially valuable in both thermodynamic and kinetic studies.[36]

Methylcyclohexane may exist either in the conformation with an equatorial substituent or in that with an axial substituent (Figure 15), the two being in rapid equilibrium with each other. The equilibrium constant corresponds to a composition of about 95% equatorial methylcyclohexane and about 5% axial methylcyclohexane; the free energy change (axial $\rightarrow$ equatorial), $\Delta G°$, is -7.5 kJ mol^{-1}. This preference of the equatorial orientation for a methyl substituent is a common phenomenon with a wide range of

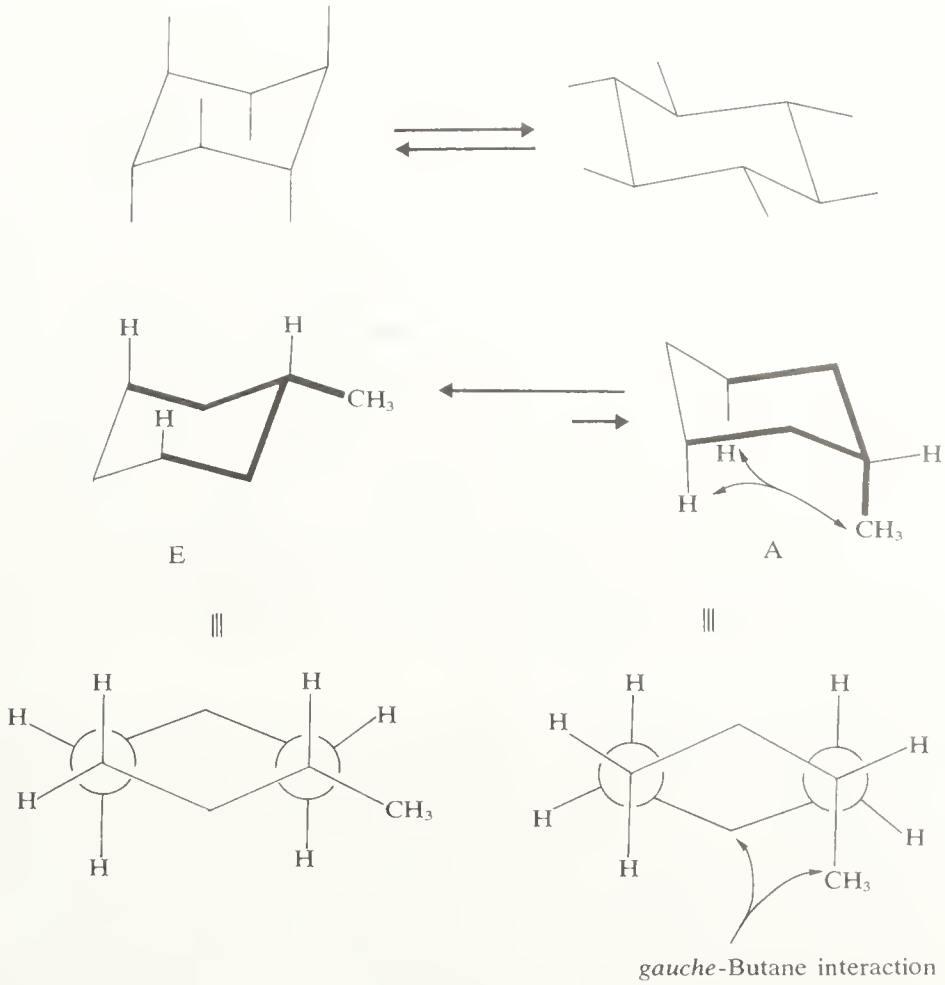


Figure 15

monosubstituted cyclohexanes and the reasons for it may be related conceptually to the greater stability of the *anti* conformation of n-butane compared with the *gauche* conformation.[21] The important conformational differences between equatorial and axial methylcyclohexane are emphasized in Figure 15. The axial isomer A has two *gauche*-butane interactions, one of which is visible in the Newman projection; both are indicated by the heavy lines in A. The equatorial isomer E, on the other hand, is conformationally similar to an *anti*-butane conformation.

The destabilizing interactions arising from the presence of *gauche* conformations in axial methylcyclohexane are often referred to as 1,3-diaxial or 'across-the-ring' interactions. These interactions are shown more clearly in Figure 16. When the hydrogen atoms of the methyl group are staggered with respect to the groups on the carbon atom to which it is attached, one of them must lie across the ring, approaching the *syn*-axial hydrogen atoms at positions 3 and 5 to within 180 pm. No such interactions occur in the equatorial isomer. Since there are two *gauche*-butane interactions in axial methylcyclohexane, the axial–equatorial energy difference should be about twice the *gauche–anti* energy difference in butane, or *ca.* 7.0 kJ mol^{-1}. This estimate is in excellent agreement with most

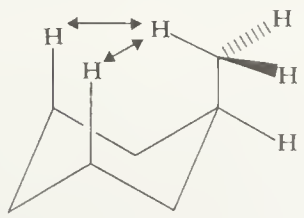


Figure 16 Across-the-ring interactions in axial methylcyclohexane

experimental determinations,[21c] the most recent of which gives a value of 7.5 kJ mol^{-1}.[37] Calculations using molecular mechanics and molecular orbital theory also give values of about this magnitude.[33,34,38]

In analysing destabilizing interactions in alkylcyclohexanes, it is usually much easier to look for 1,3-diaxial interactions than *gauche*-butane interactions; this has the additional advantage, when substituents other than methyl are being considered, of directing attention to the size of the substituent involved. The free energy differences between the axial and equatorial forms of a series of alkylcyclohexanes show that the size and nature of the group are significant: for ethylcyclohexane, the value is about the same as that for methylcyclohexane; isopropylcyclohexane has a slightly larger value (*ca.* 9 kJ mol^{-1}), and t-butylcyclohexane has a value of at least 20 kJ mol^{-1}. The similarities for the methyl, ethyl, and isopropyl groups reflect the fact that rotation about the bond between the substituent and the ring allows each to adopt a conformation that minimizes the effect of the additional methyl substituents in the ethyl and isopropyl groups.[21c] On the other hand, an axial t-butyl group experiences strong repulsive van der Waals interactions with *syn*-axial hydrogen atoms which cannot be relieved by rotation around the conjoining bond. The axial–equatorial energy difference for t-butylcyclohexane is similar to the energy difference between the chair and skew-boat conformations of cyclohexane itself and any equilibrium measurements may be complicated by the presence of non-chair conformations.[39]

That 1,3-diaxial interactions are the main cause of the relative instability of axial conformations has been questioned by Allinger,[40] who put forward an alternative interpretation which emphasizes the steric environment, not of the axial substituents, but of the equatorial hydrogen atom attached to the carbon atom bearing the substituent. In effect, the suggestion is that the instability of the axial conformation is due to steric congestion between the tertiary equatorial hydrogen atom and its nearest neighbours. Schleyer and his co-workers have reviewed this interpretation using structural data and molecular mechanics calculations and have concluded that it is incorrect.[31]

The conformational analysis of cyclohexane rings bearing two or more alkyl substituents is similar to that described above, except that configurational relationships may also have to be considered when the substituents are attached to different ring carbon atoms.[21] If two dissimilar substituents are attached to the same carbon atom, ring inversion will interchange the axial and equatorial positions and the molecule will tend to adopt the conformation in which the larger substituent occupies the equatorial position.

For systems in which the substituents are attached to different carbon atoms we can recognize a number of stereochemical relationships which we will illustrate here using the dimethylcyclohexanes in chair conformations only: 1,2-, 1,3-, and 1,4-dimethylcyclohexane may exist in *cis* and *trans* forms (*i.e.* as diastereoisomers). Each diastereoisomer can exist in two chair conformations and the relationship between the two conformations is determined by the substitution pattern. *trans*-1,2-Dimethylcyclohexane can be either diequatorial (*e*,*e*) or diaxial (*a*,*a*) (Figure 17). The *a*,*a* form has four *gauche*-butane interactions whereas the *e*,*e* form has only one *gauche*-butane interaction. Accordingly we would expect the latter to be favoured over the former at equilibrium by about 3× 3.5 kJ mol^{-1} or 10.5 kJ mol^{-1}. Both conformations of *trans*-1,2-dimethylcyclohexane are chiral and each possesses a non-superimposable mirror image. Therefore, the molecule exists as a (±)-pair, *i.e.* racemic modification. In *cis*-1,2-dimethylcyclohexane (Figure 17) the chair conformation has one axial and one equatorial substituent (*a*,*e*). Ring inversion produces an energetically equivalent conformation (*e*,*a*). The molecule does not possess an element of symmetry. Although the two chair conformations are non-superimposable mirror images, the molecule is incapable of optical activity; the potential energy barrier to chair–chair interconversion is so low that one is dealing with a rapidly inverting, non-resolvable (±)-pair. *cis*-1,2-Dimethylcyclohexane has three *gauche*-butane interactions (see Figure 17); accordingly, the energy difference between this and the *trans* isomer should be equivalent to that of two *gauche*-butane interactions in favour of the latter. The experimentally determined free energy change, *cis* → *trans*, is 7.9 kJ mol^{-1}.

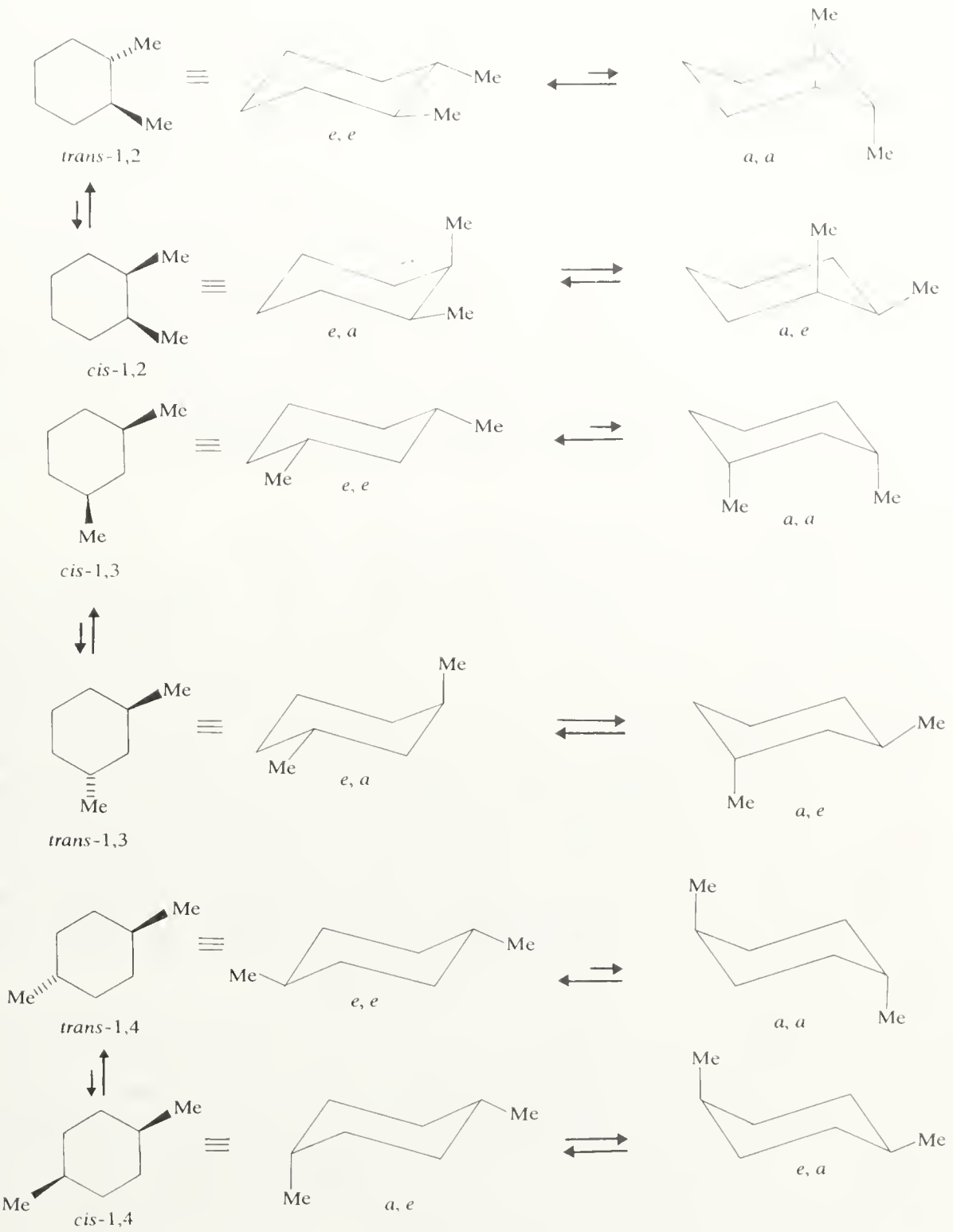


Figure 17 Configurational and conformational relationships in 1,2-, 1,3-, and 1,4-dimethylcyclohexane

In *cis*-1,3-dimethylcyclohexane the substituents can be either diequatorial (*e*,*e*) or diaxial (*a*,*a*). The *a*,*a* form should be the much less stable of the two since in this conformation there will be severe 1,3-diaxial interactions between the substituents; both forms have planes of symmetry passing through carbon atoms 2 and 5. In *trans*-1,3-dimethylcyclohexane one substituent is axial and the other equatorial (*a*,*e*). Ring inversion transforms one *a*,*e* arrangement into an energetically equivalent *e*,*a* arrangement. These

a,e and *e,a* forms are not enantiomeric; rather, they are superimposable. The molecule does not have a plane of symmetry and (+) and (−) forms are capable of existence. Since there are two *gauche*-butane interactions in *trans*-1,3-dimethylcyclohexane and none in the *cis* isomer in the *e,e* conformation, the energy difference should be 7.5 kJ mol^{-1}; the experimentally determined ΔG° value, *cis* → *trans*, is 8 kJ mol^{-1}.

A plane of symmetry exists in both *cis*- and *trans*-1,4-dimethylcyclohexane, passing through carbon atoms 1 and 4, and both are therefore incapable of exhibiting optical activity. The *trans* isomer has available to it an *e,e* and an *a,a* conformation; on the basis of *gauche*-butane interactions, the *a,a* form will contribute very little to the conformational equilibrium. The *cis* isomer has an *a,e* and an *e,a* arrangement which are superimposable. The *trans* isomer is the more stable of the two by 8 kJ mol^{-1}.

The conformational principles described above can be applied to any polyalkylcyclohexane provided one is dealing with chair conformations. In general, conformations in which there is a 1,3-diaxial interaction between substituent groups more sterically demanding than hydrogen atoms are strongly destabilized. For example, equilibration of *cis*- and *trans*-1,1,3,5-tetramethylcyclohexane[41] with a palladium catalyst gives a direct measure of the 1,3-diaxial methyl–methyl interaction, determined to be 15.5 kJ mol^{-1}.

2.1.5.3 Conformations of carbocyclic rings larger than cyclohexane

Whereas the conformational properties of carbocyclic rings from cyclobutane to cyclohexane are now quite well understood, those of rings larger than cyclohexane pose more difficult problems. This is due to the fact that, as ring size increases, there are progressively more conformations that need to be considered. In many cases the various conformations may differ by only a small amount in energy, and the equilibrium state of the molecule is represented by several interconverting discrete conformations. Thus pseudorotation of the type existing in cyclopentane is possible. Hendrickson has studied the conformations of cycloheptane using molecular mechanics calculations to probe structure (*i.e.* conformation)–energy relationships.[42] These calculations, the basis of which are discussed in the next section, suggest that there are four particularly stable cycloheptane conformations. These are the twist-chair, chair, boat, and twist-boat forms shown in Figure 18. N.m.r. spectroscopic measurements on dimethyl derivatives suggest that of the four, the twist-chair is the most stable and the boat the least stable, although the total energy spread is small (*ca.* 11 kJ mol^{-1}).[43] The evidence suggests that there is rapid pseudorotation among the various twist-chair conformations.

Molecular mechanics calculations have also been applied to cyclo-octane, for which Hendrickson suggests that a total of 11 conformations should be considered.[42] The boat-chair conformation (Figure 19) was found by calculation to be the most stable. More recent molecular mechanics calculations disagree on the low-energy conformation of cyclo-octane. Thus Allinger's calculations (MM1)[34] find the boat-chair conformation to be more stable than the twist-chair-chair and crown conformations, whereas Schleyer's calculations (EAS)[33] indicate that these three conformations are of almost equal energy. Experimentally, both the boat-chair and crown conformations have been found in the solid state in X-ray crystal structure determinations on cyclo-octyl derivatives;[44] the

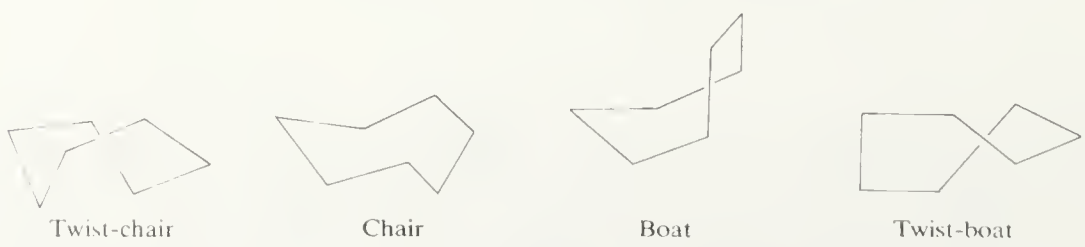


Figure 18 Conformations of cycloheptane

Figure 19 Conformations of cyclo-octane

majority of structures studied favour the former conformation. ^{19}F N.m.r. spectroscopic measurements with fluorinated derivatives also support the boat-chair conformation in solution.[45,46] On the other hand, gas-phase electron diffraction data on cyclo-octane itself are not compatible with the assumption of a single geometry, rather with a mixture of conformations.[47]

The conformation properties of cycloalkanes of nine and more carbon atoms are quite complicated. Several conformations for cyclononane have been examined by calculation.[33,48] Again, several are found to be quite close in energy. The twist-chair-boat conformation has been found experimentally for crystalline cyclononylamine hydrobromide.[44] Studies of cyclodecane derivatives by X-ray crystallographic methods have demonstrated that the boat-chair-boat conformation (Figure 20) is adopted in the solid state.[44] According to electron diffraction measurements, this conformation is the dominant one for cyclodecane itself.[49] At 130 °C in the gas phase, the boat-chair-boat form is adopted by 49±3% of the molecules, and the twist-boat-chair form by 35±3% of the molecules. The remaining molecules are divided evenly between boat-chair-chair and twist-boat-chair-chair conformations.

As far as identifying the single most stable conformation for an even-membered ring of ten or more carbon atoms is concerned, an interesting fact has emerged which is simple to apply. The stability of the diamond-lattice structure is well established, and it was anticipated that for ring systems of sufficient flexibility, the lowest-energy conformation would correspond to that which adopted the diamond-lattice arrangement. The relationship of the boat-chair-boat conformation of cyclodecane to the diamond lattice is shown in Figure 20. Computer-assisted analysis of diamond-lattice sections has provided a very convenient way of studying stable conformations of carbocyclic rings containing up to 24 carbon atoms.[50] Dunitz has provided a comprehensive review of the conformational analysis of medium- and large-ring compounds in the crystalline state.[44]

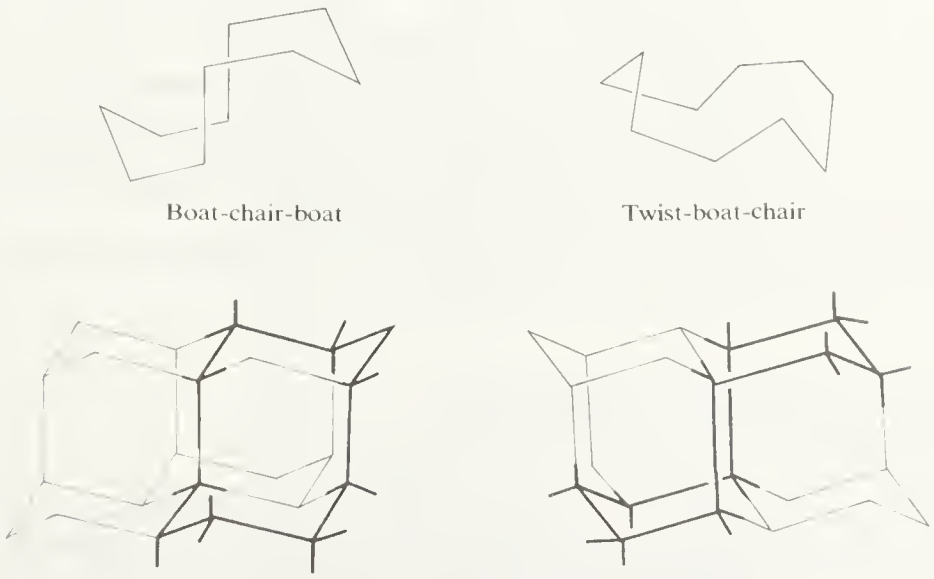


Figure 20 Conformations of cyclodecane

Thermodynamic measurements and molecular mechanics calculations indicate that the medium-sized rings have higher strain energies than have cyclohexane and rings larger than cyclododecane.[21c,33,48] We saw earlier that in small rings the distortion of bond angles is a major source of strain; in five- and six-membered rings, where angles are nearly normal, the major source of strain is bond-opposition, *i.e.* eclipsing effects. Also in the medium rings, the excess of strain is associated with a combination of these two effects plus an additional source associated with transannular interactions in which methylene groups on opposite sides of the ring are forced into close proximity. X-Ray crystallographic studies show that cyclic compounds with eight, nine, and ten carbon atoms have valence angles larger than the tetrahedral value and groups in 1,2-vicinal positions partially eclipsed.[44] These components of ring strain are not mutually independent, and the molecule adopts as its equilibrium conformation that in which the total of these destabilizing interactions is minimized.[51]

Systems which contain cyclohexane rings fused together can be studied conformationally in much the same way as cyclohexane itself.[21] The compound decalin (bicyclo[4,4,0]-decane) is one of the most important examples of a molecule with two rings fused in this way. From the point of view of each ring, the other appears to be a 1,2-disubstituent. If the rings are fused in a *cis* fashion (Figure 21), one bond from each ring is axial and one is

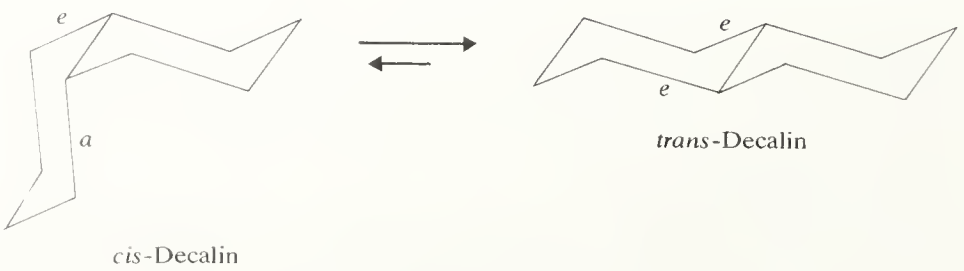


Figure 21 *cis*- and *trans*-decalin

equatorial. Of two conceivable *trans* arrangements, *a,a* and *e,e*, only the latter is structurally possible (Figure 21). Because axial–axial bonds point 180° away from each other it is physically impossible to bridge them with only four carbon atoms (the four that complete the second ring). *trans*-Decalin has a centre of symmetry (midway between C-9 and C-10) and is therefore incapable of optical activity. *cis*-Decalin, which is dissymmetric (chiral), has two interconvertible chair conformations, similar to *cis*-1,2-dimethylcyclohexane. Ring inversion in *cis*-decalin converts the molecule into its mirror image; *cis*-decalin is therefore a non-resolvable (±)-pair. Examination of the *gauche*-butane interactions in *cis*- and *trans*-decalin shows that there are three in the former and none in the latter. On this basis, the *trans* isomer should be lower in enthalpy than the *cis* isomer by about 11 kJ mol^{-1}. Experimental values from equilibration and heats of formation differences (Table 20, p. 86) are 11–12 kJ mol^{-1}.

A detailed account of the stereochemistry of fused cycloalkanes containing more than two cyclohexane rings has been given by Eliel.[21a]

2.1.6 THERMOCHEMICAL PROPERTIES

2.1.6.1 Combustion: alkanes and cycloalkanes as fuels

Combustion reactions form the basis for producing heat from fossil fuels and hence for generating much of the motive and electric power used at the present time. The maximum amount of energy that can be generated by combustion of unit mass of fuel can in principle be precisely calculated *a priori* if the composition of the fuel and the composition and mean temperature of the products of combustion are known.

Complete combustion of saturated hydrocarbons in oxygen yields only carbon dioxide and water:

$$C_aH_b + (a + b/2)O_2 \rightarrow aCO_2 + bH_2O \quad (1)$$

The heat of this combustion reaction can be deduced from the following standard reactions:

$$C(\text{graphite}) + O_2(\text{gas}) \rightarrow CO_2(\text{gas}) \quad (2)$$
$$\Delta H^\circ_r = \Delta H^\circ_f(CO_2)$$
$$H_2(\text{gas}) + \tfrac{1}{2}O_2(\text{gas}) \rightarrow H_2O(\text{liquid}) \quad (3)$$
$$\Delta H^\circ_r = \Delta H^\circ_f(H_2O)$$
$$a\,C(\text{graphite}) + b/2\,H_2(\text{gas}) \rightarrow C_aH_b \quad (4)$$
$$\Delta H^\circ_r = \Delta H^\circ_f(C_aH_b)$$

Therefore for:

$$C_aH_b \rightarrow a\,C + b/2\,H_2 \xrightarrow{(a+b/2)O_2} a\,CO_2 + b/2\,H_2O$$

which is equivalent to equation (1)

$$\Delta H^\circ_r = \Delta H^\circ_{\text{combustion}}(C_aH_b) = -\Delta H^\circ_f(C_aH_b) + a\,\Delta H^\circ_f(CO_2) + b/2\,\Delta H^\circ_f(H_2O) \quad (5)$$

Since ΔH°_f for an alkane is small compared with the other terms in equation (5), the heat of combustion of any alkane, ΔH°_c, is given to a good approximation by:

$$\Delta H^\circ_c(C_aH_b) \approx a\,\Delta H^\circ_f(CO_2) + b/2\,\Delta H^\circ_f(H_2O) = -393.5a - 142.9b \text{ kJ mol}^{-1} \quad (6)$$

Table 10 gives the heats of combustion of some actual and potential fuels in kJ mol^{-1} and kJ g^{-1}. In terms of heat available from combustion, alkanes and cycloalkanes are superior to oxygen- and nitrogen-containing fuels and are marginally better than

TABLE 10

Heats of Combustion of Some Common and Potential Fuels

Fuel		*Heat of combustion*[a] (kJ mol^{-1})	(kJ g^{-1})
Hydrogen	(g)	286	143
Methane	(g)	890	56
Ethylene	(g)	1411	50
n-Butane	(g)	2876	50
Acetylene	(g)	1247	48
n-Octane	(l)	5472	48
Cyclohexane	(l)	3920	47
Benzene	(l)	3268	42
Nitrobenzene	(l)	3298	36
Charcoal	(s)	—	~33
Coal	(s)	—	~32
Ethanol	(l)	1368	30
Methanol	(l)	725	23
Peat	(s)	—	17–23
Wood	(s)	—	~19
Sucrose	(s)	5641	17
Glucose	(s)	2803	16

[a] For reaction yielding liquid water; under most actual combustion conditions water is produced in the vapour state.

unsaturated hydrocarbons. Hydrogen is clearly a better fuel than alkanes, although transportation and storage difficulties, and explosion hazards, reduce its appeal. On the other hand, hydrogen is readily available from electrolysis of water and its combustion produces no pollutants, so that as a secondary fuel in an economy geared to electricity as a primary energy source, either from nuclear power stations or other sources, hydrogen has considerable potential.[52] Alcohol fuels such as methanol and ethanol are generally more suitable for use in internal combustion engines than are alkanes.

The major problem, of course, with the use of alkanes as fuels stems from pollutants which are produced either as a result of combustion of impurities in the alkane, the incomplete combustion of the alkane itself, or from oxidation of atmospheric nitrogen during the combustion process. These problems are most acute with internal combustion engines burning alkane fuels. The technological aspects of fuel performance and the extensive measures taken to reduce the emission of unburnt alkanes, carbon monoxide, and nitrogen oxides from automobile and jet-engine exhausts are beyond the scope of this chapter. For the time being at least, alkane fuels are readily available from natural gas and petroleum deposits and from the catalytic cracking of high-boiling crude oil fractions.[6]

2.1.6.2 Thermochemical properties from combustion measurements

By far the vast majority of heats of formation of alkanes and cycloalkanes available have been determined *via* measurement of the appropriate heat of combustion in oxygen. Rearrangement of equation (5) gives the heat of formation, $\Delta H_f^\circ(C_aH_b)$, from the heat of combustion, $\Delta H_c^\circ(C_aH_b)$:

$$\Delta H_f^\circ(C_aH_b) = a\,\Delta H_f^\circ(CO_2) + b/2\,\Delta H_f^\circ(H_2O) - \Delta H_c^\circ(C_aH_b) \qquad (7)$$

In principle, at least, the heat of formation of any alkane is readily determined in this way. In practice, the experimental difficulties can be considerable. Heats of formation of the heavier alkanes are usually determined by bomb calorimetry, whereas flame calorimetry is more applicable to the more volatile alkanes. A complete description of the experimental details of most types of calorimetry is to be found in the standard works on the subject.[53–55]

To measure the heat of formation of cyclohexane, for example, *via* combustion calorimetry, one must measure the difference between the heat of combustion of cyclohexane and that of six carbon atoms and six hydrogen molecules. That is, to determine a heat of $-123\ kJ\ mol^{-1}$ one must measure a heat of reaction of $-3920\ kJ\ mol^{-1}$. Thus, to obtain an error of $\pm 1\ kJ\ mol^{-1}$, or about $\pm 1\%$, in the heat of formation, the heat of combustion must be determined to $\pm 1\ kJ\ mol^{-1}$, or about 0.026%. The problem becomes progressively more acute as the molecular weight of the hydrocarbon increases: to measure ΔH_f° for a $C_{20}H_{42}$ alkane to $\pm 1\%$ requires that its heat of combustion be determined to $\pm 0.007\%$. Considerations such as sample purity become of paramount importance: combustion of a $C_{20}H_{42}$ alkane contaminated with 0.01% water produces a discrepancy of $1.5\ kJ\ mol^{-1}$ in the heat of combustion. Similarly, the precise definition of the combustion reaction, by careful analysis of starting states and products, is essential for reliable results. One further problem arises with liquid and solid hydrocarbons. Should the substance be a liquid or solid at 25 °C, the standard heat of formation, ΔH_f° (which refers to 298.15 K), includes the intermolecular binding energy of the condensed state; the latter is irrelevant to bond energy or structure–energy considerations. The heat of formation required for such considerations is that of the compound in the (hypothetical) ideal-gas state, and is obtained from the measured ΔH_f° value by making allowance for the heat of vaporization (or sublimation) to the ideal-gas state at 25 °C. Intermolecular binding energies can vary considerably even within closely related systems, thus masking true orders of thermochemical stability. Experimental gas-phase heats of formation are available for all normal and branched-chain isomers from C_1 to C_8, but data for higher members are sparse and are not being collected at a rapid rate.

The data, a selection of which is summarized in Table 11, reveal two important aspects

TABLE 11

Gas-phase Heats of Formation of Some Acyclic Alkanes (kJ mol $^{-1}$)[a]

Compound	ΔH_f° (g)	*Compound*	ΔH_f° (g)
Methane[b]	−74.45	2,2,3,4-Tetramethylpentane	−236.9
Ethane[b]	−83.45	2,2,3,3-Tetramethylpentane	−237.1
Propane[b]	−104.67	2,2,4,4-Tetramethylpentane	−241.8
n-Butane[b]	−125.66	2,2,5-Trimethylhexane[c]	−254.0
2-Methylpropane[b]	−134.19	2,2,3,4,4-Pentamethylpentane[c]	−247.0
n-Pentane[c]	−146.77	2,2,3,3,4-Pentamethylpentane[c]	−247.2
2-Methylbutane[c]	−153.68	3,4-Diethylhexane[c]	−247.6
2,2-Dimethylpropane[c]	−167.95	3,3-Diethyl-2-methylpentane[c]	−248.2
n-Hexane	−167.03	n-Decane	−249.66
3-Methylpentane	−172.1	3-Ethyl-4-methylheptane[c]	−250.5
2-Methylpentane	−174.8	4-Ethyloctane[c]	−251.1
2,3-Dimethylbutane	−178.3	2-Ethyl-2,3,4-trimethylpentane[c]	−251.4
2,2-Dimethylbutane	−186.1	2-Ethyl-2,4,4-trimethylpentane[c]	−253.3
n-Heptane	−187.7	2,2,3,3-Tetramethylhexane[c]	−257.9
3-Ethylpentane	−189.3	5-Methylnonane	−258.6
3-Methylhexane	−191.3	2-Methylnonane	−259.9
2-Methylhexane	−194.6	2,5-Dimethyloctane[c]	−261.1
2,3-Dimethylpentane	−198.0	2,4-Dimethyloctane[c]	−261.1
3,3-Dimethylpentane	−201.2	4,4-Dimethyloctane[c]	−262.2
2,4-Dimethylpentane	−201.7	2,7-Dimethyloctane[c]	−264.0
2,2,3-Trimethylbutane	−204.5	2,2-Dimethyloctane[c]	−267.5
2,2-Dimethylpentane	−205.9	2,2,3,5-Tetramethylhexane[c]	−269.0
n-Octane[d]	−208.7	2,2,5-Trimethylheptane[c]	−271.8
3-Ethylhexane	−210.7	2,2,6-Trimethylheptane[c]	−274.6
3-Ethyl-2-methylpentane	−211.0	2,2,5,5-Tetramethylhexane[c]	−285.3
4-Methylheptane	−212.0	n-Undecane	−270.9
3-Methylheptane	−212.5	3,3,5,5-Tetramethylheptane	−276.6
3,4-Dimethylhexane	−212.8	2,2,4,4,5-Pentamethylhexane	−280.8
2,3-Dimethylhexane	−213.8	2,2,5,5-Tetramethylheptane	−302.1
3-Ethyl-3-methylpentane	−214.9	n-Dodecane	−289.7
2-Methylheptane	−215.4	3,3,6,6-Tetramethyloctane	−318.0
2,3,3-Trimethylpentane	−216.3	3,5-Dimethyl-3,5-diethylhexane	−301.3
2,3,4-Trimethylpentane	−217.3	n-Tridecane[c]	−311.5
2,4-Dimethylhexane	−219.2	4,4,6,6-Tetramethylnonane	−313.4
3,3-Dimethylhexane	−220.0	n-Tetradecane[c]	−332.1
2,2,3-Trimethylpentane	−220.0	4,6-Dimethyl-4,6-diethylnonane	−346.9
2,5-Dimethylhexane	−222.5	n-Pentadecane[c]	−352.8
2,2,4-Trimethylpentane	−224.0	5,5,7,7-Tetramethylundecane	−366.5
2,2-Dimethylhexane	−224.6	n-Hexadecane	−374.8
2,2,3,3-Tetramethylbutane[d]	−225.5	n-Heptadecane[c]	−393.9
n-Nonane	−228.7	n-Octadecane[f]	−414.7
4-Ethylheptane[c]	−230.5	n-Nonadecane[c]	−435.1
3,3-Diethylpentane	−231.8	Eicosane[c]	−455.8
2,3,3,4-Tetramethylpentane	−236.1		

[a] Unless otherwise noted the data are from the compilation of Cox and Pilcher.[54] [b] Recent data from D. A. Pittam and G. Pilcher, *J.C.S. Faraday I*, 1972, **68**, 2224. [c] Recommended values from W. D. Good, *J. Chem. Thermodynamics*, 1970, **2**, 237. [d] Recommended values from W. D. Good, *J. Chem. Thermodynamics*, 1972, **4**, 709. [e] Estimated values from the compilation of Stull, Westrum, and Sinke.[55] [f] The solid phase heat of formation from Ref. 54 is combined with the heat of sublimation of E. Morawetz, *J. Chem. Thermodynamics*, 1972, **4**, 139.

of structure–energy relationships. In the first place, it is immediately clear that isomeric structures are not energetically equivalent, *i.e.* carbon–carbon and carbon–hydrogen bond contributions to ΔH_f° are not constant from one type of carbon atom to the next. For example, the isomeric butanes, each containing three C—C and ten C—H bonds, differ by 8.53 kJ mol^{-1}, the branched-chain isomer being the more thermochemically stable of the two. Similarly, the stability order of the pentanes is n-pentane < 2-methylbutane < 2,2-dimethylpropane. Some of the more important consequences in terms of energy and structure of chain branching in the C_4 to C_9 alkanes are summarized in Table 12. It is apparent that the C—C bond energy is enhanced by structures in which all four bonds formed by a given carbon atom join to other carbon atoms; the bonds appear stronger the more nearly the condition of the carbon atom resembles that in diamond. The extra stability of branched-chain isomers is evident from Table 12, the advantage being 7–12 kJ mol^{-1} per extra methyl group.

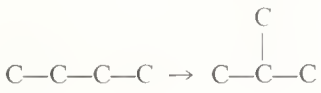
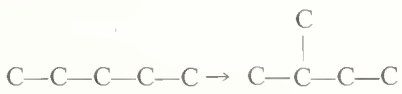
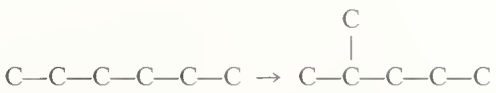
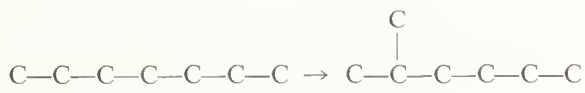
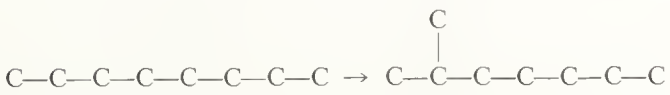
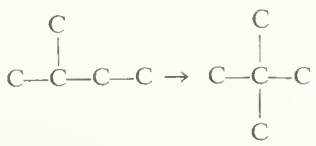
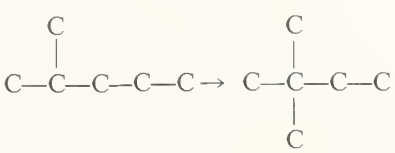
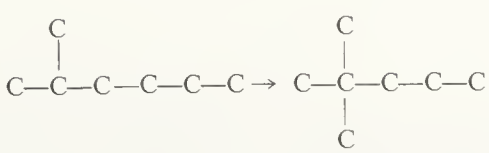
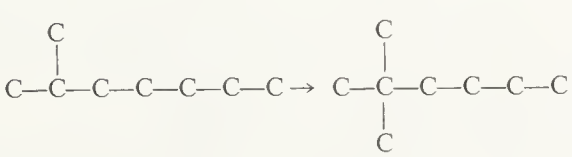
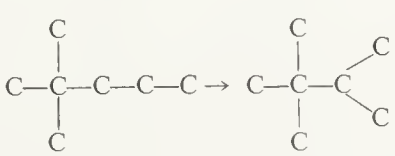
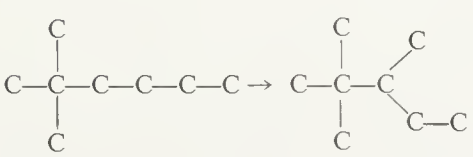
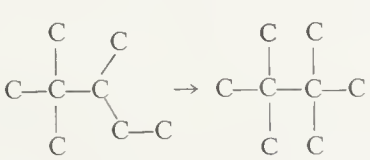
The second aspect appears to be steric in origin. A branched alkane occupies a smaller effective molecular volume than does its unbranched isomer; the non-bonded atoms are more closely packed together and will repel each other if forced in closer proximity than the sum of their van der Waals radii. This type of steric crowding leads to destabilization, and we might expect that at some stage a highly branched alkane will become so crowded that it is less stable than an isomer with a lower degree of branching. This is indeed the case: two examples involving C_7 and C_8 isomers are shown in Table 12. It is only when a tertiary carbon atom is bonded to a quaternary carbon atom that the less-branched isomer is the more stable, but it is also clear that the difference between the heats of formation of 2,2,3-trimethylpentane and 2,2,3,3-tetramethylbutane is a great deal less than that expected on the basis of extra branching. The nonanes and decanes provide further examples of the way in which these two factors operate, sometimes in opposition. The most stable of the 75 decanes is 2,2,5,5-tetramethylhexane; the least stable is not n-decane, but 2,2,3,4,4-pentamethylpentane. The first structure has two $(CH_3)_3C$ groups separated by two carbon atoms so that they do not interfere with each other. The least-stable structure has two quaternary carbon atoms adjacent to each other. In this particular isomer, the weakening ascribable to steric effects appears more than sufficient to overbalance the strengthening associated with the presence of quaternary carbon atoms. Examination of space-filling molecular models reveals very clearly the steric differences between these structures. In the nonanes, the most stable isomer is that which comes closest to having two $(CH_3)_3C$ groups separated by two carbon atoms, as in the most stable decane; one carbon atom separation is not enough. Numerous other related trends are revealed by the data in Table 12. Generally, one may expect carbon–carbon branching to increase the total bonding energy, provided that the branching does not lead to severe steric interference.

2.1.6.3 Empirical methods for estimating heats of formation of alkanes

As we have seen in the preceding section, the heat of formation of any alkane depends not only on the number of carbon and hydrogen atoms present but also on the precise structural arrangement of the molecule. Many attempts have been made to develop empirical methods of estimating such data by extrapolation and interpolation of existing data. Clearly, if precise, reliable relationships between heats of formation and molecular structure could be established, further thermochemical measurements would scarcely be necessary, since heats of formation of compounds not studied experimentally — or of unknown compounds — could be estimated from their structures. Alkanes provide an important testing ground for such structure–energy relationships; these substances form the structural backbone of many organic molecules and reliable predictions for alkanes thus become a prerequisite to applications to molecules containing functional groups. In this section we will describe the principal ways in which this problem has been approached.

TABLE 12

Heats of Chain Branching in Some Simple Alkanes Data from Gas-phase Heats of Formation (kJ mol^{-1})[a]

	Isomerization	$\Delta\Delta H_f^\circ$
C_4		−8.53
C_5		−6.91
C_6		−7.77
C_7		−6.9
C_8		−6.67
C_5		−14.27
C_6		−14.0
C_7		−11.3
C_8		−9.2
C_7		+1.4
C_8		+4.6
C_8		−5.5

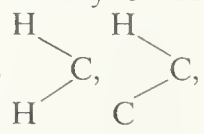
[a] Data from Ref. 54.

Chemists have for years made use of bond-energy tables, which permit one to calculate heats of formation by summing numbers and kinds of bonds in molecules. Bond-energy terms, introduced by Fajans,[56] and applied extensively Sidgwick[57] and Pauling,[58] were derived in a simple way from thermochemical data. It was assumed that each bond of a given type has a constant characteristic energy, transferrable from one molecule to another, and that bond-energy terms are additive. An alternative approach, called the group increment concept, considers the molecule as a collection of groups of atoms, each assigned energy increments whose sum equals the heat of formation. Clearly, these two concepts are closely related.

2.1.6.4 Bond-energy terms

The data in Tables 11 and 12 reveal quite clearly that the bond-energy concept, at least in its simplest form, fails completely to account for the differences in energy between a straight-chain alkane and its branched-chain isomers; these differences are sometimes large. The assumption of constant transferable bond-energy terms would require all gaseous isomerizations of alkanes to be thermochemically neutral. The additivity of bond-energy terms was first questioned in 1934 by Zahn[59], who proposed a 'more general type of energy model' in which the total heat of formation of the alkane was written as the sum of the bond-energy terms and an additional term associated with pairs of bonds attached to the same atom. Application of the Zahn model to the general case of an alkane, C_nH_{2n+2}, gives the following expression for the heat of atomization:

$$H_a^\circ(C_nH_{2n+2}) = (n-1)\,B\,(C{-}C) + (2n+2)\,B\,(C{-}H) + [N_p - 6 + \tfrac{1}{2}N_s]T$$

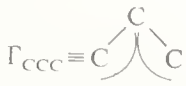
where N_p is the number of primary C—H bonds, N_s is the number of secondary C—H bonds, and T is the net interaction parameter associated with the bond pairs  and  . This relationship represented a considerable improvement on that of Fajans in that it can account for differences in the heats of formation of constitutional isomers, provided that $T \neq 0$. Although the Zahn scheme has not found wide application (it was introduced at a time when few precise thermochemical data were available) it is important historically in that it demonstrated how the original scheme of Fajans could be extended in a simple way, thus suggesting further refinement.

Since the 1940s, several bond- and group-energy schemes, which represent marked improvements on that of Zahn, have been developed. Laidler[60] suggested that the energy terms of primary, secondary, and tertiary C—H bonds should not be identical since such bonds appear to differ slightly in length according to their primary, secondary, or tertiary nature. The Laidler scheme makes no allowance for the steric interference in alkanes. The Allen[61] scheme tackles the problem of steric corrections by adding further terms to the Zahn equation, one of which contains an allowance for each pair of *gauche*-1,4 C—H pairs. Allen took the 1,4-*gauche* interaction to be constant for all cases, but Skinner[62] later suggested that Allen's estimation of steric corrections is inadequate on the grounds that the actual value may vary according to the rigidity of the alkane; in favourable cases the H · · · · · H repulsions in a given structure may be relieved by internal rotation or angle-widening. The alkane parameters recommended by Cox and Pilcher[54] for the Allen scheme are given in Table 13.

The most sophisticated bond-energy scheme is that of Somayajulu and Zwolinski,[63] which involves consideration, at least formally, of each individual interatomic interaction between non-bonded atoms within certain limits. The scheme contains a summation of all the bond energies and interactions between geminal and vicinal pairs of atoms plus

TABLE 13

Parameters for the Allen Bond Energy Scheme as recommended by Cox and Pilcher[54] for estimating Gas-phase Heats of Formation (kJ mol^{-1}) of Alicyclic Alkanes

Parameter	*Increment*
(a) Bond energies (B)	
B(C—H)	−18.70
B(C—C)	+27.66
(b) 1,3-Interaction (Γ)	
	−10.79
(c) Non-bonded trio correction (Δ)	
	+2.30

additional correction terms. The scheme is applicable to conformations of molecules which cannot be considered by group increment schemes, and hence is better suited to such specialist cases. It should be stressed, however, that the energies assigned to a given atom pair interaction do not necessarily represent a physical reality, but only a convenient means of segregating the total molecular energy.

2.1.6.5 The group increment approach

In this approach to structure–energy relationships the emphasis is on individual contributions by groups of atoms rather than on groups of bonds. Heats of formation differences between constitutionally isomeric alkanes depend on the presence of certain groups of atoms in each constitution and on their locations relative to each other. The idea that specific groups such as —CH_2— or $(CH_3)_3C$— may contribute a fixed amount to the heat of formation of a molecule was first intoduced by Parks and Huffman.[64] The total energy content of a molecule in the ideal-gas state includes (i) intramolecular energy due to the chemical binding of the constituent atoms, which may be affected by steric crowding, hyperconjugation or other effects, and (ii) translational, rotational, and vibrational energy. For the group increment to be valid, the contribution of the group to each of these energies must be almost constant from molecule to molecule. In fact, most group schemes contain steric correction terms, and for alkanes a relatively simple scheme can be made to fit the experimental data within the reliability limits. Such a scheme containing parameters for CH_3, CH_2, CH, and C was proposed by Benson and Buss[65] and good agreement was obtained for many alkanes in which steric crowding is not important. Only for very highly branched alkanes does the method yield poor results, and for these Benson and Buss made special allowances in the scheme for steric strain. Schemes of this sort have also been used to estimate 'strain free' heats of formation of imaginary molecules, thus providing strain energy estimates. The Benson and Buss increments are: CH_3—, −42.34; —CH_2—, −20.59; —$\underset{|}{C}H$—, −7.32; and —$\underset{|}{\overset{|}{C}}$—, −0.25, in which case ΔH_f°(g) (in

kJ mol^{-1}) for an acyclic alkane is given by

$$\Delta H_f^\circ(g) = -(N_{CH_3} \times 42.34 + N_{CH_2} \times 20.59 + N_{CH} \times 7.32 + N_C \times 0.25)$$

where N are the numbers of different groups present.

Other schemes of this type have been reviewed by Cox and Pilcher.[54] There are many refinements, usually involving recognition of certain patterns within a molecule which give rise to specific amounts of strain interaction requiring an extra parameter in the scheme. Such refinements are attractive but must be treated with considerable caution. Even in the more sophisticated molecular mechanics method of calculating molecular structures and energies the assignment of specific destabilization to individual strain features is difficult; these difficulties are magnified in a simple group increment approach. Nevertheless, it is possible to derive a simple group increment scheme capable of providing accurate estimates of the heats of formation of acyclic alkanes. This objective may be the limit to which we can apply such a simple concept as group additivity. Our aim here is to provide an acceptable scheme for all acyclic alkanes, avoiding wherever possible steric correction energies for specific interactions. The derivation of such a scheme provides a useful insight into the factors affecting alkane stability.

The first step is assignment of a contribution to the —CH_2— group. This is best accomplished by making use of the fact that the straight-chain alkanes differ from adjacent members of the homologous series by one —CH_2— group, and the —CH_2— contribution can be assigned on the basis of heats of formation differences between adjacent alkanes. These $\Delta\Delta H_f^\circ$ values, taken from Table 11, are plotted against the number of carbon atoms in Figure 22, producing a contribution to the heat of formation of -20.62 kJ mol^{-1} per methylene group. The next increment to be assigned is that of the methyl group. This can be done by subtracting the methylene group contribution from the heats of formation of the straight-chain alkanes and halving the remainder (each

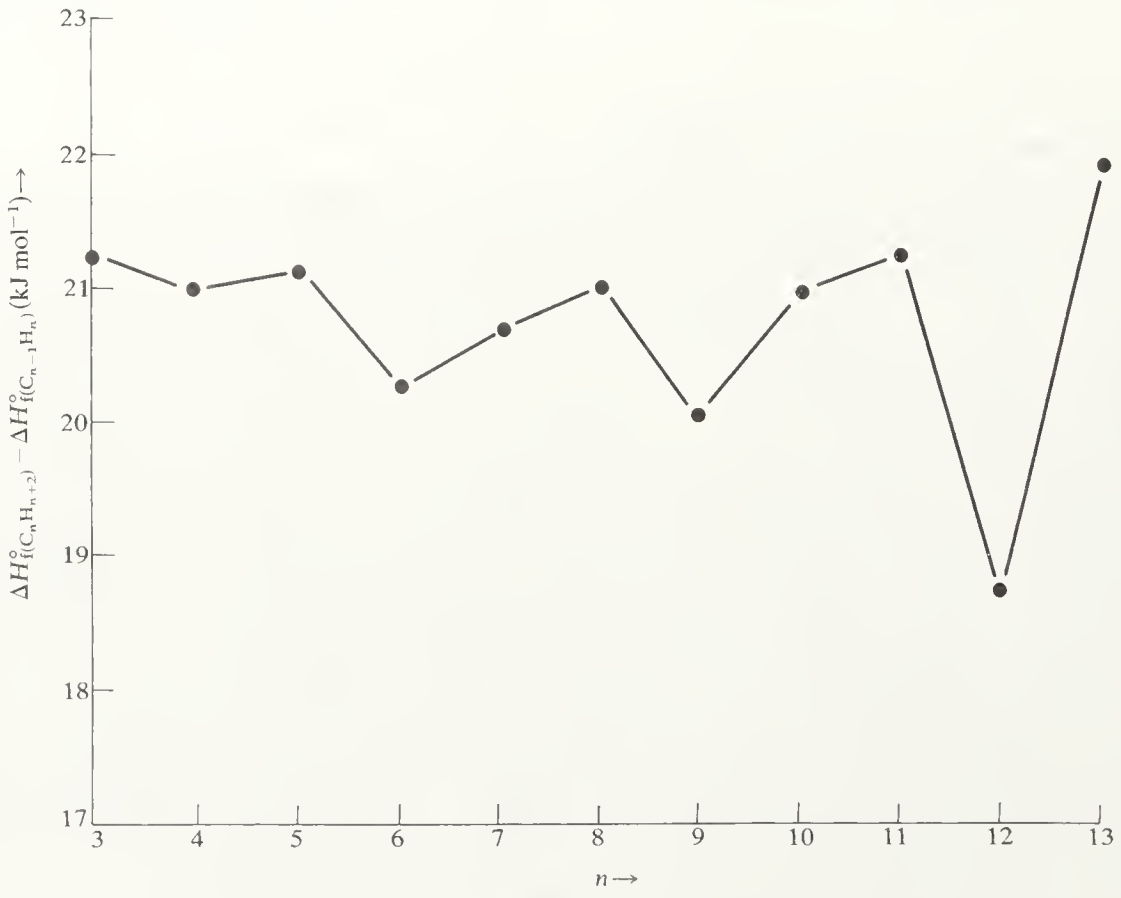


Figure 22 Plot of $\Delta H^\circ_{f(C_nH_{2n+2})} - \Delta H^\circ_{f(C_{n-1}H_{2n})}$ against n

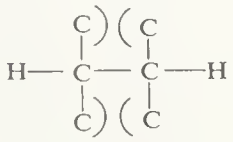
alkane contains two methyl groups). This procedure gives a value of $-42.26\ kJ\ mol^{-1}$ as the increment per methyl group. If this scheme is to reproduce differences in heats of formation between constitutional isomers, a single $-\overset{|}{\underset{|}{C}}H$ group increment cannot be used. A simple solution is chosen whereby the $-\overset{|}{\underset{|}{C}}H$ and $-\overset{|}{\underset{|}{C}}-$ increments in uncrowded alkanes are dependent upon the number of methyl groups bonded to the group in question. A procedure similar to that used for the CH_3- group increment gives values of $-1.06-(2.12\times N_{CH_3})$ and $+19.70-(5.00\times N_{CH_3})\ kJ\ mol^{-1}$ for the $-\overset{|}{\underset{|}{C}}H$ and $-\overset{|}{\underset{|}{C}}-$ groups, respectively. Better agreement with experimental data could undoubtedly be obtained by using separate increments for each type of $-\overset{|}{\underset{|}{C}}H$ and $-\overset{|}{\underset{|}{C}}-$ group. Nevertheless,

TABLE 14

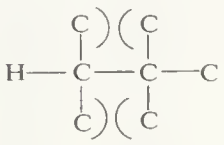
Recommended Group Increments and Steric Corrections for estimating Gas-phase Heats of Formation of Acyclic Alkanes ($kJ\ mol^{-1}$)

Group	*Increment or correction*
$-CH_3$	−42.46
$-CH_2-$	−20.62
$-CH-$	$[-1.06-(2.12\times N_{CH_3})]$
$-C-$	$[19.70-(5.00\times N_{CH_3})]$

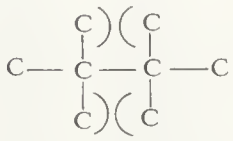
where N_{CH_3} is the number of methyl groups bonded to the group in question



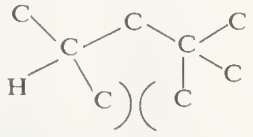
+3.00



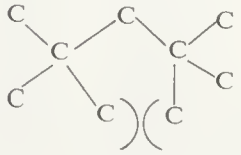
+9.55



+20.80



+9.50



+22.50

TABLE 15

Comparison between Experimental Gas-phase Heats of Formation and Values Calculated using the Parameters in Table 14 [ΔH_f°(g) in kJ mol^{-1}]

	Calc.	*Exp.*
Ethane	−84.5	−83.5
Propane	−105.1	−104.7
Butane	−125.8	−125.7
2-Methylpropane	−134.2	−134.2
Pentane	−146.4	−146.8
2-Methylbutane	−152.7	−153.7
2,2-Dimethylpropane	−169.3	−168.0
Hexane	−167.0	−167.0
2-Methylpentane	−173.3	−174.8
3-Methylpentane	−171.2	−172.1
2,2-Dimethylbutane	−185.0	−186.1
2,3-Dimethylbutane	−176.6	−178.3
Heptane	−187.6	−187.7
2-Methylhexane	−193.9	−194.6
3-Methylhexane	−191.8	−191.3
3-Ethylpentane	−189.7	−189.3
2,2-Dimethylpentane	−205.6	−205.9
2,3-Dimethylpentane	−195.1	−198.0
2,4-Dimethylpentane	−200.3	−201.7
3,3-Dimethylpentane	−200.6	−201.2
2,2,3-Trimethylbutane	−202.4	−204.5
Octane	−208.2	−208.7
2-Methylheptane	−214.6	−215.4
3-Methylheptane	−212.4	−212.5
4-Methylheptane	−212.4	−212.0
3-Ethylhexane	−210.3	−210.7
2,2-Dimethylhexane	−226.2	−224.6
2,3-Dimethylhexane	−215.8	−213.8
2,4-Dimethylhexane	−218.8	−219.2
2,5-Dimethylhexane	−220.9	−222.5
3,3-Dimethylhexane	−221.2	−220.0
3-Ethyl-2-methylpentane	−213.6	−211.0
3-Ethyl-3-methylpentane	−216.2	−214.9
2,2,3-Trimethylpentane	−220.9	−220.0
2,2,4-Trimethylpentane	−223.0	−224.0
2,3,3-Trimethylpentane	−218.0	−216.3
2,3,4-Trimethylpentane	−219.1	−217.3
2,2,3,3-Tetramethylbutane	−223.4	−225.5
Nonane	−228.9	−228.7
2,2-Dimethylheptane	−246.8	−246.1
2,2,3-Trimethylhexane	−241.5	−241.4
2,2,4-Trimethylhexane	−241.5	−243.2
2,2,5-Trimethylhexane	−253.1	−253.3
2,3,3-Trimethylhexane	−238.6	−239.8
2,3,5-Trimethylhexane	−242.7	−242.5
2,4,4-Trimethylhexane	−238.6	−240.5
3,3,4-Trimethylhexane	−236.5	−236.1
3,3-Diethylpentane	−231.8	−231.8
2,2,3,3-Tetramethylpentane	−239.0	−237.1
2,2,3,4-Tetramethylpentane	−235.3	−236.9
2,2,4,4-Tetramethylpentane	−242.3	−241.8
Decane	−249.5	−249.7
2-Methylnonane	−255.8	−259.9
5-Methylnonane	−253.7	−258.6
Undecane	−270.1	−270.9
2,2,5,5-Tetramethylheptane	−301.0	−302.1
3,3,5,5-Tetramethylheptane	−273.5	−276.6
2,2,4,4,5-Pentamethylhexane	−275.3	−280.8
Dodecane	−290.7	−289.7
3,3,6,6-Tetramethyloctane	−316.6	−318.0

TABLE 15 (*continued*)

	Calc.	*Exp.*
4,4,6,6-Tetramethylnonane	−314.8	−313.4
3,5-Diethyl-3,5-dimethylheptane	−304.8	−301.5
4,6-Diethyl-4,6-dimethylnonane	−346.0	−346.9
5,5,7,7-Tetramethylundecane	−356.0	−366.5
Hexadecane	−373.2	−374.8
Octadecane	−414.4	−414.7
5-Butyldocosane	−581.5	−587.4
11-Butyldocosane	−581.5	−593.3
11-Decylheneiocosane	−684.6	−705.8
Dotricosane	−703.1	−697.5

for many acyclic alkanes the above four increments lead to excellent agreement with experimental data. With highly branched alkanes in which steric interference is important, there is considerable overestimation of thermochemical stability. It is possible, however, to deal with steric crowding by the use of five separate corrections of two different types.

The first type of crowding occurs when highly substituted carbon atoms are bonded to each other. Although there are always 1,4-interactions across every C—C bond, these are usually dealt with in the basic increment system and need only be considered for highly crowded systems. We will use the following corrections: $R_2CH—CHR_2$, +3.00 kJ mol^{-1}; $R_3C—CHR_2$, +9.55 kJ mol^{-1}; and $R_3C—CR_3$, +20.80 kJ mol.$^{-1}$ These corrections are simply added to the group increments whenever the appropriate arrangement occurs in an alkane. The second type of crowding occurs when two highly substituted groups are bonded to the same carbon atom. For such situations we recommend corrections of +9.5 kJ mol^{-1} for $R_2CH—C—CR_3$ and +22.5 kJ mol^{-1} for $R_3C—C—CR_3$. Table 14 contains the entire array of nine increments necessary to apply the above scheme to any acyclic alkane, and Table 15 shows the results so obtained for 70 alkanes for which experimental data are available. The correlation coefficient between calculated and experimental values is 0.9996 and the slope given by linear regression is 1.01. Twice the standard precision error, $2[\Sigma\Delta^2/N(N-1)]^{1/2}$ is ±1.05 kJ mol^{-1} for the entire range of structures. Omission of the 'worst' points, notably those associated with very large alkanes where we would expect experimental difficulties, considerably improves these figures.

Although both bond-energy and group-increment approaches are capable of refinement to the point where excellent agreement with experimental data can be achieved, the latter method is simpler and less artificial in its final application, and can be used within the framework of conformational analysis. Examples of the predictive power of five schemes are given in Table 16.

TABLE 16

Experimental and Calculated Gas-phase Heats of Formation for Isomeric Heptanes (kJ mol^{-1})

Compound	*Exp.*	*Allen*[a]	*Allen/Skinner*	*Benson and Buss*[b]	*Somayajula and Zwolinski*[63]	*This work*[c]
n-Heptane	−187.7	−187.2	−187.8	−187.9	−187.9	−187.6
2-Methylhexane	−194.6	−195.7	−194.9	−193.7	−196.2	−193.9
3-Methylhexane	−191.3	−195.7	−192.3	−190.7	−192.5	−191.8
3-Ethylhexane	−189.3	−195.7	−190.3	−187.8	−190.7	−189.7
2,2-Dimethylpentane	−205.9	−201.4	−206.2	−202.2	−204.6	−205.6
2,3-Dimethylpentane	−198.0	−204.2	−196.1	−196.5	−195.6	−195.1
2,4-Dimethylpentane	−201.7	−204.2	−202.0	−199.4	−199.7	−200.3
3,3-Dimethylpentane	−201.2	−210.4	−201.5	−196.3	−200.5	−200.6
2,2,3-Trimethylbutane	−204.5	−218.9	−203.2	−205.0	−203.7	−202.4

[a] Calculated using the increments given by Cox and Pilcher,[54] and in Table 13. [b] Calculated using the increments given in Ref. 65 including the *gauche* correction. [c] Calculated using the increments in Table 14.

2.1.6.6 Cyclic, polycyclic, and bridged-ring alkanes: 'skew separate' and 'single conformation' group increments

A number of problems arise when these incremental schemes are applied to cyclic alkanes. Schleyer *et al.*[66] have pointed out that schemes derived only for acyclic alkanes are not directly applicable to cyclic systems because of the absence of acyclic-type skew interactions in the latter. Consider the two C_4 fragments in Figure 23. The acyclic fragment (a) is destabilized in the conformation shown by the proximity of the methyl groups; this destabilization arises primarily from hydrogen–hydrogen interactions. The cyclic fragment (b), however, contains no such interactions; accordingly, any incremental scheme which implicitly contains these acyclic skew interactions is not directly applicable to cyclic alkanes. Skew interactions are usually included in increments for R_3C— groups as they cannot be avoided when the group is bonded to any group other than a methyl group. In our group-increment scheme described above, the unavoidable skew interactions are implicit in the group increments, whereas more extreme skew interactions are accounted for by steric corrections. Schleyer *et al.*,[66] following a procedure outlined by Benson and Buss,[65] have derived a 'skew separate' scheme in which each skew interaction is treated explicitly, thus allowing cyclic alkanes to be included.

There is yet another aspect of the difference between acyclic and cyclic alkanes. Most molecules in the gas phase at 25 °C are conformationally mobile, and although there may be a single conformation of lowest energy, there are also contributions from conformational isomers of comparable energy. Using a skew interaction of 2.93 kJ mol^{-1}, Mann has calculated the population of these higher energy conformations for a number of alkanes.[67] These values can then be used to correct the experimental gas-phase heat of formation to that of the single conformational isomer of lowest energy. However, cyclic alkanes at 25 °C (cyclohexane, for example) are generally much less conformationally mobile than are acyclic alkanes (n-hexane, for example), and in many cases a single ground-state conformational isomer only need be considered. For this reason, Schleyer *et al.* have argued that increments based on 'single conformation' heats of formation are the only increments applicable to cyclic and polycyclic systems. These increments are listed in Table 17.

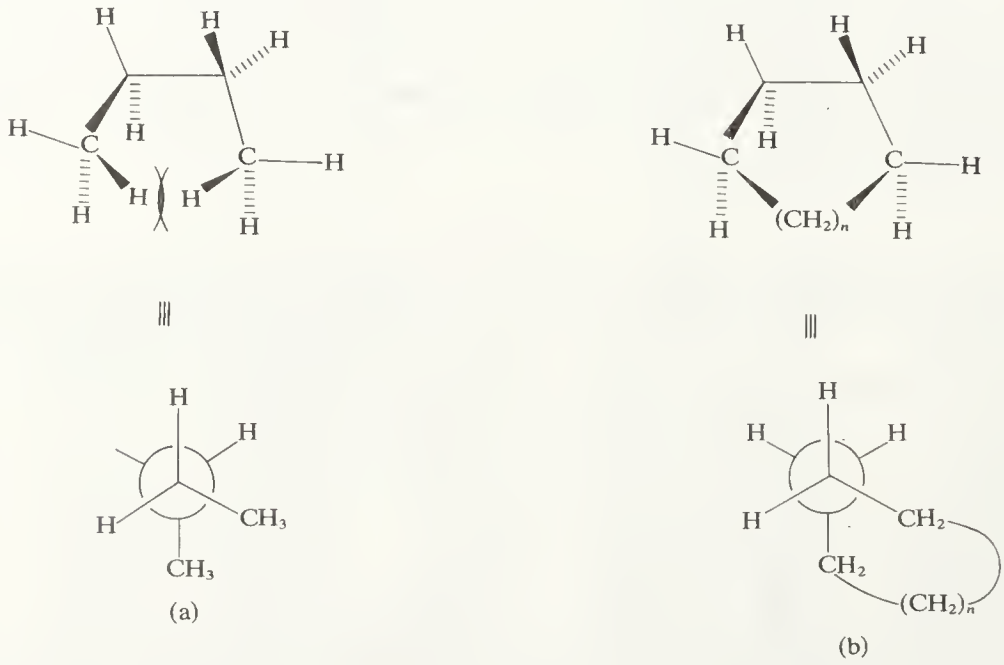


Figure 23

TABLE 17

Single Conformation Group Increments from Ref. 66 (kJ mol^{-1})

Group	*Increment*
$-CH_3$	−42.05
$-CH_2-$	−21.46
$-\overset{|}{C}H-$	−9.04
$-\overset{|}{\underset{|}{C}}-$	−1.26
Acyclic skew correction	+2.93

2.1.6.7 Heats of formation and strain energies from molecular mechanics calculations

Although the bond-energy and group-increment schemes discussed above are capable of refinement to a high degree of accuracy and precision, they do lack flexibility and versatility. Systems possessing these qualities, based on molecular mechanics calculations (also known as empirical force field calculations), are now being used widely in organic chemistry. Although the discussion here is limited to the evaluation of heats of formation, energy differences, strain energies, and molecular structure of saturated hydrocarbons, one of the strengths of the molecular mechanics approach is its applicability to problems involving, for example, functional groups, alkenes, aromatics, organometallics, polymer and peptide conformations, and reactive intermediates. In the molecular mechanics approach, pioneered by Westheimer[68] and later extended and enlarged by Hendrickson[69] and Wiberg,[70] a molecule is viewed as a collection of particles (atoms) held together by springs (bonds) and calculations are performed on this type of molecular model. The electronic system is not considered explicitly. Deformation of the model by stretching or bending the springs or displacing the particles relative to each other will result in energy changes which can be calculated if the necessary force laws and constants are known. Classical mechanical equations are used to define stretching, bending, non-bonded, and stretch-bend potential functions, the combination of which gives the geometry of a single minimum-energy conformation and the total steric energy of the molecule. The geometry of the molecular model is allowed to relax to an energy minimum by systematic variation of the molecular parameters. The technical details of the energy minimization procedure, which is carried out on high-speed computers, have been described in several reviews.[71,72] By careful choice of the potential functions for each type of interaction within the molecule, a force field is obtained capable of fitting to experimental data.

The steric energies may be used directly to obtain energy differences between stereoisomers and isologous molecules (*i.e.* molecules differing in connectivity but possessing the same numbers of CH_3, CH_2, CH, and C groups). The energy differences between the boat and chair forms of cyclohexane, the diastereoisomers of 1,4-dimethylcyclohexane, and ethylcyclopentane and methylcyclohexane, are examples where steric energies are applicable directly. Heats of formation, necessary for other types of energy comparisons, are calculated from the steric energy by deriving group increments or bond-energy increments based on optimization of the steric energies with an assortment of experimentally known heats of formation. By a trial and error process the parameters can be successively modified so as to achieve an acceptable fit for a balanced set of hydrocarbons of diverse structural type.

One of the most difficult aspects of setting up a force field is the assignment of the potential functions associated with non-bonded atoms. DeTar and Tenpas[73] have pointed out that heats of formation calculations are not a sensitive test for the accuracy of van der

Waals interactions in alkanes. This point is borne out by the generally good agreement between some force fields which use very different potential interactions for non-bonded interactions. Force fields are usually parameterized to fit energy and structure data, however, and there is evidence that the various non-bonded potentials will converge to a single set of values as the methods are refined. Allinger[72] has emphasized that one must not confuse the molecular model with physical reality; if the force fields do not converge on one another, it simply means that we cannot obtain information on physical reality with respect to those particular phenomena from the model being used. Interpretations of phenomena which change abruptly from one force field to another are of questionable physical reality.

A point has now been reached where there are several force fields in routine use today. The most widely used models for hydrocarbons are those of Bartell,[74] Boyd,[75] Allinger (MM1[34] and MM2[76] force fields), and Schleyer (EAS force field).[33] The Allinger MM2 force field was introduced to minimize some of the deficiencies of the earlier MM1 version. In our discussion on cycloalkanes and polycycloalkanes, we shall compare experimental data with molecular mechanics data, concentrating on the MM1, MM2, and EAS predictions since these provide the most comprehensive set of data presently available. The strength of the molecular mechanics approach is its ability to treat systems which are inaccessible by ordinary incremental methods. The molecular mechanics method is of course also a method of interpolation and extrapolation from existing experimental data, and the general lack of sufficient, reliable experimental data makes accurate parameterization more difficult. Because of this, there remains the problem of extending molecular mechanics calculations to structural types not represented in the data set used for parameterization. However, the calculations have to some extent catalysed their own refinement by stimulating new experimental work upon which the next generation of force fields will be based.

2.1.6.8 Cycloalkanes and polycycloalkanes

Most of the available gas-phase thermochemical data for monocycloalkanes are given in Table 18. When one considers the enormous number of cycloalkanes and substituted

TABLE 18

Gas-phase Heats of Formation of Some Monocycloalkanes (kJ mol^{-1})[a]

Compound	$\Delta H_f^\circ(g)$	*Compound*	$\Delta H_f^\circ(g)$
Cyclopropane	+53.26	*cis*-1,4-Dimethylcyclohexane	−176.6
1,1-Dimethylcyclopropane[b]	−8.2	*trans*-1,4-Dimethylcyclohexane	−184.5
Cyclobutane	+28.37	Ethylcyclohexane	−171.7
Ethylcyclobutane[b]	−26.3	n-Propylcyclohexane	−193.2
Cyclopentane	−77.2	1-Isopropyl-4-methylcyclohexane	−230.6
Methylcyclopentane	−105.73	n-Butylcyclohexane	−213.0
1,1-Dimethylcyclopentane	−138.2	n-Heptylcyclohexane	−288.1
cis-1,2-Dimethylcyclopentane	−129.5	n-Decylcyclohexane	−339.5
trans-1,2-Dimethylcyclopentane	−136.6	n-Dodecylcyclohexane	−374.1
cis-1,3-Dimethylcyclopentane	−135.9	Cycloheptane	−118.03
trans-1,3-Dimethylcyclopentane	−133.6	Cyclo-octane	−124.4
Ethylcyclopentane	−126.9	Cyclononane	−132.8
n-Propylcyclopentane	−147.99	Cyclodecane	−154.3
Cyclohexane	−123.4	Cycloundecane	−179.4
Methylcyclohexane	−154.7	Cyclododecane	−230.2
1,1-Dimethylcyclohexane	−180.9	Cyclotridecane	−246.4
cis-1,2-Dimethylcyclohexane	−172.1	Cyclotetradecane	−239.0
trans-1,2-Dimethylcyclohexane	−179.9	Cyclopentadecane	−301.4
cis-1,3-Dimethylcyclohexane	−184.6	Cyclohexadecane	−321.7
trans-1,3-Dimethylcyclohexane	−176.5	Cycloheptadecane	−364.3

[a] All data from Ref. 54 unless otherwise stated. [b] W. D. Good, R. T. Moore, A. G. Osborn, and D. R. Douslin, *J. Chem. Thermodynamics*, 1974, **6**, 303.

cycloalkanes which have been synthesized, it is clear that only a small fraction have been examined thermochemically. Actually, the situation is not quite that implied by Table 18; rather more compounds have had their liquid- or solid-phase heats of formation measured, but there seems to be a substantial bottleneck in the measurement of heats of vaporization or sublimation. Of the data listed in Table 18, those of cyclononane, cyclodecane, cycloundecane, cyclododecane, and cyclotridecane are based on estimated heats of vaporization or sublimation.

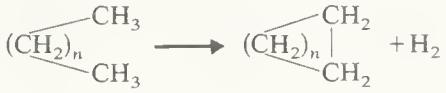
An important consideration in any discussion of structure–energy relationships in cyclic systems is the question of strain energy. The strain energy of a molecule, not to be confused with the steric energy, can be defined in many ways.[77] Qualitatively, one recognizes features of a molecule or a part of a molecule which are stretched or forced beyond the normal, customary limits of structural theory. Cyclopropane, for example, is clearly more strained than is either propane or cyclohexane. We shall discuss strain energy in the context of two standard models: the conventional ring strain energy (CRSE) used by Cox and Pilcher[54] and the single conformation strain energy (SCSE) outlined by Schleyer *et al.*[66]

The CRSE method derives the ring strain energy of a cyclic molecule from the relationship:

$$\text{Ring strain energy} = [\Delta H_f(\text{estimated}) - \Delta H_f(\text{observed})] \text{ (at 298.15 K)}$$

where ΔH_f(estimated) is the heat of formation obtained by application of a bond-energy or group-increment scheme; CRSE values obtained in this way are given in Table 19.

Let us now consider an alternative approach iltustrated by the following cyclization:



One might reasonably expect that the enthalpy change in such a cyclization, ΔH°_{cycl}, should reflect any strain present in the cycloalkane. That this is so in a general sense is shown by the ΔH°_{cycl} data in Table 19. Thus, propane → cyclopropane is a much more endothermic cyclization than is hexane → cyclohexane. We can translate the enthalpy of cyclization into group increments so that for a strain-free C_{n+2} ring

$$\begin{aligned}\Delta H^\circ_{cycl} &= -[n(CH_2) + 2(CH_3)] + (n+2)(CH_2) \\ &= 2[(CH_2) - (CH_3)]\end{aligned}$$

where (CH_2) and (CH_3) are the appropriate group increments.
For a ring with strain energy S,

$$\Delta H^\circ_{cycl} = 2[(CH_2) - (CH_3)] + S$$

and the heat of formation of the cycloalkane is given by

$$\begin{aligned}\Delta H^\circ_{f(C_nH_{2n})} &= \Delta H^\circ_{f(C_nH_{2n+2})} + 2(CH_2) - 2(CH_3) + S \\ &= (n-2)(CH_2) + 2(CH_3) + 2(CH_2) - 2(CH_3) + S \\ &= (n-2)(CH_2) + 2(CH_3) + S \\ &= n(CH_2) + S\end{aligned}$$

Therefore the strain energy can be defined as

$$\Delta H^\circ_{f(C_nH_{2n})} - n(CH_2) = S$$

This derivation is useful for two reasons: (i) it is applicable to any group increment method and can be used in both the CRSE and SCSE approaches, and (ii) it avoids the necessity of introducing the so-called 'strain-free isomer' as a point of reference.[78] Using the latter, the strain energy is defined as the calculated or experimental heat of formation, corrected for the energy increase brought about by the presence of high-energy conformations mixed in with the most stable conformations, minus the heat of formation of the corresponding strain-free isomer. The strain-free isomer is taken to be the n-alkane of the same molecular formula, corrected for chain branching by incremental additions. The use

of the concept of a strain-free isomer has been a consistent stumbling block in strain energy definitions.[78] For example, the strain-free isomer of adamantane ($C_{10}H_{16}$), with six CH_2 and four CH groups, is a particularly abstract concept, whereas the cyclization process (Figure 24) whereby adamantane is assembled from an acyclic precursor is easily

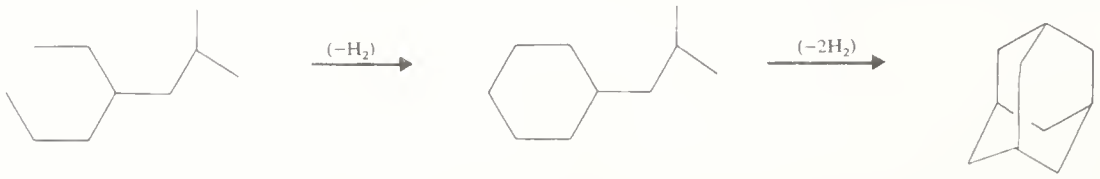


Figure 24 Conversion of an acyclic precursor into adamantane

visualized and the end result is exactly the same as in the strain-free isomer approach, *i.e.* the strain energy is defined as the difference between the heat of formation and the sum of the group increments for the molecule's constituent groups. The choice of group increments is, however, less clear cut. The simple CRSE approach uses normal acyclic alkane group increments, $(CH_3) = -42.34$; $(CH_2) = -20.59$; $(CH) = -7.32$; $(C) = -0.25$, though, as we emphasized in the discussion on skew separate and single conformation group increments, there are reservations as to the applicability of such multi-conformation increments with implicit skew corrections to cyclic molecules. The single conformation increments of Schleyer *et al.*,[66] $(CH_3) = -42.05$; $(CH_2) = -21.46$; $(CH) = -9.04$; $(C) = -1.26$, present a more precise picture of strain energies and provide a more rigorous approach to the question of using acyclic models to estimate strain energies of monocyclic and polycyclic alkanes; SCSE values for cyclopropane to cycloheptadecane are given in Table 19; included also are the experimental and calculated heats of formation, CRSE values, and experimental cyclization enthalpies. The sources of strain in some individual members of the series will now be examined.

TABLE 19

Experimental and Calculated (kJ mol^{-1}) Gas-phase Heats of Formation. Cyclization Energies and Strain Energies for Unsubstituted Cycloalkanes, C_nH_{2n}

	$\Delta H_f^\circ(g)$						
n	*Exp.*[a]	*EAS*[b]	*MM1*[b]	*MM2*[c]	ΔH_{cycl}°[a]	*CRSE*[a]	*SCSE*[a]
3	+53.26				+157.2	115.0	117.6
4	+28.37	+24.2	+23.1	+26.4	+155.4	110.7	114.2
5	−77.2	−76.9	−75.7	−76.4	+69.7	25.8	30.1
6	−123.4	−122.8	−125.2	−123.6	+43.6	0.1	5.3
7	−118.03	−118.2	−119.2	−116.6	+69.6	26.1	32.2
8	−124.4	−122.0	−122.4	−123.5	+84.2	40.3	47.3
9	−132.8	−128.4	−130.8	—	+95.9	52.5	60.3
10	−154.3	−146.1	−156.5	−154.8	+95.2	51.6	60.3
11	−179.4	−172.0	−181.1	—	+91.5	47.1	59.7
12	−230.2	−208.2	−219.5	—	+59.5	16.9	27.3
13	−246.4				+65.0	21.3	32.6
14	−239.0				+92.9	49.3	61.4
15	−301.4				+51.2	7.4	20.5
16	−321.7				+54.1	7.7	21.7
17	−364.3				+29.5	−14.3	0.5

[a] Data from Ref. 54. [b] Ref. 33. [c] Ref. 76.

(*i*) *Cyclopropane*

The cause of strain in cyclopropane (SCSE = 117.6 kJ mol^{-1}) is readily apparent: with CCC bond angles of 60° this necessarily planar molecule exhibits severe angle distortion from the normal tetrahedral value, and the hydrogen atoms are perfectly eclipsed. In

molecular orbital terms the angle strain arises from the combination of atomic orbitals on carbon which are not directed along the C—C vector, but rather outside it. This type of bond (sometimes referred to as a bent bond) is less effective than that involving fully directed sp^3–sp^3 orbitals. A detailed account of the physical manifestations of strain in cyclopropane has been given by Ferguson[79] and by Liebman and Greenberg.[77]

(ii) Cyclobutane

The strain energy of cyclobutane is comparable with that of cyclopropane and the cause again is severe angle distortion. The heat of formation of cyclobutane predicted by the MM2 force field agrees very closely with the experimental value. Cyclobutane adopts a non-planar structure in which 1,2- and 1,3-non-bonded repulsions are minimized, and the barrier to planarity is about 6 kJ mol^{-1}. A further source of strain in cyclobutane is the presence of only two 1,3-carbon–carbon stabilizing interactions for four CH_2 groups. In larger rings there is one such interaction for each CH_2 group.[80]

(iii) Cyclopentane

A planar, regular cyclopentane has a CCC angle of 108°, only 1.5° from the normal tetrahedral angle. However, cyclopentane, whose experimental heat of formation is reproduced rather well by the EAS,[33] MM1,[34] and MM2[76] calculations, has an SCSE value of 30.1 kJ mol^{-1}. The origin of this strain energy clearly cannot be angle strain. However, cyclopentane, like cyclobutane, contains C—C and C—H non-bonded repulsions and although it is not possible to assign a value to the staggered–eclipsed energy difference for a cyclic CH_2—CH_2 group, a value of 10–11 kJ mol^{-1} can be deduced from the strain energy of planar cyclopentane if torsional strain is taken to be the only source of strain energy. The corresponding barrier in ethane is 12 kJ mol^{-1} and that in propane 14 kJ mol^{-1}; note that the butane barrier of 20 kJ mol^{-1} is not applicable to a cyclic molecule owing to the presence of skew interactions. By relaxing from a planar conformation the strain in cyclopentane is not eliminated, merely lessened.

(iv) Cyclohexane

Is cyclohexane a strained or strain-free system? The CRSE approach regards cyclohexane as strain free whereas the SCSE value is 5.3 kJ mol^{-1}. The problem of identifying the elements of strain in the chair conformation of cyclohexane becomes important when discussing the strain energy of bridged ring molecules which contain CCC bond angles close to the tetrahedral angle and bonds in the staggered arrangement, *e.g.* adamantane. It now seems clear that the question of strain in such molecules can only be interpreted in terms of single-conformation, skew-free increments (*i.e.* SCSE increments). The coincidence that the normal, multi-conformation CH_2 increment successfully predicts the heat of formation of cyclohexane has obscured the nature of cyclohexane strain energy. The small strain in cyclohexane arises in part from across-the-ring hydrogen–hydrogen interactions which are repulsive. Consequently, the molecule relaxes from a perfect chair conformation to a flatter structure. The minimum-energy structure is thus a compromise between the relief of non-bonded strain by the ring-flattening process and the increase in torsional distortion associated with moving away from ideal tetrahedral geometry. The inability of cyclohexane rings to relax in this way in caged structures such as adamantane is an important factor in the strain energies of such systems.

(v) The 'medium-ring hump'

The SCSE values in Table 19 show a rapid decline in going from cyclopropane to cyclohexane. After cyclohexane, the strain energies increase again, reaching a maximum

at cyclononane and cyclodecane, and then declining to an almost constant value for rings larger than cyclododecane. The strain energies and cyclization enthalpies for the C_9–C_{13} cycloalkanes are in fact estimates since the $\Delta H_f^\circ(g)$ values are based on assumed heats of vaporization or sublimation which may be in error by 10 kJ mol^{-1} or more. Nevertheless, there is little doubt that the medium-ring cycloalkanes are more strained than cyclohexane and cyclododecane. The causes of this extra strain have already been discussed.

(*vi*) *Molecular mechanics calculations on cycloalkanes*

Most simple molecular mechanics methods are applicable to cyclobutanes and larger rings. The large angle deviation from the tetrahedral value in cyclopropane is outside the range of the bending functions used for larger rings. Boyd[75] and Allinger[76] have used a separate set of parameters for four-membered rings in order to achieve satisfactory results, and Schleyer[33] employed a modified bending function at high deformations from the tetrahedral value. The predicted heats of formation of the C_5–C_8 cycloalkanes show generally good agreement with the experimental values (Table 19). Two problems arise with larger rings. The first is the lack of reliable experimental data and the second is that of finding the correct minimum-energy conformation of the molecule. In such cases, the experimental $\Delta H_f^\circ(g)$ value refers to an equilibrium mixture of conformations, and the molecular mechanics value should include contributions from energetically accessible conformations.

(*vii*) *Strain energies of polycyclic alkanes. The* Σ*RSE approach*

Most of the available thermochemical data for polycyclic alkanes are given in Table 20. Strain energies and molecular mechanics predictions of heats of formation are given in Table 21. Qualitatively, one finds that polycyclic systems containing small rings have high strain energies. The simplest way of estimating strain energies of a polycyclic system is to sum the strain energies of the component rings. This ΣRSE approach represents a first approximation of the total strain energy which in simple bicyclic cases such as cyclopropylcyclopropane can be quite accurate. There is an inconsistency, however, in the way ΣRSE treatments operate. Consider bicyclo[4,1,0]heptane and bicyclo[2,2,1]heptane. The former is composed of one six-membered ring and one three-membered ring whereas the latter has two five-membered rings and a six-membered ring held in the boat conformation. Thus, although the compounds are both bicycloheptanes, we sum two ring strains for the former and three ring strains for the latter. This approach has been used by Cox and Pilcher for cubane and by Schleyer for adamantane. The ΣRSE approach provides a useful first estimate of polycyclic strain energies but, as the data show, these are only approximations. There is little to choose between ΣRSE and ΣSCSE (single conformation strain energies), the difference between observed strain energies and ΣRSE values being roughly equal in both systems.

The conventional ring strain in cyclohexane is essentially zero. The extension of the CRSE approach to *trans*-decalin and *trans,cisoid,trans*-perhydroanthracene leads to negative strain energies, −2.7 and −8.0 kJ mol^{-1}, respectively. These molecules provide the first indications that the CRSE approach is deficient when applied to fused and bridged cyclohexyl systems. Schleyer considered the adamantane case in detail and attributed the strain in this molecule to steric crowding and angle strain, despite the fact that the CCC angles are close to the 'ideal' value, which they are not in unstrained alkanes. The single conformation approach avoids negative strain in *trans*-decalin and in *trans,cisoid, trans*-perhydroanthracene but is unable to account for the magnitude of the strain in adamantane and its derivatives. To understand fully the origins of strain in adamantane we must examine the relaxation process whereby strain in cyclohexane is relieved. In cyclohexane, the across-the-ring 1,3-diaxial H · · · · · H interactions are relieved by the

TABLE 20

Gas-phase Heats of Formation of Some Polycyclic and Bridged-ring Alkanes (kJ mol^{-1})

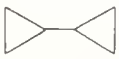
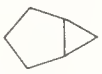
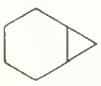
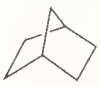
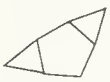
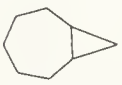
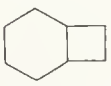
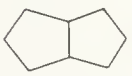
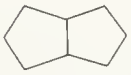
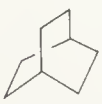
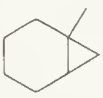
Compound	*Structure*	ΔH_f°(g)
Bicyclo[1,1,0]butane[a]		+217.2
Spiro[2,2]pentane[a]		+185.14
Bicyclo[2,1,0]pentane[b]		+158.2
Cyclopropylcyclopropane[a]		+129.3
Bicyclo[3,1,0]hexane[c]		+38.9
Bicyclo[4,1,0]heptane[c]		+1.7
Norbornane[d]		−52.7
1-Methylbicyclo[3,1,0]hexane[e]		+1.5
Nortricyclane[d]		+69.1
Quadricyclane[d]		+253.3
Tricyclo[3,1,1,$0^{3,4}$]heptane[b]		+149.2
Bicyclo[5,1,0]octane[c]		−16.1
cis-Bicyclo[4,2,0]octane[c]		−26.8
cis-Bicyclo[3,3,0]octane[c]		−92.2
trans-Bicyclo[3,3,0]octane[c]		−66.0
Bicyclo[2,2,2]octane[f]		−99.1
1-Methylbicyclo[4,1,0]heptane[e]		−20.8
Cubane[a]		+622.2

TABLE 20 (*continued*)

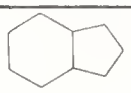
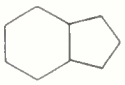
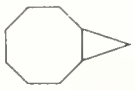
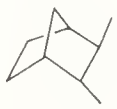
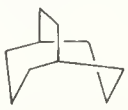
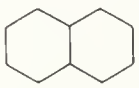
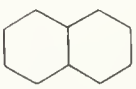
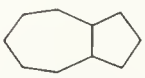
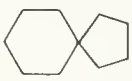
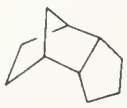
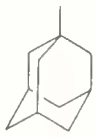
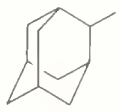
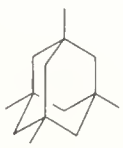
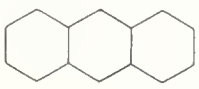
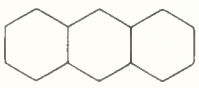
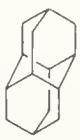
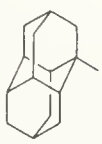
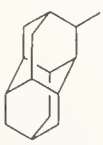
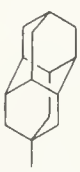
Compound	*Structure*	$\Delta H_f^\circ(g)$
cis-Bicyclo[4,3,0]nonane[a]		−127.1
trans-Bicyclo[4,3,0]nonane[a]		−131.5
cis-Bicyclo[6,1,0]nonane[c]		−31.8
1,4-Dimethylnorbornane[e]		−128.2
trans-2,3-Dimethylnorbornane[e]		−107.6
Bicyclo[3,3,1]nonane[g]		−127.6
Bicyclo[3,3,2]decane[g]		−105.9
cis-Bicyclo[4,4,0]decane[a]		−169.2
trans-Bicyclo[4,4,0]decane[a]		−182.1
cis-Bicyclo[5,3,0]decane[a]		−130.1
Spiro[5,4]decane[h]		−145.4
endo-Tetrahydrodicyclopentadiene[a]		−60.2
Perhydroquinacene[i]		−102.4
Adamantane[j,k,l,m]		−137.9 −128.2 −132.9 (recommended) −133.5
Protoadamantane[m]		−85.9
Spiro[5,5]undecane[h]		−190.5
Bicyclo[3,3,3]undecane[n] (Manxane)		−89.0

TABLE 20 (*continued*)

Compound	*Structure*	$\Delta H_f^\circ(g)$
1-Methyladamantane[m]		−169.7
2-Methyladamantane[m]		−149.2
1,3,5,7-Tetramethyladamantane[m]		−281.0
trans,cisoid,trans-Perhydro-anthracene[a]		−243.2
trans,transoid,trans-Perhydro-anthracene[a]		−220.6
Diamantane[o]		−144.5
1-Methyldiamantane[m]		−166.7
3-Methyldiamantane[m]		−157.3
4-Methyldiamantane[m]		−182.1

[a] Ref. 54. [b] M. P. Kozima, 'Current Problems in Physical Chemistry,' Moscow University Press, 1976, vol. 9, p. 198. [c] S. Chang, D. McNally, S. Shary-Tehrany, M. J. Hickey, and R. H. Boyd, *J. Amer. Chem. Soc.*, 1970, **92**, 3109. [d] Solid heat of formation from Ref. 54 combined with heat of sublimation from H. K. Hall, Jr., C. D. Smith, and J. M. Baldt, *J. Amer. Chem. Soc.*, 1973, **95,** 3197. [e] M. P. Kozina, L. P. Timofeeva, S. M. Skuratov, N. A. Belikova, E. M. Milvitskaya, and A. F. Plate, *J. Chem. Thermodynamics*, 1971, **3**, 563. [f] S. S. Wong and E. F. Westrum, Jr., *J. Amer. Chem. Soc.*, 1971, **93**, 5317; E. F. Westrum, Jr., W.-K. Wong, and E. Morawetz, *J. Phys. Chem.*, 1970, **74**, 2542. [g] W. Parker, W. V. Steele, and I. Watt, *J. Chem. Thermodynamics*, 1977, **9**, 307. [h] Ref. b and D. J. Subach and B. J. Zwolinski, *J. Chem. Thermodynamics*, 1975, **7**, 493; *J. Chem. Eng. Data*, 1975, **20**, 232. [i] T. Clark, T. McO.Knox, H. Mackle, and M. A. McKervey, *J.C.S. Chem. Comm.*, 1975, 666. [j] M. Mansson, N. Rapport, and E. F. Westrum, Jr., *J. Amer. Chem. Soc.*, 1970, **92,** 7296. [k] R. S. Butler, A. S. Carson, P. G. Laye, and W. V. Steele, *J. Chem. Thermodynamics*, 1971, **3**, 277. [l] R. H. Boyd, S. N. Sanwal, S. Shary-Tehrany, and D. McNally, *J. Phys. Chem.*, 1971, **75,** 1264. [m] T. Clark, T. McO. Knox, H. Mackle, M. A. McKervey, and J. J. Rooney, *J. Amer. Chem. Soc.*, 1975, **97**, 3835. [m] W. Parker, W. V. Steele, W. Stirling, and I. Watt, *J. Chem. Thermodynamics*, 1975, **7**, 795. [o] Value redetermined since data in Ref. m, T. Clark, T. McO.Knox, H. Mackle, M. A. McKervey, and J. J. Rooney, *J. Amer. Chem. Soc.*, in press.

TABLE 21

Experimental Strain Energies and Calculated Heats of Formation from Molecular Mechanics (kJ mol^{-1})

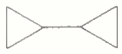
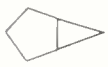
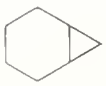
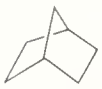
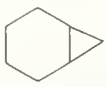
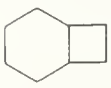
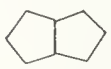
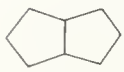
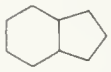
	CRSE	Σ*CRSE*	*SCSE*	Σ*SCSE*	ΔH_f°(g) *EAS*[a]	*MM1*[a]	*MM2*[b]
	273.0	230.0	278.2	235.2			
	267.7	230.0	272.2	235.2			
	234.6	225.7	240.7	231.8			
	226.3	230.0	233.2	235.2			
	135.9	140.8	142.8	147.7			
	119.3	115.1	127.1	122.9			
	64.9	75.5	72.7	89.3	−54.4	−56.4	−53.8
	133.8	140.8	139.7	147.7			
	160.3	192.4	169.6	207.9			
	317.8	392.3	329.0	409.6			
	240.3	255.8	249.7	265.3			
	121.1	141.1	130.7	149.8			
 *cis*	111.4	110.8	120.0	119.5	−18.4	−14.5	−24.0
 *cis*	46.0	51.6	54.6	60.2	−94.6	−86.5	−95.3
 *trans*	72.2	51.6	80.8	60.2	−66.4	−64.8	−65.8
	39.1	71.7	47.7	87.3	−92.7	−101.3	−95.3
	132.1	115.1	138.9	122.9			
	680.8	664.2	694.5	685.2	+621.3	+626.2	+622.7
 *cis*	31.7	25.9	41.2	35.4	−127.1	−125.3	−127.4

TABLE 21 (*continued*)

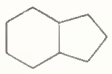
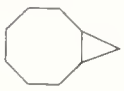
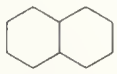
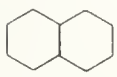
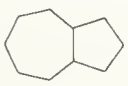
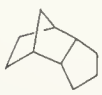
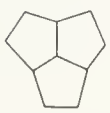
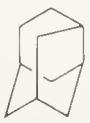
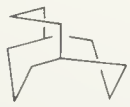
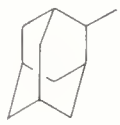
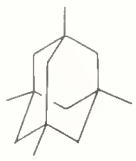
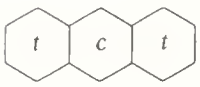
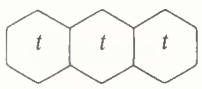
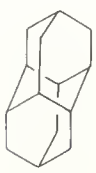
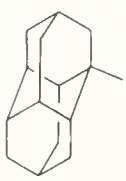
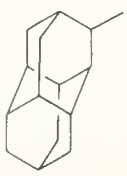
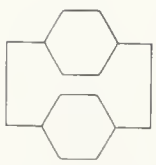
		CRSE	Σ*CRSE*	*SCSE*	Σ*SCSE*	*EAS*	*MM1*	*MM2*
	*trans*	27.3	25.9	36.8	35.4	−131.7	−130.2	−132.3
		127.0	155.3	136.5	164.9			
		59.9	75.5	65.7	89.3	−134.4	−134.3	
		54.0	75.5	61.5	89.3	−110.2	−107.6	
		31.2	40.5	40.7	57.9	−128.2	−127.1	
		73.5	92.5	83.9	111.7	−109.5	−105.4	
	*cis*	10.2	0.2	20.6	10.6	−170.3	−172.4	−171.7
	*trans*	−2.7	0.2	7.7	10.6	−181.7	−183.2	−183.1
	*cis*	49.3	51.9	59.7	62.3			
		40.2	25.9	49.0	35.4	−155.6	−155.1	
		92.6	101.3	104.7	119.4	−51.5	−46.4	
		50.4	77.4	62.5	90.3	−99.3	−82.6	−92.7
		19.3	0.4	31.4	21.2	−136.0	−141.5	−132.0
		66.9	52.1	79.0	72.9	−88.4	−94.7	−86.7
		15.7	0.2	25.4	10.6	−195.8	−190.9	
		111.1	120.9	122.2	141.9	−95.4	−105.5	

TABLE 21 (*continued*)

	CRSE	Σ*CRSE*	*SCSE*	Σ*SCSE*	*EAS*[a]	*MM1*[a]	*MM2*[b]
	18.4	0.4	29.5	21.2	−175.0	−179.5	−168.4
	32.7	9.2	45.4	29.4	−158.7	−163.3	
	12.9	0.4	21.0	21.2	−294.0	−293.8	−278.1
	−8.0	0.3	7.6	15.9			−243.1
	14.6	24.0	30.2	39.7			−217.7
	37.6	0.7	56.6	37.1	−156.4	−159.5	−143.5
	50.7	9.1	68.7	45.3	−185.9	−182.3	
	53.9	9.1	73.4	45.3	−182.1	−179.5	
	35.3	0.7	53.3	37.1	−197.5	−195.9	
	120.3	81.6	137.6	112.8			

[a] Ref. 33. [b] Ref. 76.

ring-flattening process and the final equilibrium structure is thus a compromise in which the relief of 1,3-diaxial interactions is balanced by the extra torsional strain associated with the ring-flattening process. Pople *et al.*[38] have allowed cyclohexane to relax from ideal geometry to equilibrium geometry using *ab initio* molecular orbital theory at the minimal basis set level and obtained a relaxation energy of 2.9 kJ mol^{-1}. The relaxation energy can be estimated from the thermochemistry of the hypothetical gas-phase reaction in Figure 25. In this reaction, two moles of adamantane are converted into one mole each of diamantane and cyclohexane. The only difference between reactants and products is the freedom of the product cyclohexane to relax to the equilibrium energy and geometry. The experimental enthalpy for this reaction is -1.6 kJ mol^{-1}; the molecular mechanics predictions are -7.2 (EAS),[33] -1.7 (MM1),[34] and -3.1 (MM2)[76] kJ mol^{-1}. Using the ΣSCSE approach the strain energy of every cyclohexane ring in adamantane or diamantane is 7.9 kJ mol^{-1}, compared with 5.3 kJ mol^{-1} for cyclohexane itself. The strain energy in diamondoid molecules can therefore be attributed entirely to the restriction of the constituent cyclohexane rings to non-equilibrium conformations. The origin of the strain is steric crowding but it is manifested in the different bond angles in adamantane and cyclohexane.

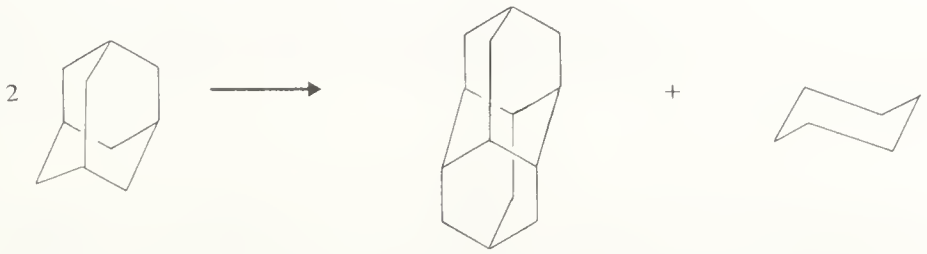


Figure 25 Hypothetical conversion of adamantane into diamantane and cyclohexane

Molecular mechanics calculations have been applied extensively to polycyclic alkanes; indeed, at present, they represent the only reliable method available for predicting structures and energies. The EAS and MM1 force fields are reliable within 10–15 kJ mol^{-1} limits but suffer from the limitation that they were parameterized to fit experimental data for monocyclic and acyclic molecules. More experimental $\Delta H_f^\circ(g)$ data on polycyclic systems are now available and the most recent force field, MM2, gives excellent agreement for a range of such systems.

2.1.7 PREPARATION OF ACYCLIC ALKANES

Because of the relatively wide differences in boiling points of the lower members of the homologous series (see Table 6), methane, ethane, propane, n-butane, isobutane, and the isomeric pentanes may be obtained by careful fractional distillation of natural gas or petroleum. Although some other pure alkanes may be obtained from petroleum by a combination of physical methods, in general, if a pure alkane is required, it must be synthesized from a functionalized precursor. The present section is concerned with synthetic methods which are of general application to laboratory preparations. For isomerization and alkylation reactions which may be useful for the preparation of other alkanes, see Section 2.1.9.4.

2.1.7.1 Alkanes from olefins by reduction

Alkanes are readily available from olefins by reduction.[81] Olefins can be prepared by a wide variety of procedures (See Section 2.2.2) and hydrogenation of an olefin is frequently

important as the last stage in the synthesis of an alkane. Catalytic hydrogenation, either homogeneously or heterogeneously, is by far the most popular procedure.[81] Most olefins will add hydrogen over a hydrogenation catalyst at temperatures between 0 and 300 °C. Typical catalysts for use under heterogeneous conditions are platinum, palladium, nickel, rhodium, and copper chromite.[81] Platinum and palladium have been used as the finely divided metals, as oxides (which are reduced to the metal under the conditions of hydrogenation), and in finely divided form on supports such as charcoal, calcium carbonate, kieselguhr, barium sulphate, and silica gel. The most commonly used heterogeneous catalysts are platinum oxide (Adams catalyst) and Raney nickel. Highly active catalysts can be obtained by reduction of metal salts with sodium borohydride.[82] Finely divided rhodium, platinum, and palladium metals can be obtained in this way and used directly as catalysts or adsorbed on carbon prior to use.

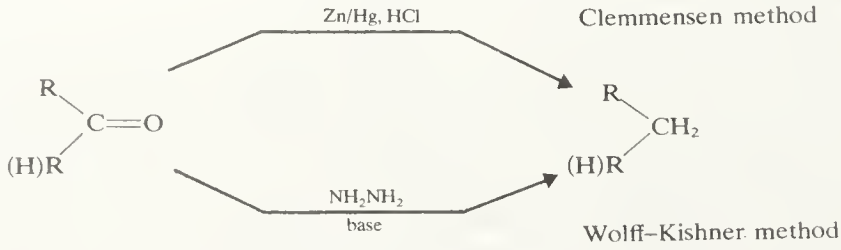
Of more recent vintage are the homogeneous hydrogenation catalysts, the archetype of which is chlorotris(triphenylphosphine)rhodium(I), discovered by Wilkinson.[83] This soluble catalyst is effective for the addition of hydrogen to olefins at room temperature in a variety of solvents; terminal olefins are hydrogenated more rapidly than are internal olefins. Homogeneous catalysts of this type are particularly useful for the synthesis of specifically labelled alkanes. Two deuterium atoms can be introduced in a 1,2-relationship, since the extensive hydrogen–deuterium scrambling often encountered with heterogeneous catalysts is not normally observed. Thus, dec-1-ene can be converted into 1,2-dideuteriodecane (equation 7).[84]

$$n\text{-}C_8H_{17}CH{=}CH_2 \xrightarrow[D_2]{(Ph_3P)_3RhCl} n\text{-}C_8H_{17}CHDCH_2D \qquad (7)$$

Amongst reagents that are generally useful for the non-catalytic reduction of alkanes are di-imide (HN=NH)[85] and sodium dissolved in hexamethylphosphoric triamide.[86] Di-imide, generated *in situ* from oxidation of hydrazine with one of several oxidants, or elimination from an acyl or sulphonyl hydrazide, or decomposition of azodicarboxylic acid, transfers its two hydrogen atoms in a *cis* fashion to an *alkane via* a non-polar transition state with concomitant loss of nitrogen. It is thus useful for the introduction of deuterium atoms in a 1,2-relationship. Sodium in HMPT containing a proton donor reduces hex-1-ene to n-hexane in 98% yield.[86,87]

2.1.7.2 Alkanes from aldehydes and ketones

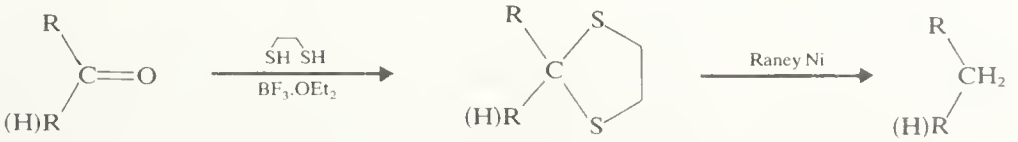
The carbonyl group of aldehydes and ketones can be converted readily into a methylene group in a variety of synthetically useful ways. The most common methods are the Clemmensen[88] and Wolff–Kishner[89] reductions (equation 8).



(8)

The Clemmensen procedure is conducted under strongly acidic conditions whereas the Wolff–Kishner procedure is conducted under strongly basic conditions. The two thus complement each other in that aldehydes and ketones which are sensitive to acid but not to base are more appropriately reduced by the Wolff–Kishner method whereas when the reverse holds the Clemmensen conditions should be used. In the Clemmensen method, the aldehyde or ketone is converted to an alkane containing the same number of carbon atoms by heating with an excess of amalgamated zinc and concentrated hydrochloric acid; co-solvents such as acetic acid or toluene are frequently used. The oxygen atom is lost as

water from a partially reduced intermediate bound to zinc; the corresponding alcohols are not intermediates in the overall process since they are not reduced to alkanes under the Clemmensen conditions. In its original form, the Wolff–Kishner procedure involved conversion of the carbonyl compound into its hydrazone or semicarbazone which was then treated with potassium hydroxide at 180–200 °C in a sealed tube or autoclave. This procedure has now been largely replaced by the Huang–Minlon modification in which a mixture of the carbonyl compound, excess of hydrazine hydrate, sodium or potassium hydroxide, and diethylene glycol are first heated under reflux. Water and excess of hydrazine are then allowed to distil from the mixture and the temperature is raised to *ca.* 200 °C until evolution of nitrogen is complete. The mechanism is believed to involve the formation of an alkyl di-imide whose base loses nitrogen to form a carbanion which is protonated by the solvent. The use of dimethyl sulphoxide as the solvent allows the reduction to be carried out at room temperature.[90] The reaction is also facilitated by the use of potassium t-butoxide under anhydrous conditions in boiling toluene.[91] The Wolff–Kishner procedure works well for all but the most hindered aldehydes and ketones. The Clemmensen procedure is much more sensitive to steric hindrance. The reduction of tosylhydrazones by lithium aluminium hydride or sodium borohydride also converts carbonyl groups to methylene groups.[92] This procedure is related to the Wolff–Kishner procedure in that an alkyl di-imide is thought to be an intermediate. Thioacetals, obtained from aldehydes and ketones and a thiol under acid catalysis, are smoothly converted into the corresponding methylene compound by Raney nickel.[93] The ethylenedithio derivatives are frequently used (equation 9).



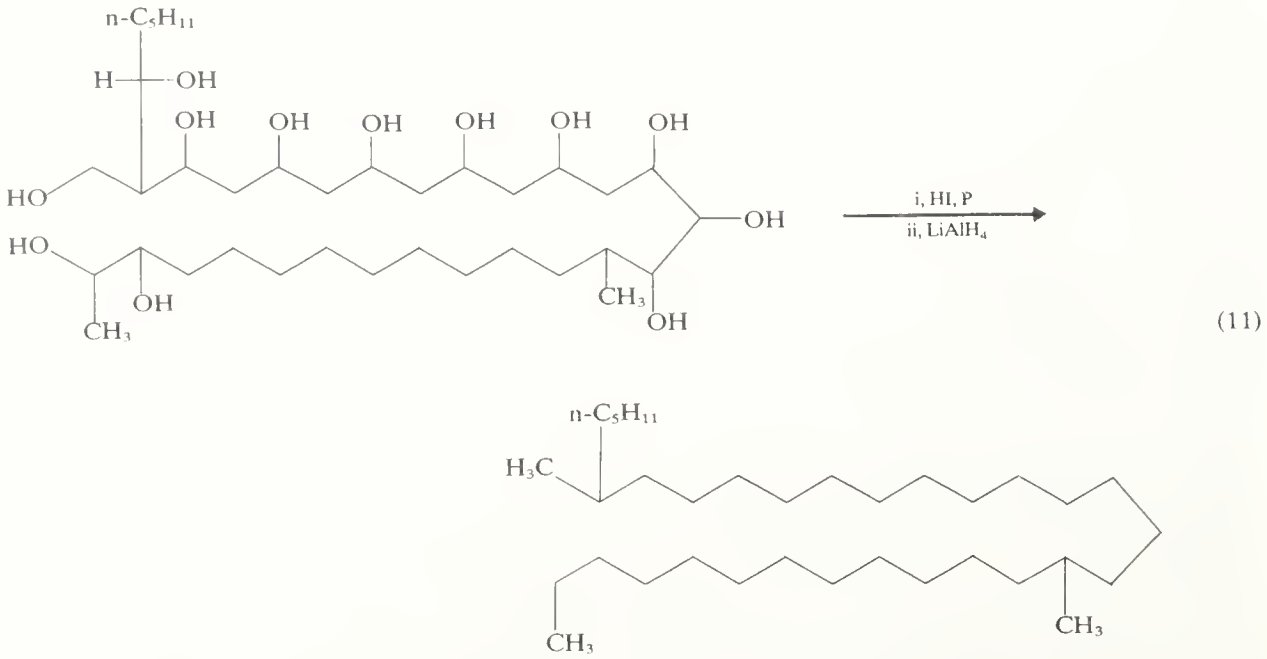
(9)

The ability of chlorotris(triphenylphosphine)rhodium(I) to abstract carbon monoxide from aldehydes serves as a useful synthetic procedure for alkanes containing one carbon atom less than the aldehyde.[94] However, as the following example illustrates, the alkane may be contaminated with olefinic products (equation 10).

$$CH_3(CH_2)_5CHO \xrightarrow{(Ph_3P)_3RhCl} \underset{(80\%)}{CH_3(CH_2)_4CH_3} + \underset{(10\%)}{CH_3(CH_2)_3CH{=}CH_2} + \underset{(10\%)}{CH_3(CH_2)_2CH{=}CHCH_3} \quad (10)$$

2.1.7.3 Alkanes from alcohols and alkyl halides

Alkanes are not readily obtainable from alcohols directly. Reduction of alcohols is usually effected indirectly. The alcohol may be converted into an alkene by dehydration and one of the hydrogenation methods described above then applied to give the alkane. Where structural considerations permit, the dehydration works well for tertiary and secondary alcohols, and this route is widely used. Alternatively, the alcohol is converted into a derivative in which the carbon–oxygen bond is more labile and the derivative is then subjected to reduction. Derivatives which have been used extensively in this way include halides, methanesulphonates, and toluene-*p*-sulphonates; bromides and iodides are usually preferred to chlorides. The reducing agents used include lithium aluminium hydride,[95] lithium triethylborohydride,[96] sodium borohydride,[97] and sodium cyanoborohydride;[98] the latter two work best in DMSO and HMPT, respectively. This approach can be used with polyhydroxy compounds. In a structural study of the antifungal macrolide antibiotic fungichromin, Cope *et al.* converted a polyol fragment into a polyiodo compound with red phosphorus in hot hydriodic acid (equation 11). Reduction of the polyiodo compound with lithium aluminium hydride gave the homogeneous C_{34} alkane in 13% yield.[99] This reduction was also performed successfully on the corresponding polytoluene-*p*-sulphonate.



(11)

Tri-n-butyltin hydride and triphenyltin hydride are specific reducing agents for alkyl halides whose order of reactivity is RI > RBr > RCl > RF.[100] These reductions can be carried out in hydrocarbon solvents and mechanistic studies suggest a radical chain reaction. Older direct methods which have been largely superseded by the techniques described above involve the use of reducing agents such as sodium, aluminium amalgam, zinc dust, zinc–copper couple, and magnesium. The last named metal involves the formation of the Grignard reagent with subsequent reaction of the organometallic intermediate with water or dilute acid. n-Pentane has been prepared in this way; n-butyl ether was used as solvent in this case rather than diethyl ether to permit separation of the product (b.p. 36 °C) from the solvent (b.p. 141 °C) by distillation.[101] n-Hexadecane has been obtained from the 1-iodo compound in 85% yield by treatment with zinc dust in glacial acetic acid containing dry hydrogen chloride.[102] Another useful technique for reduction of alkyl halides is catalytic hydrogenation, a typical catalyst being palladium on calcium carbonate in the presence of potassium hydroxide.[81a]

With the exception of decarbonylation of aldehydes using a soluble rhodium complex, all the synthetic methods discussed so far are for reductions in which the precursor and alkane contain the same number of carbon atoms. A number of procedures are available in which the final alkane contains more carbon atoms than does the precursor. These procedures require the formation of carbon–carbon single bonds, most directly by the coupling together of two alkyl groups. There are numerous variations on this procedure, some of which involve organometallic intermediates (see Table 22). One of the earliest is the Wurtz reaction in which alkyl groups are coupled by treatment of an alkyl halide with metallic sodium. The reaction works best with primary alkyl iodides and it has been used to prepare hectane ($C_{100}H_{202}$) from 1-iodopentacontane.[103] The yields are generally poor, however, and the desired coupled product may be contaminated with the alkene and alkane corresponding to the alkyl halide (direct reduction). Very poor yields of coupled product are obtained by application of the Wurtz procedure to secondary halides. The coupling of two different alkyl halides by the Wurtz procedure is impractical; the organosodium intermediates, being so reactive, couple as they are formed and three coupled products are obtained in addition to the usual by-products. The reaction is thus limited to the synthesis of constitutionally symmetrical alkanes, R—R. Coupling of Grignard reagents has also been used to prepare constitutionally symmetrical alkanes from alkyl halides. The Grignard reagent is prepared and treated with a metal salt. Cobalt,[104] silver,[105] and thallium[106] salts have been used; some examples of this procedure are given in Table 22. Pyrophoric lead induces a Wurtz-type reaction with alkyl bromides,

giving symmetrically coupled products in good yield.[107] Alkylation of organometallic reagents with alkyl halides, a reaction formally analogous to the Wurtz coupling reaction, has been applied to the synthesis of a variety of constitutionally unsymmetrical and symmetrical alkanes. For example, alkylation of methylmagnesium chloride with t-butyl chloride gives neopentane in 50% yield.[108] With alkyl-lithiums, the simple alkylation product is usually accompanied by products formed by disproportionation and symmetrical coupling.

TABLE 22

Alkanes from Alkyl Halides, Olefins, and Carboxylic Acids *via* Coupling Reactions

1. Wurtz coupling:

$$C_{50}H_{101}I \xrightarrow{Na} C_{100}H_{202}$$

2. Grignard coupling:

$$MeCH_2CH_2CH_2MgCl \xrightarrow{Ag(I)\ salt} Me(CH_2)_6Me$$

$$MeCH_2CH_2\underset{\displaystyle Me}{\underset{|}{C}}HMgBr \xrightarrow{Tl(I)\ salt} MeCH_2CH_2\underset{\displaystyle Me}{\underset{|}{C}}H\overset{\displaystyle Me}{\overset{|}{C}}HCH_2CH_2Me$$

3. Grignard alkylation:

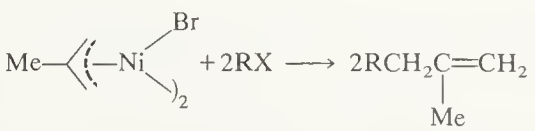
$$MeMgCl + Me_3CCl \longrightarrow Me_4C$$

4. Alkylation of lithium dialkylcopper reagents, R_2CuLi:

$$MeLi + CuI \longrightarrow Me_2CuLi \xrightarrow{n\text{-Octyl iodide}} Me(CH_2)_7Me$$

$$MeCH_2\underset{\displaystyle Me}{\underset{|}{C}}HLi + CuI \longrightarrow (MeCH_2\underset{\displaystyle Me}{\underset{|}{C}}H)_2CuLi \xrightarrow{MeBr} MeCH_2\underset{\displaystyle Me}{\underset{|}{C}}HMe$$

5. Alkylation of π-allylnickel complexes:



6. Coupling of trialkylboranes with $AgNO_3$:

$$Me(CH_2)_3CH{=}CH_2 \longrightarrow (Me(CH_2)_5CH_2)_3B \xrightarrow{AgNO_3} Me(CH_2)_{10}Me$$

7. Coupling by Kolbe electrolysis:

$$2R{-}CO_2^- \xrightarrow{anode} R{-}R + 2CO_2$$

A very versatile method for unsymmetrical coupling of two alkyl groups involves the use of organocopper reagents.[109,110] Coupling takes place in the reaction between a lithium dialkylcopper, R^1_2CuLi, and an alkyl halide, R^2X (Table 22). The lithium dialkylcopper reagent is prepared from the appropriate alkyl-lithium and cuprous halide and then treated with the second alkyl halide. For good yields, R^2X should be a primary halide; the alkyl group in the organometallic intermediate may be primary, secondary, or tertiary; examples of this procedure are given in Table 22. A study of the relative rates of reaction of lithium di-n-butylcuprate with a series of organic halides has shown that the relative reactivity of the halides is very similar to that exhibited in S_N2 reactions.[111]

Allyl halides react with nickel carbonyl to give π-allyl complexes of nickel. An important feature of these compounds in synthesis is their ability to react with a wide variety of organic halides to give coupled products (Table 22).[112] The reaction of trialkylboranes with alkaline silver nitrate proceeds *via* coupling of the alkyl groups.[113,114] Isolation of the borane is unnecessary and this sequence provides a synthetic route from olefins to the saturated dimer. Hex-1-ene gives a 79% yield of dodecane with 6% of 5-methylundecane, and 2-methylpent-1-ene gives 4,7-dimethyldecane exclusively (Table 22).

2.1.7.4 Alkanes from carboxylic acids

Alkanes can be obtained from carboxylic acids by direct or indirect methods. Depending on the procedure used, the alkane can have the same number of carbon atoms as the carboxylic acid, or it may have a smaller or larger number of carbon atoms. Procedures in which the number of carbon atoms remains unchanged usually involve reduction of the acid to an alcohol, which is then converted to the alkane using procedures discussed above.

Oxidative decarboxylation of acids provides a route to alkanes containing one less carbon atom than the original acid. Good yields of alkanes (70–80% based on carboxylic acid) have been obtained from the photochemical decarboxylation of primary carboxylic acids by lead tetra-acetate in chloroform. Decarboxylation of secondary acids under the same conditions afford alkanes in moderate yields, while tertiary acids produce olefins and esters.[115] Other decarboxylation reactions giving esters, olefins, and alkyl halides which may be intermediates in alkane synthesis have been reviewed by Sheldon and Kochi.[115] One of these is the Hunsdiecker reaction[81c] in which the carboxylic acid is first converted into an acyl hypohalite which then undergoes thermal decarboxylation to form an alkyl halide. The homolytic decarboxylation of peresters of carboxylic acids has been used to prepare alkanes directly in a few cases.[116]

Carboxylic acids can also be used as direct precursors for alkanes in which an increase in the carbon chain length is required. The most widely used method for this purpose is the Kolbe electrolytic process (Table 22).[117] Electrolysis of the alkali metal salt of a carboxylic acid gives carbon dioxide and an alkane which contains twice as many carbon atoms as the alkyl radical of the acid used. The reaction involves formation of the carboxylate radical. Decarboxylation of this radical gives an alkyl radical which forms the alkane on dimerization. Good yields of alkanes are obtained on electrolysis of fatty acids possessing six or more carbon atoms. The lower members of the series, with the exception of acetic acid, give rather poorer yields and large amounts of olefins, esters, and other by-products are obtained. Long-chain alkyl diacyl peroxides undergo thermal decomposition in the presence of 1,2-diphenylethane, yielding alkanes *via* a homolytic decarboxylation mechanism.

2.1.8 SYNTHESIS OF CYCLIC AND POLYCYCLIC ALKANES

In discussing methods for the synthesis of cyclic and polycyclic alkanes, it is convenient to use two general classifications: (i) methods using precursors in which the desired ring system is already present in a modified form, and (ii) methods in which the key operation is the construction of the desired ring system. In practice, realisation of the objective in (ii) is often followed by application of an appropriate procedure from (i).

In the previous section on synthetic methods for acyclic alkanes we listed standard ways whereby various functional groups can be removed from alkyl halides, olefins, carbonyl compounds, *etc.*, and replaced by hydrogen or by another alkyl group. In the vast majority of cases, these procedures are of such general applicability that it matters little whether or not the alkyl group itself is cyclic or acyclic. The Wolff–Kishner reduction, for example,

usually works equally well with acyclic and cyclic ketones, and the hydrogenation of a carbon–carbon double bond will usually proceed satisfactorily whether or not it is part of a ring system. The latter reaction applies equally well to double bonds which are also part of an aromatic ring system.[81] Many cyclohexane derivatives are conveniently prepared by catalytic hydrogenation of the corresponding benzenoid system using the heterogeneous catalysts discussed in Section 2.1.7.1. In general, more drastic reaction conditions are required for reduction of the benzene nucleus than for isolated double bonds. Benzene and many alkylbenzenes, however, are smoothly hydrogenated under pressure at temperatures in the range 100–300 °C over Raney nickel. Polynuclear aromatics can also be hydrogenated, and decalin, perhydroanthracene, perhydrophenanthrene, and similar fused ring polycycloalkanes can all be obtained in this way.[81]

In this section, attention will be focused on methods of construction of carbocyclic rings, bearing in mind that once the desired ring system has been obtained it may be necessary to remove extraneous functionality by one or other of the methods discussed already for acyclic alkanes.

Many cycloalkanes can be obtained directly by a variety of coupling procedures, one of the earliest of which involved the intramolecular version of the Wurtz-type reaction.[118] In this reaction an α,ω-dihalide is converted into an organometallic intermediate which cyclizes *via* carbon–carbon single bond formation. Treatment, of 1,3-dibromopropane with sodium metal yields cyclopropane inefficiently; better yields are obtained when the metal used is zinc dust. This type of 1,3-elimination has found wide application in the synthesis of some highly strained cyclopropanes, examples of which are given in Table 23. Cyclobutane and some derivatives have also been obtained in this way, but for larger rings, intramolecular coupling of a dihalide with zinc or an alkali metal ceases to be synthetically useful. Whitesides has developed an extremely useful variation of the Wurtz-type reaction.[119] It involves the conversion of the α,ω-dihalide into the di-Grignard reagent which is then treated with a silver(I) salt. An alkylsilver(I) intermediate is formed which decomposes by concerted carbon–silver bond breaking and carbon–carbon bond forming. The reaction occurs under mild conditions to give the cycloalkane in yields which depend on the ring size. Cyclobutane and cyclopentane are obtained in excellent yield; for cyclohexane and cycloheptane the yields are fair; medium-sized rings are formed not at all or only in trace amounts; and cyclododecane is obtained in 10–15% yield. The reaction has been used also for the construction of some bicyclic alkanes; these are shown in Scheme 1.

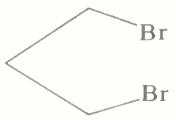
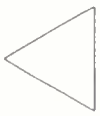
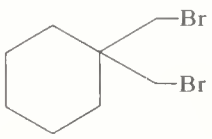
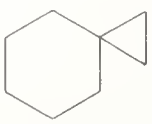
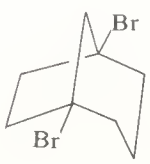
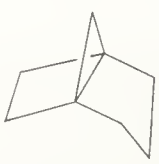
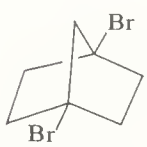
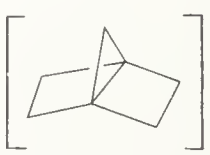
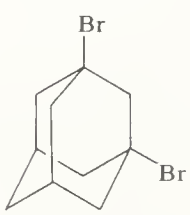
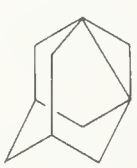
The intermolecular coupling reaction between alkyl halides and π-allylnickel(I) bromides also has its intramolecular counterpart.[120] α,ω-Dibromides of the type shown in Scheme 2 cyclize with nickel carbonyl, forming cyclic olefins which are useful precursors for the corresponding cycloalkane. 12-, 14-, and 18-membered rings were obtained in this way in excellent yield, but the reaction failed for the eight- and ten-membered rings. Some exocyclic olefins are also available by this procedure by varying the structure of the initial α,ω-dibromide as in Scheme 2; these olefins are attractive precursors for 1,4-dimethylcycloalkanes. However, one limitation of these direct coupling procedures is their failure with medium-ring carbocycles.

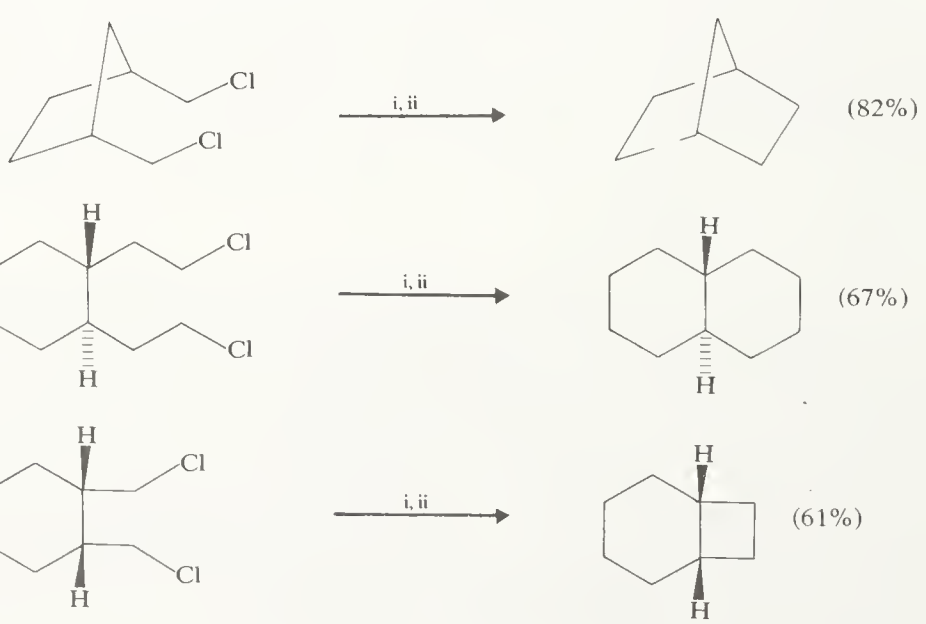
Several methods are available for the construction of oxygenated carbocycles from open-chain diacids, diesters, and dinitriles (Figure 26). These methods provide useful, though more roundabout, routes to cycloalkanes since the oxygen function can usually be replaced by hydrogen using reactions already discussed. These methods are also important in that some of them help fill the gap for medium-ring cycloalkanes which exists in the direct coupling procedures. Dry distillation of the alkaline earth salts of carboxylic acids is a standard reaction for the preparation of dialkyl ketones. The intramolecular version of this reaction may be applied to the synthesis of cyclic ketones through the use of salts of dicarboxylic acids. Cyclopentanones and cyclohexanones are formed quite readily and in high yield. Cyclopentanone may be obtained in 80% yield by dry distillation of adipic acid in the presence of catalytic amounts of barium hydroxide.

Similarly, cycloheptanone can be obtained by pyrolysis of the calcium salt of suberic

TABLE 23

Cyclopropyl Compounds from 1,3-Dihalides

1.		Zn	
2.		Zn	
3.		Zn	
4.		K	
5.		K	
6.		K	



i, Mg, THF; ii, CF_3SO_3Ag

SCHEME 1

Ring size: 14, 16, 18

Ring size: 16, 18

SCHEME 2

acid. Ruzicka and co-workers studied the preparation of cyclic ketones by distillation of a number of different metallic salts of dicarboxylic acids.[121,122] Calcium and barium salts gave good results for formation of five- and six-membered rings only. For larger rings, thorium salts are particularly useful. Table 24 gives a comparison of the yields of various cycloalkanones by pyrolysis of the calcium and thorium salts of dicarboxylic acids. Small amounts of cycloalkanediones are formed as by-products during these pyrolytic reactions. Thus, the 34-membered cycloalkanedione was a by-product in the synthesis of cycloheptadecanone. The Ruzicka synthesis is inherently unfavourable to ring formation, because the reaction occurs in a condensed phase which favours intermolecular as opposed to intramolecular reaction (*i.e.* polymerization rather than cyclization). The ring size *versus* yield data for the Ruzicka synthesis shows an extreme drop in yields on passing from the

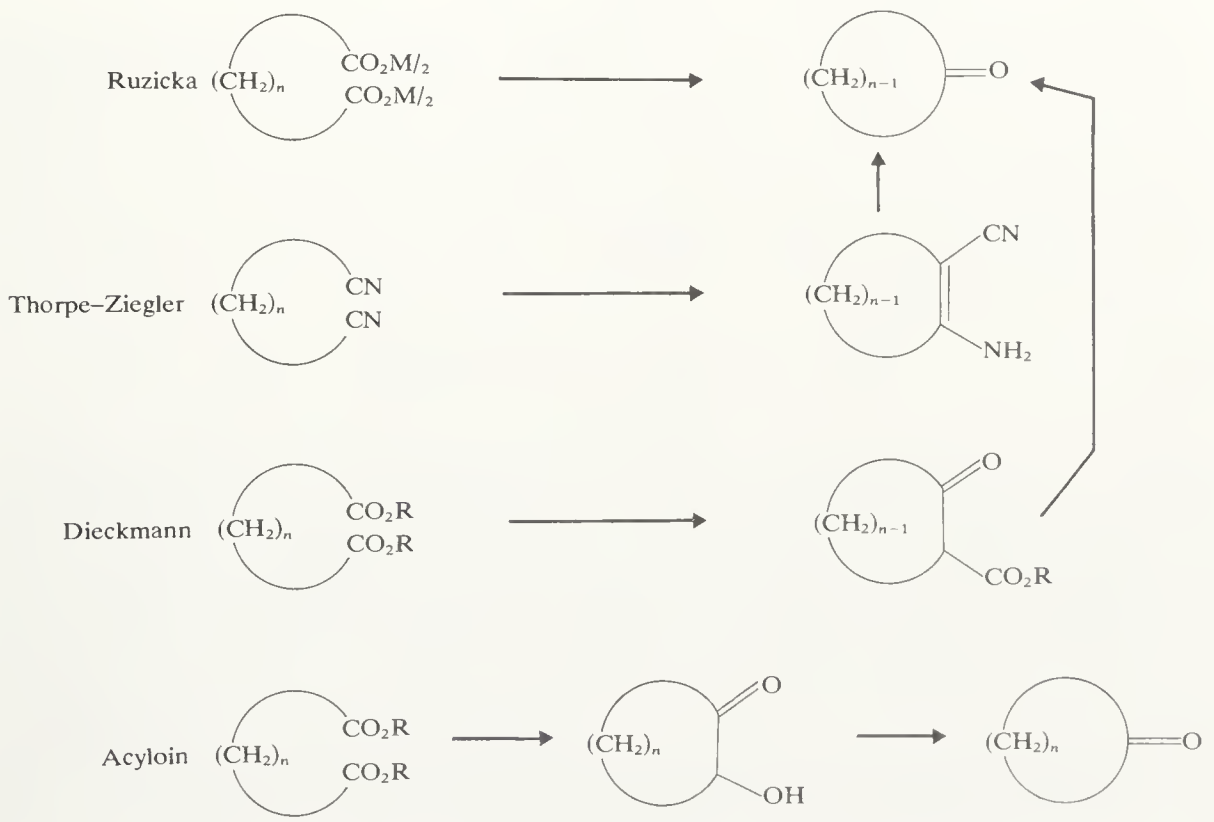


Figure 26 Synthesis of cycloalkanones from acyclic precursors

common- to the medium-sized rings and a very small increase from this minimum to a very low maximum (5%) in the region of the 16-membered ring.

TABLE 24

Cycloalkanes from Pyrolysis of Salts of Dicarboxylic Acids

Size of ring formed	*Yield from pyrolysis of*	
	calcium salt	*thorium salt*
5	45	15
6	40–50	70
7	35	50
8	5	20
9–12	—	1
15–16	—	5

Ideally, cyclization should be carried out at high dilution so that intramolecular reaction (concentration independent) will be favoured over intermolecular reaction. In order to apply this principle it is, of course, necessary to use a process which takes place in solution. Ziegler adapted the Thorpe reaction by using high-dilution conditions.[123] The original Thorpe process involves the intermolecular, base-promoted condensation of nitriles which Thorpe later showed could be converted to the intramolecular mode by using an α,ω-dinitrile. This reaction is suitable for cycloalkanone formation since the initial product, an enamineonitrile, can be hydrolysed and decarboxylated under acidic conditions. Ziegler showed that, after modification, the Thorpe reaction could be applied to the synthesis of cyclic ketones containing from five to 33 carbon atoms. The modifications involved were the use of high-dilution conditions, employing diethyl ether as solvent, and using the lithium or sodium salt of *N*-methylaniline as the base. Although the Thorpe–Ziegler reaction works well for common rings and large rings containing more than 13 carbon atoms (cyclo-octadecanone can be obtained in 80% yield, notwithstanding the high-dilution conditions), nine-, ten-, eleven-, and twelve-membered rings are obtained only in very poor yields.

The Dieckmann cyclization is an application of the acetoacetic ester condensation to the formation of a cyclic system.[123] It is very similar in character to the Thorpe–Ziegler reaction in that it is brought about by base and the initial product, a keto-ester, is readily converted into a cyclic ketone by hydrolysis and decarboxylation. The ring sizes available by the Dieckmann cyclization are, however, more limited than those from the Thorpe–Ziegler cyclization, and the reaction is best suited to the construction of five-, six-, and seven-membered rings. Despite the limitations of these two cyclization procedures, they are of great utility in the synthesis of polycyclic systems containing the common rings.

The acyloin condensation of α,ω-dicarboxylic esters (Figure 27) is by far the most useful method for the synthesis of medium- and large-ring ketones.[124] Whereas the Dieckmann and Thorpe–Ziegler reactions are virtually ineffective for rings in the C_9–C_{12} range, the intramolecular acyloin condensation followed by a reduction step produces cyclic ketones in the medium- and large-ring range in excellent yields. The condensation involves the reductive cyclization of an α,ω-dicarboxylic ester using an alkali metal (frequently sodium), and the initial product is an enediolate which on acidification yields an α-hydroxyketone (an acyloin). When the reaction is conducted in the presence of trimethylchlorosilane, the enediolate is trapped as its bistrimethylsilyoxy derivative. The latter procedure has greatly expanded the scope and power of the acyloin condensation and the use of trimethylchlorosilane has become almost routine as the method of choice in all acyloin condensations; higher yields are obtained, there are fewer side reactions, the products are more easily isolated, and the trimethylsilyloxy groups are easily removed by hydrolysis. Furthermore, the ring sizes available by this modification are greater than with the normal method, and there are now several examples of the construction of small (three- and four-membered) medium, and large (>20-membered) rings in this way.

As one would expect, high-dilution conditions are desirable for the formation of medium and large rings by the acyloin condensation. Although the mechanistic details of the reaction are still unclear, it appears that the fact that the reaction is heterogeneous is beneficial for ring formation. At high dilution the two electrophilic ends of the diester chain approach each other on the metal surface until a bond is formed. Acyloins can be reduced to ketones by various modifications of the Clemmensen technique. Under mild conditions the ketone will predominate, whereas more vigorous conditions will cause complete reduction to the cycloalkane. Examples of the use of the acyloin condensation in the synthesis of mono- and poly-cyclic compounds are given in Figure 27. Other cyclization reactions which give large ring cycloalkanones include the diketen dimer procedure of Blomquist[125] and the pyrolysis of triperoxides described by Story.[126]

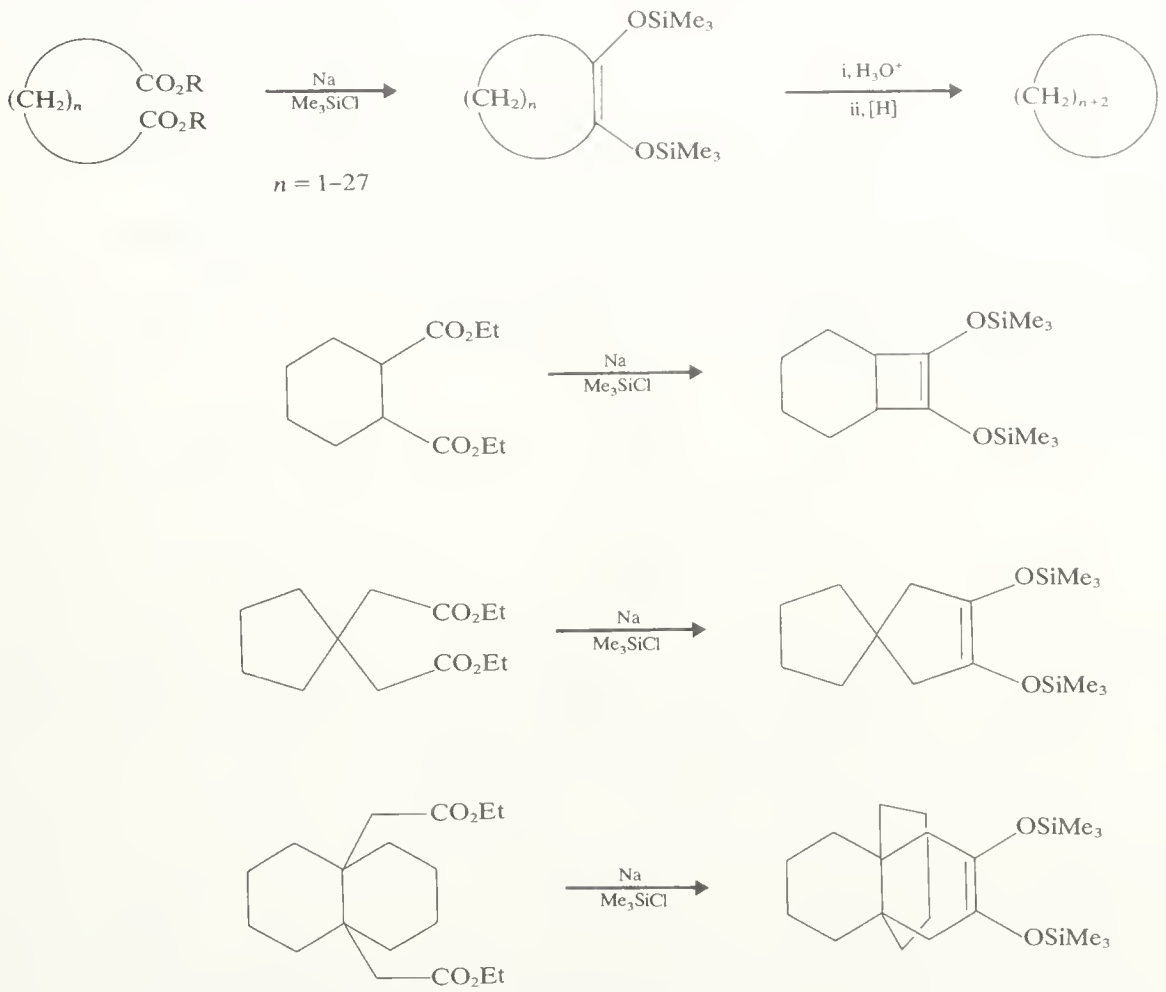


Figure 27 Acyloin condensations

Cycloalkanes can be obtained from cycloalkynes by hydrogenation. The oxidative coupling of certain terminal diacetylenes by means of oxygen in the presence of cuprous chloride and ammonium chloride in aqueous ethanol (see Section 2.6.2.1) yields cyclic dimers, trimers, tetramers, pentamers, and higher cyclic polyacetylenes. Full hydrogenation of these cyclic polyacetylenes yields the corresponding saturated hydrocarbons. Using this method, Sondheimer and co-workers have obtained cycloalkanes containing 16, 18, 20, 21, 24, 27, 28, 30, 32, 36, 40, 45, and 54 carbon atoms; prior to this work, the largest cycloalkane known was 34-membered.[127]

Thermal and photochemical cycloadditions and electrocyclic reactions provide important routes to mono- and poly-cycloalkanes. The Diels–Alder reaction, which is a thermal $[_{\pi}4_{s}+{}_{\pi}2_{s}]$ cycloaddition, provides a very useful, though indirect, method for the formation of mono- and poly-cycles containing six-membered rings. The reaction involves the

1,4-addition of an alkene (a dienophile) to a conjugated diene, the simplest example being the addition of ethylene to buta-1,3-diene to give cyclohexene. This particular example (Figure 28) is a poor one since the yield is low, but it does illustrate the general point that, where a six-membered ring can be constructed in this way, conversion of the product into the cycloalkane can be readily achieved by hydrogenation. Addition occurs much more easily when the dienophile bears electron-withdrawing groups such as carboxyl, cyano, carbonyl, and cyclic anhydrides. Such groups can be subsequently removed or reduced to alkyl groups. For example, many cyclic dicarboxylic acids are readily available from the Diels–Alder addition of maleic anhydride to acyclic and cyclic dienes. Dicarboxylic acids of this type can be decarboxylated to alkenes and the combination of two reactions with a hydrogenation step provides a route to cyclic and polycyclic alkanes; some examples are given in Figure 28. Another reason why the reaction is so useful in synthesis is its high stereospecificity. The configurations of the diene and dienophile are retained in the

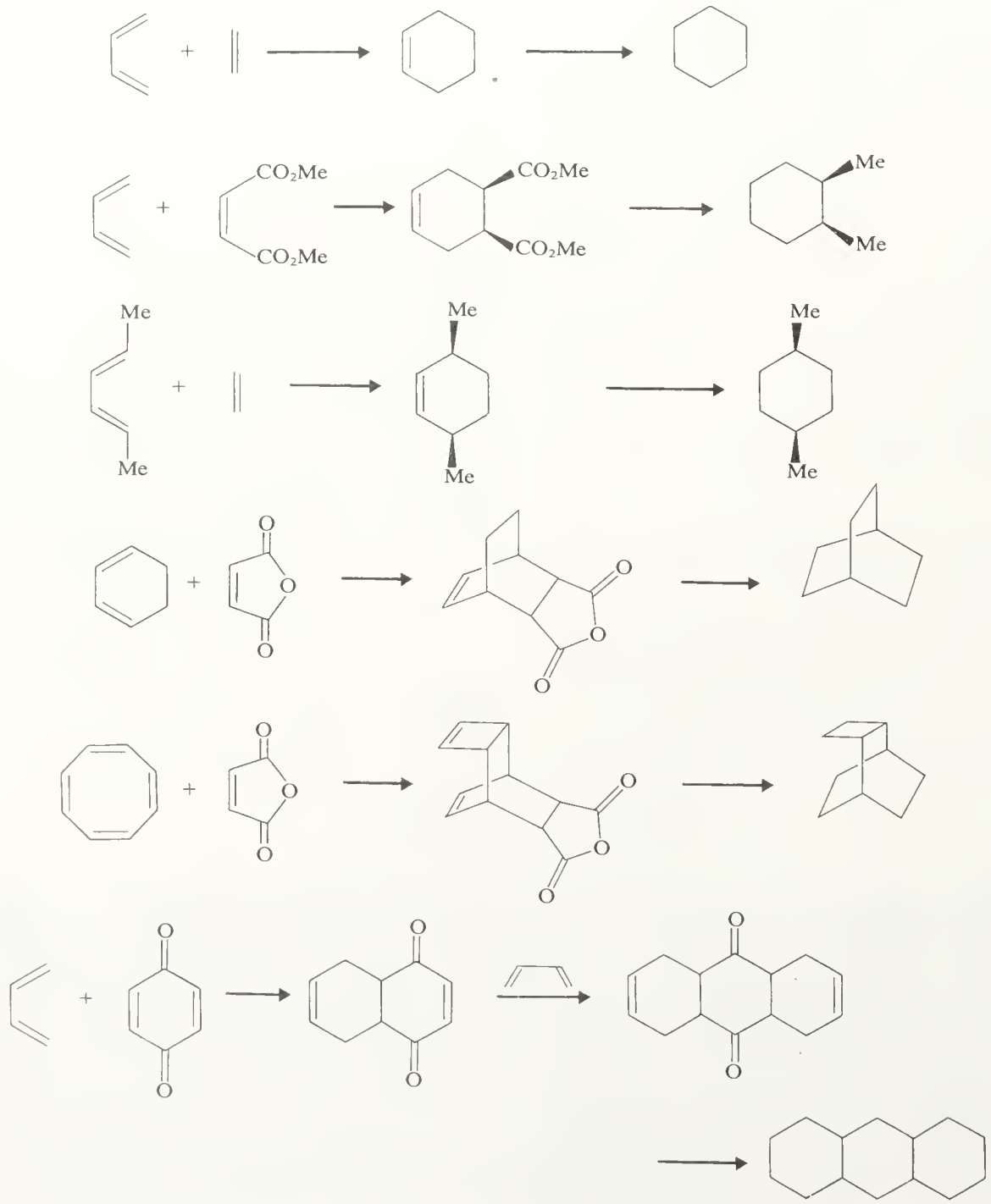


Figure 28 Synthesis of some cycloalkanes *via* Diels–Alder reactions

adduct. Thus the addition of dimethyl maleate with buta-1,3-diene gives a *cis*-substituted cyclohexene (Figure 28) with retention of configuration in the dienophile. That retention of configuration in the diene, if substituted, occurs, is shown by the product obtained from ethylene and *trans,trans*-hexa-2,4-diene (Figure 28). Thus if one wished to use these reactions as routes to 1,2- and 1,4-dimethylcyclohexanes, the configurations of the products are established at the cycloaddition stage. Another feature of the Diels–Alder reaction which is important in determining the stereochemistry of bicyclic and bridged-ring carbocycles is the preference for *endo* addition. Thus the cycloaddition of cyclopentadiene with itself gives *endo*-tetrahydrodicyclopentadiene as the major product. Other examples of Diels–Alder reactions which give products suitable for transformation into cycloalkanes are shown in Figure 28.[128]

Among other cycloadditions that have been shown to have general synthetic utility are [2+2] cycloadditions which produce cyclobutanes. Both thermal and photochemical modes are known. The most widely exploited photochemical [2+2] cycloadditions of alkenes are intramolecular reactions that have been used in the synthesis of polycyclic caged hydrocarbons. Some inter- and intra-molecular examples are listed in Figure 29.[129,130]

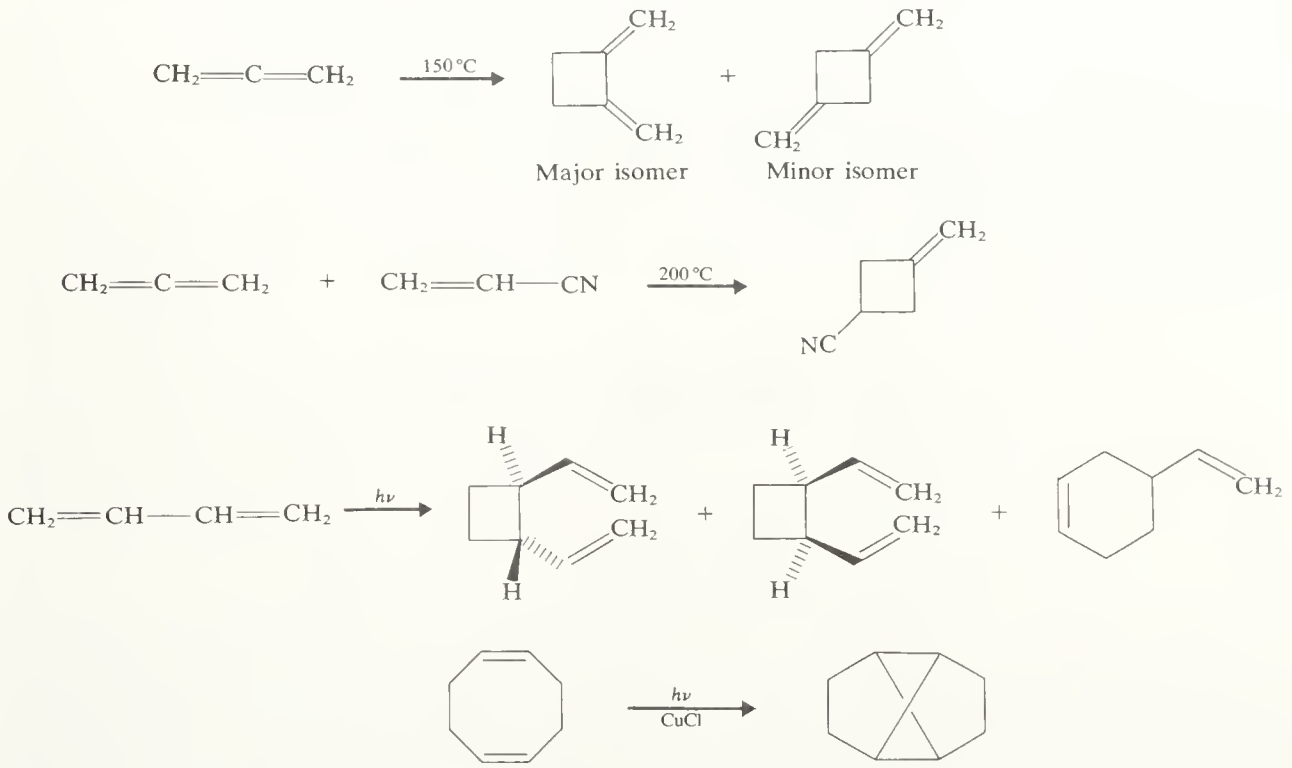


Figure 29 Formation of cyclobutanes in thermal and photochemical [2+2] cycloadditions

Electrocyclic ring closure reactions, which may be thermally or photochemically induced, provide routes to unsaturated carbocycles suitable for reduction to cycloalkanes and substituted cycloalkanes.[131]

Carbene and carbenoid additions to olefins provide general synthetic routes to a variety of substituted cyclopropanes. A particularly useful combination of reagents is methylene di-iodide and zinc–copper couple, commonly known as the Simmons–Smith reagent (Figure 30).[132] Free methylene is not an intermediate in this reaction; rather, it is transferred to the C—C double bond *via* an organometallic intermediate. There are numerous ways of generating carbene and carbenoid intermediates. The most general are (i) photolysis, thermolysis, or metal ion-catalysed decomposition of diazoalkanes; (ii) photolysis or thermolysis of salts of sulphonylhydrazones, in which case diazoalkanes are intermediates; (iii) photolysis of diazirines; (iv) the action of strong base or organometallic

reagents on alkyl halides; and (v) the thermolysis of α-halomercury compounds.[133] These reactions all lead to cyclopropanes if conducted in the presence of an olefin. A number of examples of the use of carbene and carbenoid reagents intermolecularly and intramolecularly are given in Figure 30. Another feature of the chemistry of carbenes is their ability to undergo insertion reactions into C—H bonds. The intramolecular version of this reaction has been used to construct some highly strained cyclopropyl systems.

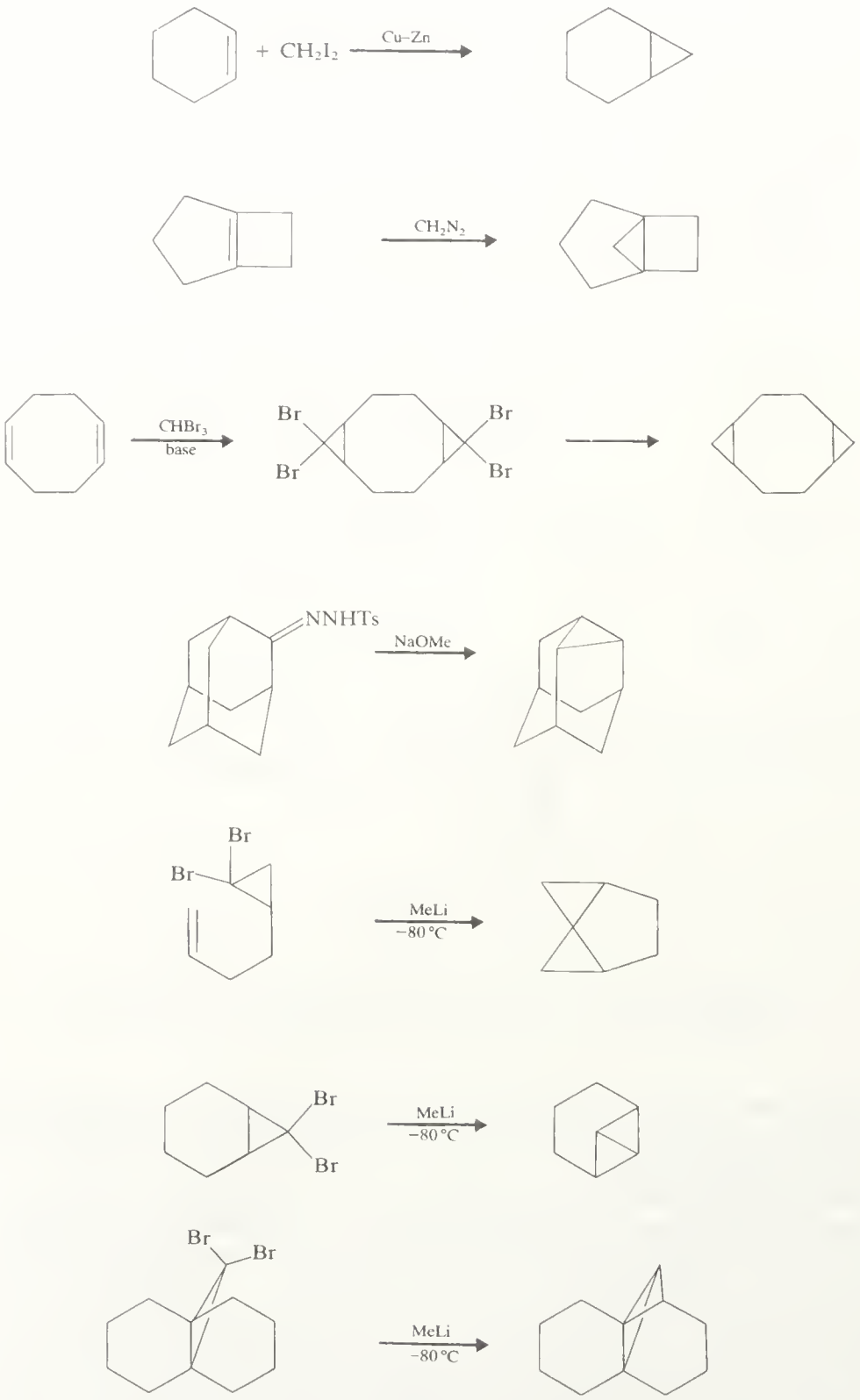


Figure 30 Some cyclopropanes from carbene reactions

Most other polycyclic bridged-ring alkanes (see Figure 7) have been prepared by rational multi-step synthesis. The diamondoid cycloalkanes constitute an homologous series for which a special, essentially one-step, procedure has evolved. Schleyer discovered that adamantane could be obtained from *endo*-tetrahydrodicyclopentadiene by rearrangement. Subsequently, diamantane and triamantane were also obtained from suitable precursors (Figure 31).[134] The success of this route rests on (i) the high thermodynamic stability of each member of the diamondoid series relative to that of isomeric hydrocarbons, *e.g.* the energy change in the conversion of *endo*-tetrahydrodicyclopentadiene into adamantane is about 65 kJ mol^{-1} exothermic; (ii) the availability of strained precursors isomeric with the product; and (iii) the ability of certain Lewis acids to produce and sustain the cationic intermediates essential to the propagation of the rearrangement. The fourth member of the series, *anti*-tetramantane, has been prepared by a gas-phase rearrangement on platinum.

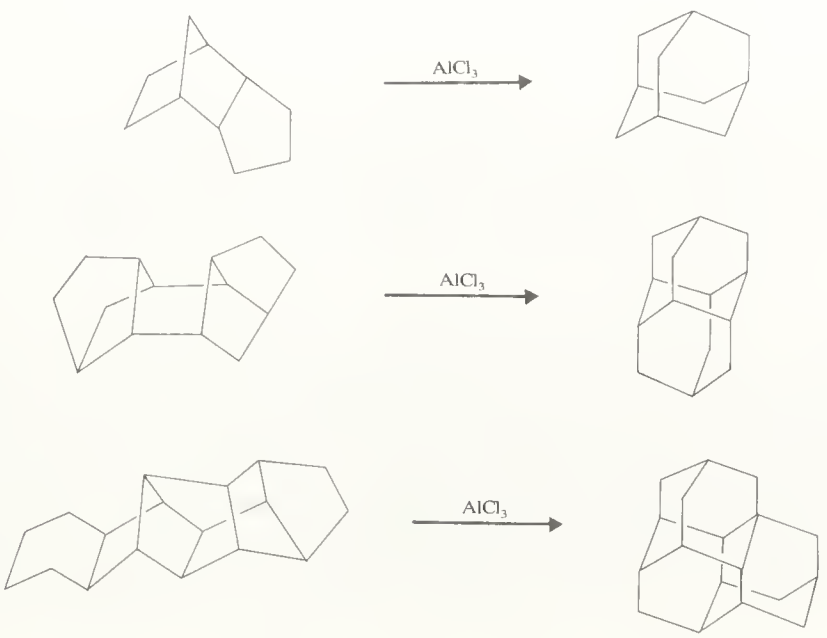


Figure 31 Synthesis of some adamantanes by rearrangement

2.1.9 REACTIONS OF ACYCLIC ALKANES

The name saturated hydrocarbon or 'paraffin', which literally means too little affinity (L. *parum*, too little, plus *affinis*, affinity), was originally introduced to indicate that the chemical affinity of this class of compound for most common reagents may be regarded as saturated or satisfied. While it is generally true that the alkanes as a class are among the least reactive of organic compounds, they are by no means chemically inert, and during the past 50 years reaction conditions have been discovered under which they undergo a wide variety of new reactions. The alkanes are now the major source of raw materials in the organic chemical industry and there are numerous chemical processes of commercial importance which involve the functionalization of natural gas and oil fractions. These processes, which involve reactions such as halogenation, oxidation, nitration, dehydrogenation, aromatization, and isomerization, will be discussed here.

2.1.9.1 Halogenation

Alkanes are important starting materials for the production of alkyl halides. Fluorine, chlorine, and bromine react readily with alkanes to form mono- and poly-halogenated products with an order of reactivity fluorine > chlorine > bromine. Iodine is generally

unreactive. Little or no halogenation occurs in the dark at ordinary temperatures except with fluorine, but in violet or ultraviolet light, or at high temperatures, reaction occurs with chlorine and bromine, often with explosive violence. This type of halogenation occurs by a radical chain mechanism which we shall illustrate here for the chlorination of methane. The important steps are (i) initiation, (ii) propagation, and (iii) termination.

(*i*) *Initiation*

The influence of light or heat on the chlorination of methane is consistent with a mechanism initiated by homolytic cleavage of a chlorine molecule producing two chlorine atoms. This process (equation 12) is endothermic by 244 kJ mol^{-1}.

$$Cl_2 \rightarrow 2Cl\cdot \quad \Delta H = +244 \text{ kJ mol}^{-1} \tag{12}$$

(*ii*) *Propagation*

After some chlorine atoms have been produced, two energetically favourable steps are possible. Firstly, a chlorine atom can abstract a hydrogen atom from methane (equation 13), producing a molecule of hydrogen chloride and a methyl radical. The bond energies of CH_4 and HCl suggest that the energy change here is favourable, though small (*ca.* -5 kJ mol^{-1}).

$$Cl\cdot + CH_4 \rightarrow HCl + CH_3\cdot \qquad \Delta H = -5 \text{ kJ mol}^{-1} \tag{13}$$

Secondly, the methyl radical can then remove a chlorine atom from a chlorine molecule, forming methyl chloride and a new chlorine atom. This reaction is calculated to be exothermic by 96 kJ mol^{-1}. An important feature of the mechanism is that the chlorine atom consumed in the first propagation step is replaced by another in the second (equation 14). This type of behaviour is typical of a chain process and, in principle, one chlorine atom can bring about the chlorination of an infinite number of methane molecules. In practice, the chain length is limited by recombination reactions which terminate the chain.

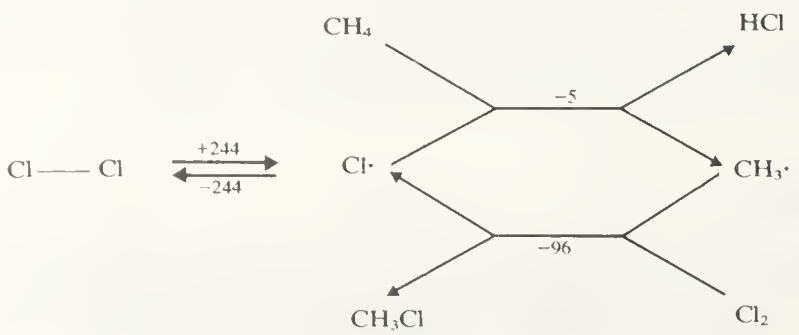
$$CH_3\cdot + Cl_2 \rightarrow CH_3Cl + Cl\cdot \qquad \Delta H = -96 \text{ kJ mol}^{-1} \tag{14}$$

(*iii*) *Termination*

Chain termination occurs when chlorine atoms and methyl radicals combine as follows:

$$2Cl\cdot \rightarrow Cl_2$$
$$2CH_3\cdot \rightarrow CH_3CH_3$$
$$Cl\cdot + CH_3\cdot \rightarrow CH_3Cl$$

We can summarize the mechanism and energetics of methane chlorination in the following way (numbers have the units of kJ mol^{-1}):



The chlorination of methane is usually conducted in the gas phase at temperatures ranging from 350–750 °C. It is a classic example of a situation where initial products can undergo further reaction, and where the product distribution obtained depends on the conversion to which the reaction is taken:

$$CH_4 \xrightarrow{Cl_2} CH_3Cl + HCl \xrightarrow{Cl_2} CH_2Cl_2 + HCl \xrightarrow{Cl_2} CHCl_3 + HCl \xrightarrow{Cl_2} CCl_4 + HCl$$

The conversion of methane is generally controlled by the ratio of chlorine to methane used, chlorine being completely consumed under the process conditions. Operation at low conversion favours methyl chloride and operation at high conversion, the more highly chlorinated products.

$$-\overset{|}{\underset{|}{C}}-H + X_2 \longrightarrow -\overset{|}{\underset{|}{C}}-X + HX \qquad X = F, Cl, Br, I \tag{15}$$

Direct halogenation of alkanes works satisfactorily only with chlorine and bromine. For the general reaction in equation (15), we find that the enthalpy change, ΔH_R, is very exothermic for fluorine, moderately exothermic for chlorine and bromine, but endothermic for iodine. The relevant thermochemical data are given in Table 25. After initiation, every step in fluorination is very strongly exothermic, and unless the reaction is moderated in some way, vapour-phase fluorination can cause complete decomposition of the alkane since the energy liberated in replacing a hydrogen atom by fluorine is sufficient to break carbon–carbon single bonds. The direct fluorination of methane even produces some pure carbon. For this reason, direct fluorination of alkanes is of very limited value. Nevertheless, fluorine can be substituted for hydrogen *via* the use of a less reactive fluorinating agent such as cobaltic fluoride. When methane is passed over cobaltic fluoride, methyl fluoride is produced and the cobaltic salt is reduced to cobaltous fluoride. Bromination of alkanes is much less endothermic than are fluorination and chlorination, though the reaction appears to follow the same general course both at high temperatures and with activation by light. Iodine is unreactive.

TABLE 25

Enthalpy of Reaction (ΔH_R) for Methane Halogenation (kJ mol^{-1})

Reaction	*Halogen* F	Cl	Br	I
$X_2 \rightarrow 2X\cdot$	+155	+244	+193	+152
$X\cdot + CH_4 \rightarrow HX + CH_3\cdot$	−138	−5	+63	+130
$CH_3\cdot + X_2 \rightarrow CH_3X + X\cdot$	−298	−96	−88	−71
$2X\cdot \rightarrow X_2$	+155	+244	+193	+152
$\Delta H_R =$	−436	−101	−25	+59

Chlorination of ethane produces a single monochloro product (ethyl chloride), but with propane and the higher alkanes, where more than one kind of substitution product is possible, mixtures of products are usually obtained. On purely statistical grounds, one would expect to replace the six primary hydrogen atoms of propane for every two replacements of the secondary hydrogen atoms. If the reaction is conducted at high temperatures (>450 °C) one does indeed observe the predicted ratio of 3 : 1 for the n-propyl chloride, and isopropyl chloride produced. If, however, the reaction is performed at low temperatures the chlorine atom appears more selective in that there is now a distinct preference for the secondary hydrogen atoms. For abstraction by a chlorine atom at room temperature, secondary hydrogen atoms are about four times more reactive than are primary hydrogen atoms. At low temperatures, tertiary hydrogen atoms are the most

reactive: chlorination of isobutane gives 36% t-butyl chloride and 64% isobutyl chloride. On the basis of a variety of rate data, the relative reactivities of tertiary, secondary, and primary hydrogen atoms in alkanes at room temperature are 5 : 4 : 1 per hydrogen atom. These partial rate ratios are relatively independent of hydrocarbon structure and can be used to compute product ratios in the monochlorination of a variety of alkanes. It must be stressed that these rate ratios refer to low temperature chlorination. As the temperature is raised, the ratio approaches 1 : 1 : 1. In such circumstances the composition of monochlorination products will correspond to that expected from a statistical attack by the chlorine atom.

Alkane chlorination can also be brought about with agents such as sulphuryl chloride, t-butyl hypochlorite, iodine monochloride, and iodobenzene dichloride. Radical mechanisms are believed to apply with these reagents, although in the case of sulphuryl chloride an ionic mechanism has also been proposed. For n-hexane, with a substrate : sulphuryl chloride ratio of 1 : 3 in sulpholan as solvent, the products are 2-chlorohexane (56%), 3-chlorohexane (24%), and 1-chlorohexane (20%). For iso-octane, under similar conditions, the products are 1-chloro-2,2,4-trimethylpentane (43%), 3-chloro-2,2,4-trimethylpentane (28%), and 4-chloro-2,2,4-trimethylpentane (29%).

Recent work has shown that chlorination and bromination of alkanes can be carried out under strongly acidic conditions which favour ionic intermediates. The chlorinations involve a super-acid system, but for brominations the solvent is dichloromethane. If SbF_5 with Cl_2 in SO_2ClF is used at −78 °C, both chlorination by substitution and chlorinolysis by bond cleavage occur. The final products from methane, ethane, and propane are the corresponding dialkylchlorinium ion. The mechanism of these reactions is believed to involve electrophilic attack by Cl^+ on a C—H bond of the alkane. With methane, methyl chloride is produced in 2–5% yield with no detectable amounts of further chlorination. The reaction for ethane (Figure 32) gives the dimethylchlorinium ion and the diethylchlorinium ion in the ratio 7 : 3. The selectivity is changed if the Friedel–Crafts catalyst is changed: with $AlCl_3$ instead of SbF_5, only substitution is observed. Isobutane and isopentane are brominated by Br_2–$AgSbF_6$ in dichloromethane.[135]

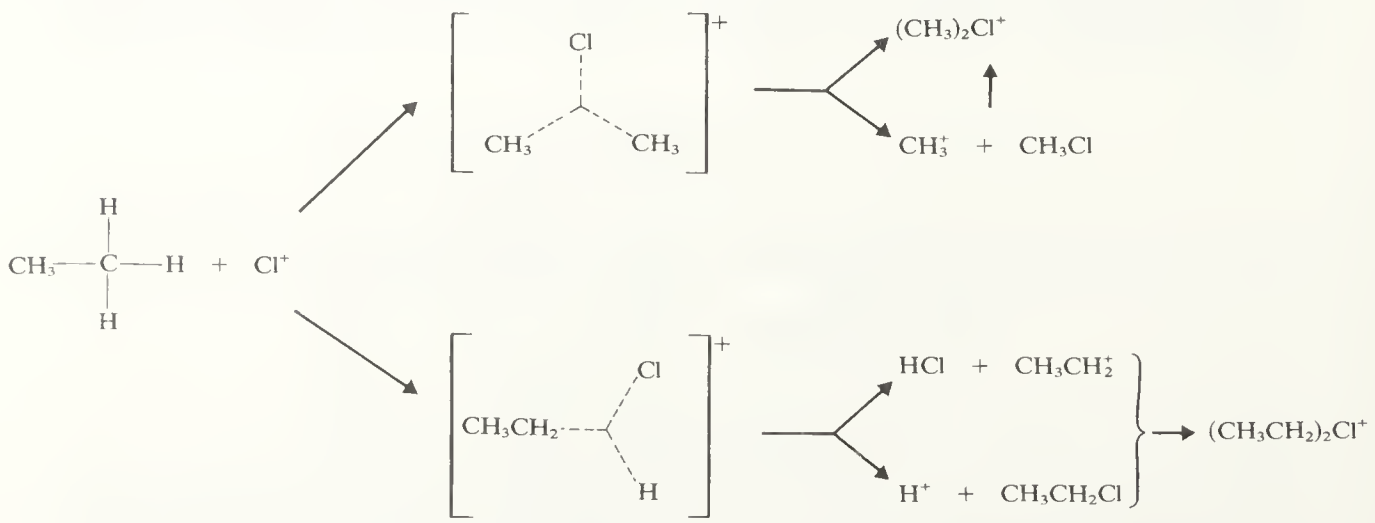


Figure 32 Chlorinolysis of ethane

Shilov and his co-workers have found that alkanes are chlorinated in aqueous H_2PtCl_6 containing 5% K_2PtCl_4 at 120 °C. The chloro products were mainly due to substitution at primary positions.[136]

2.1.9.2 Nitration

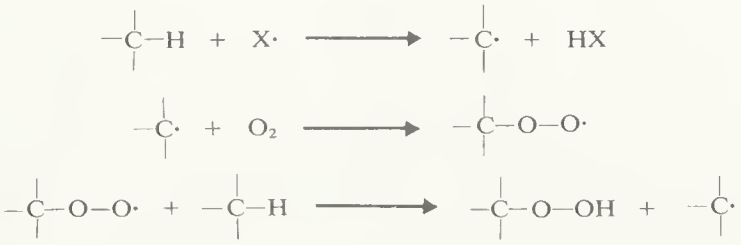
Alkanes react with nitric acid or dinitrogen tetroxide in the vapour phase to form nitro derivatives. Mixtures are usually obtained and the available evidence suggests a radical

mechanism. The vapour phase nitration of propane gives 1-nitropropane, 2-nitropropane, nitroethane, and nitromethane, the latter two products indicating that some C—C bond cleavage also occurs.

Nitration of alkanes is also possible under conditions which favour ionic intermediates. Olah and Lin found that electrophilic nitration of methane and ethane is possible using stable nitronium salts, such as $NO_2^+PF_6^-$ in aprotic solvents such as methylene chloride–sulpholan, although yields of nitromethane and nitroethane were low. In HF or HSO_3F solutions, much higher yields of nitration were obtained. The mechanism proposed for nitrations involves electrophilic attack by NO_2^+ on a C—H bond of the alkane.[135]

2.1.9.3 Oxidation

Alkanes react with oxygen at elevated temperatures and if excess of oxygen is used, complete combustion gives carbon dioxide and water. The oxidation process in engines and furnaces is rarely complete, particularly if insufficient oxygen is present, and carbon monoxide, a health hazard, is produced daily in large quantities. On a laboratory scale, the complete oxidation of alkanes under carefully defined conditions in a calorimeter is used to measure heats of combustion and formation. Quantitative aspects of such thermochemical processes are discussed in Section 2.1.6. Although the oxidation of alkanes, either completely to carbon dioxide and water, or incompletely to intermediate products, is highly exothermic, it does require initiation. There is general agreement that the mechanism of alkane oxidation involves a radical chain process, although the details of how the chain is initiated and the differences in mechanism between oxidation in the gas phase and in the liquid phase are still unclear. Oxygen itself is too unreactive to abstract a hydrogen atom from an alkane to form an alkyl radical, but if this process is brought about by some other initiating species the alkyl radical produced can react with oxygen to give a peroxy radical. The peroxy radical can then abstract a hydrogen atom from another alkane molecule to give an alkyl hydroperoxide and another substrate radical so that a new alkyl radical is produced for each one that reacts until no alkane remains:



The net effect of the chain process is the combination of oxygen with the alkane to form an alkyl hydroperoxide. As in all radical chain reactions, the chain length is limited by the occurrence of termination reactions in which the radicals combine with each other.

Organic hydroperoxides are usually very reactive substances; the oxygen–oxygen bond is easily broken homolytically, giving products or mixtures of products depending on the oxidation conditions and the structure of the alkane. Gas-phase oxidation is generally much less important as a method of chemical manufacture than is liquid-phase oxidation, mainly because it is much less selective. The most important commercial application of the liquid-phase process is the manufacture of acetic acid from n-butane or from low-boiling petroleum fractions. In this process, alkoxy radicals, produced from the decomposition of alkyl hydroperoxides, disproportionate *via* C—C bond fission to give, *inter alia*, ethyl radicals and acetaldehyde which are further oxidized to acetic acid. The products of gas-phase oxidation are temperature dependent: at low temperatures, the principal products are alcohols, aldehydes, and ketones, whereas at higher temperatures, particularly with low oxygen concentrations, the products are those of dehydrogenation and cracking. The chief commercial use of gas-phase oxidation is in the production of acetaldehyde, methanol, and formaldehyde from propane and butane.[137]

The use of transition metal oxidants with alkanes has been studied extensively.

Stewart[138] and Wiberg[139] have reviewed the mechanisms of reactions in which manganese(VII), chromium(VI), vanadium(V), cobalt(III), manganese(III), cerium(IV), and lead(IV) are used as oxidants. The oxidation of saturated hydrocarbons by inorganic oxidants requires quite vigorous conditions and, since the initial products of these reactions are usually more prone to oxidation than are alkanes, considerable second-stage oxidation is observed. It is difficult, for example, to oxidize a methylene group to a secondary alcohol without further oxidation to a ketone; in some cases, the conditions are sufficiently vigorous to cause C—C bond cleavage. Usually, it is possible to convert C—H bonds into tertiary alcohols, but since many tertiary alcohols undergo easy dehydration, these products may not be obtained in good yield. Wiberg and Foster have found that oxidation of 3-methylheptane by dichromate ion gives a 10% yield of 3-methylheptan-3-ol.[140] Small alkanes (C_1 to C_4) are oxidized to alcohols at room temperature in acetonitrile solution by oxygen in the presence of stannous chloride; methane is much less reactive than ethane, propane, and butane. The use of Co(III) salts to catalyse the oxidation of butane to acetic acid is of industrial interest. Oxidation of n-pentane also gives acetic acid as the major product, with minor products including propanoic, butanoic, and pentanoic acids.

Some oxidations of alkanes can be carried out electrochemically. In solution in fluorosulphonic acid containing carboxylic acids, alkanes undergo anodic oxidation to form α,β-unsaturated ketones. The Ritter reaction can be carried out with alkanes under electrolytic conditions. In this way, oxidation of alkanes in acetonitrile solution produces *N*-alkylacetamides.

A further oxidative conversion of considerable significance in the petrochemical industry is the microbiological transformation of alkanes, using either bacteria or yeasts, into protein-containing materials; the straight-chain alkanes are more readily metabolized.

2.1.9.4 Catalytic isomerization of alkanes

In Section 2.1.6 on the thermochemical properties of alkanes we drew attention to the important fact that isomeric constitutions are not energetically equivalent. For example, the isomeric butanes differ in enthalpy by 8.53 kJ mol^{-1}, the branched chain isomer being the more thermochemically stable of the two. Similarly, the thermochemical stability order of the pentanes is n-pentane < 2-methylbutane < 2,2-dimethylpropane. Although thermochemical stability is not synonymous with thermodynamic stability, we can use the generalization that in alkanes chain branching is thermodynamically favourable also. n-Alkanes can be converted into their branched-chain isomers in the presence of catalysts such as the aluminium halides, sulphuric acid, hydrogen fluoride, certain oxides, and hydrogenation catalysts such as platinum, palladium, nickel, and rhodium with or without oxide supports. Catalytic isomerization is an important operation in petroleum refining. As we pointed out in the introduction, n-alkanes have lower octane ratings than their branched-chain counterparts and are generally unsuitable as engine fuels. Catalytic isomerization allows the conversion of n-butane into isobutane, an important component for alkylations, and also the conversion of higher molecular weight alkanes in the petrol range to branched-chain isomers possessing more favourable octane numbers. The isomerization process is usually accompanied by other reactions such as cracking and polymerization, leading to products of lower and higher molecular weight than the starting alkane. These side reactions can be minimized by selection of suitable experimental conditions. The n-butane–isobutane isomerization can be brought about at room temperature with aluminium bromide catalysis; at equilibrium the mixture contains about 80% isobutane. All the available evidence suggests that this isomerization occurs *via* the sequence: (i) formation of a cation by intermolecular hydrogen transfer; (ii) rearrangement of the cation; (iii) saturation of the cations by hydride transfer; and (iv) in heterogeneous reactions, distribution of the products between the acid and hydrocarbon phases.[141] Pure n-butane does not isomerize easily in the presence of aluminium halides,

suggesting that the initiation process does not involve the direct abstraction of a hydride ion from n-butane to the aluminium halide. It is now generally accepted that the true initiators in this type of isomerization are species of the type $R^+AlX_4^-$, generated from the aluminium halide and trace impurities present in the alkane. This species abstracts a hydride ion from n-butane and the resulting cation rearranges as shown in Figure 33. In super-acid media, protolysis of a C—H bond of an alkane can occur directly to give a cation and molecular hydrogen (protolysis of the alkane); the cation undergoes rearrangements of the type shown in Figure 33.

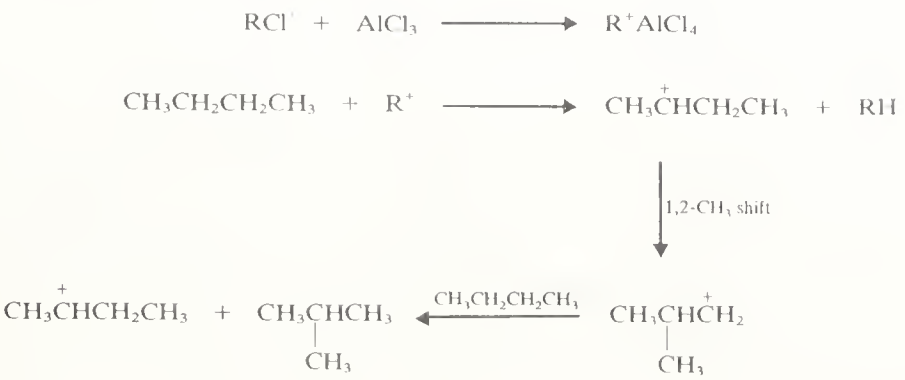


Figure 33 Isomerization of n-butane to isobutane

2.1.9.5 Catalytic alkylation of alkanes

Alkanes, particularly isoalkanes, interact with alkenes in the presence of such catalysts as aluminium halides, boron trifluoride, hydrogen fluoride, and sulphuric acid to produce higher alkanes. Catalytic alkylation thus provides a method of producing fuels with high octane numbers from some of the gaseous low-molecular-weight alkanes produced in refining operations. We have seen previously that the isoalkanes necessary for the alkylation reaction are available from isomerization processes. The alkane of greatest commercial interest as an alkylation reactant is isobutane, itself available from isomerization of n-butane. The olefins needed in catalytic alkylation, *e.g.* propene and butene, are by-products of another refinery process, catalytic cracking. Alkylation gives fairly complex mixtures of products. For example, alkylation of isobutane with propene in the presence of hydrogen fluoride at 40 °C gives the following products: propane, 2,3-dimethylpentane, 2,4-dimethylpentane, 2,2,4-trimethylpentane, 2,3,4-trimethylpentane, 2,2,3-triethylpentane, and 2,3,3-triethylpentane. The products are thus mixtures of highly branched alkanes with high octane numbers. The reaction is a chain process initiated by protonation of the olefin by the hydrogen fluoride. The isopropyl cation abstracts a hydride ion from isobutane, giving a t-butyl cation which adds to propene. The product of the latter reaction, a dimethylpentyl cation, can undergo intramolecular rearrangement to give isomeric constitutions which are converted into dimethylpentanes by hydride abstraction. The C_8 products arise from the combination of isobutene, formed from the t-butyl cation by proton elimination, and propene.

2.1.9.6 Alkane cracking reactions

Because of the industrial importance of the cracking of petroleum fractions to produce higher total yields of materials suitable for use as fuels or as petrochemical intermediates (*e.g.* alkenes), the decomposition of alkanes *via* C—C and C—H bond breaking has been extensively investigated. The type of cracking process used depends very much on the type of product required. There are two general reaction types, one involving thermal cracking in which alkenes are the major products, and the second involving catalytic cracking in which the objective is to obtain alkanes of high octane ratings; only small amounts of alkenes are produced in the latter process.

2.1.9.7 Thermal cracking

Methane is very resistant to thermal decomposition. At very high temperatures (>800 °C) and short contact times, methane gives ethane, ethylene, acetylene, hydrogen, and some aromatics, principally benzene. At temperatures of about 800 °C, the decomposition products of all alkanes become similar, the most important being ethylene, propene, butenes, butadiene, and hydrogen. In industrial operations, light petroleum fractions, diluted with steam, are passed through an empty tube at temperatures of about 800 °C with a contact time of 1 second or less. When ethane is the reactane the principal products are ethylene and hydrogen; at the present time, this reaction is the most widely used.

Thermal cracking is believed to involve a radical chain process in which, taking ethane as an example, the first step is homolysis of the C—C bond to give two methyl radicals. A methyl radical then abstracts a hydrogen atom from an ethane molecule and the ethyl radical eliminates a hydrogen atom which can abstract another hydrogen atom from an ethane molecule to give molecular hydrogen and an ethyl radical and thus the chain is propagated. Further details of the mechanism and the occurrence of β-cleavage in large alkyl radicals are discussed by Wiseman.[7]

2.1.9.8 Catalytic cracking

The gas oils and fractions obtained by fractional distillation of heavy fuel oils are used in catalytic cracking. The process is carried out at high temperatures (>450 °C) on an acidic catalyst, usually silica–alumina, a molecular sieve, or a zeolite. The reactions involved are thought to involve carbonium ion processes in which cleavage of C—C bonds occurs accompanied by isomerization of n-alkanes to branched-chain alkanes. The cleavage reaction can be looked on as the reverse of the alkane alkylation reaction discussed earlier. Formation of aromatics is also observed in catalytic cracking. The overall result is the conversion of high-boiling petroleum fractions into fuels of high octane grading. A related process is that of hydrocracking in which the oil fractions are treated with hydrogen over a dual-functional catalyst with both cracking and hydrogenation activity. The cracking function of the catalyst is provided by silica–alumina, and the hydrogenation activity is provided by a metal such as nickel, platinum or palladium. Thus alkenes formed in the cracking process are rapidly hydrogenated to alkanes.

2.1.9.9 Catalytic reforming and dehydrocyclization of alkanes

Catalytic reforming is applied to alkanes and cycloalkanes in the petrol boiling range to improve the octane number of potential fuels and as a commercial source of aromatic hydrocarbons. Like hydrocracking, catalytic reforming is conducted on a dual-functional catalyst such as platinum–alumina in the presence of hydrogen. The main reactions which occur are (i) dehydrocyclization of alkanes to aromatics (*e.g.* n-heptane to toluene), (ii) hydrocracking of alkanes (*e.g.* n-heptane to propane and butane), (iii) dehydrogenation of cyclohexane to benzene, (iv) isomerization of alkylcyclopentanes to aromatics (*e.g.* methylcyclopentane to benzene), and (v) isomerization of n-alkanes to isoalkanes. The mechanisms of some of these processes on both monofunctional and dual-functional catalysts are still the subject of much discussion; a recent summary of alkane reactions on platinum is available.[143]

2.1.10 REACTIONS OF CYCLOALKANES AND POLCYCLOALKANES

Many of the reactions of acyclic saturated hydrocarbons discussed above apply equally well to cycloalkanes and polycycloalkanes. Thus many cycloalkanes undergo halogenation,

both ionic and free-radical, oxidation, and nitration without skeletal change or carbon–carbon bond rupture. Where differences in chemical behaviour do occur, these are frequently associated with the presence of excessive angle strain in some cyclic structures. As we pointed out in the sterochemistry and thermochemistry sections, angle strain is a feature of small ring cycloalkanes which is reflected in their heats of combustion and cyclization energies (Table 19). It is to be expected that some chemical properties will also reflect the presence of severe angle strain. Cyclopropane is much more reactive than the other cycloalkanes, owing to the release of strain energy when the ring is opened. Thus one of the easiest of cycloalkane isomerizations is the conversion of cyclopropane into propene. This reaction may be effected thermally, or over catalysts such as platinum, palladium, iron, nickel, rhodium, or alumina at much lower temperatures. Cyclobutane is less reactive than is cyclopropane, and cycloalkanes with larger rings react for the most part in a manner similar to that of their acyclic counterparts. The behaviour of cycloalkanes in catalytic hydrogenolysis provides an illustrative example.[81] Catalytic hydrogenolysis of the carbon–carbon single bond in acyclic alkanes occurs only at high temperatures (>250 °C) and ultimately leads to methane. With cyclopropane and many alkylcyclopropanes, however, hydrogenolysis occurs readily at room temperature on platinum. Cyclobutane can be similarly hydrogenolysed to n-butane, but higher temperatures are required. Very highly strained polycycloalkanes consisting of several interconnecting cyclopropane or cyclobutane rings undergo catalytic hydrogenolysis with great ease, and it seems to be general that the bond or bonds cleaved are those which release the largest amount of strain energy. This generalization also applies to the hydrogenolysis of simple alkylcyclopropanes.[81] Some examples of small ring hydrogenolysis are given in Figure 34.

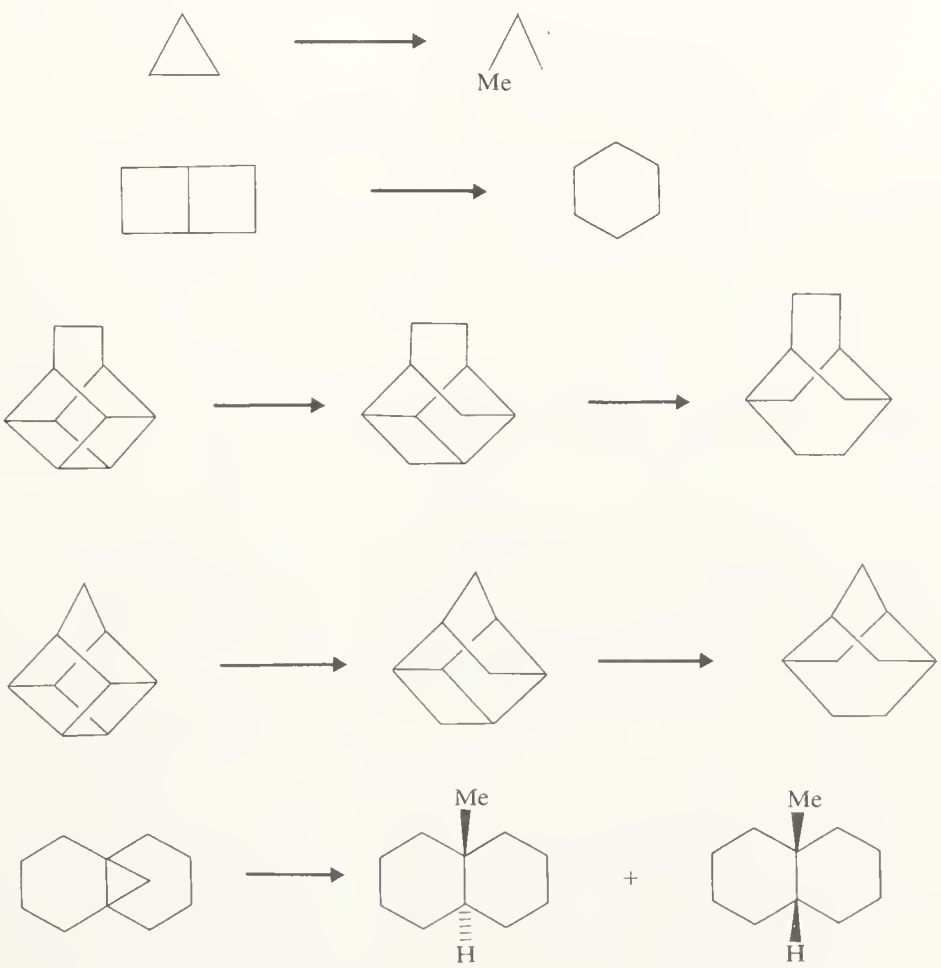


Figure 34 Hydrogenolysis of cyclopropanes

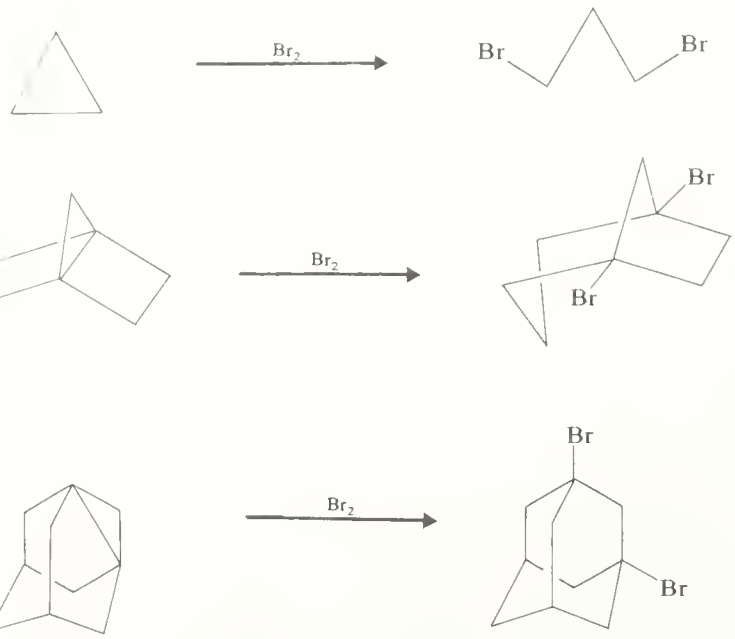


Figure 35 Ring opening of cyclopropanes with bromine

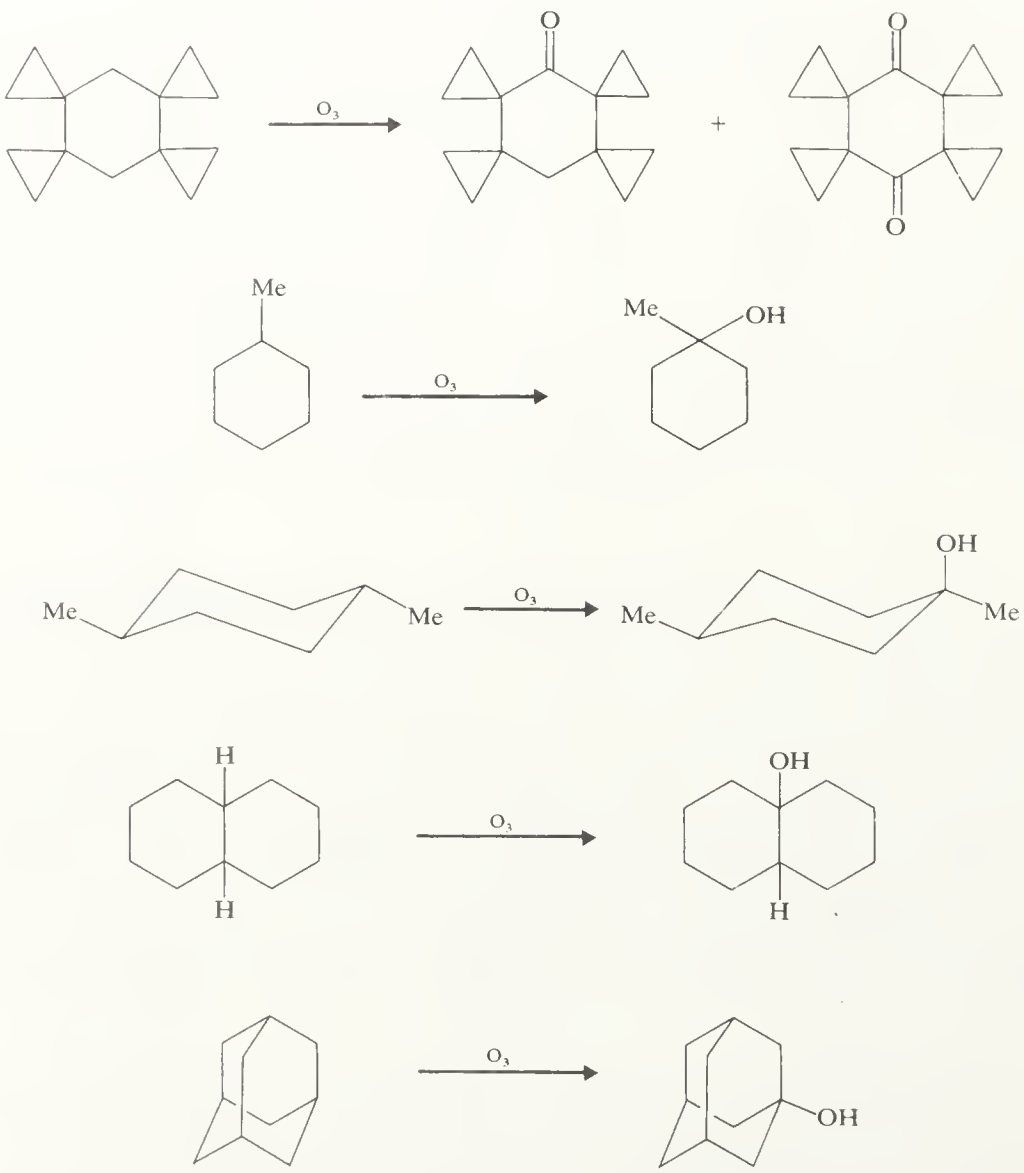


Figure 36 Oxidation of cycloalkanes with ozone

Ring opening of cyclopropane is also observed in some ionic addition reactions. With bromine, hydrogen halides, and sulphuric acid, cyclopropane gives 1,3-dibromocyclopropane, n-propyl halide, and n-propanol, respectively. Simple cyclobutanes do not undergo such reactions readily. Examples of electrophilic additions to cyclopropanes are given in Figure 35. However, not all reactions of cyclopropanes result in acyclic products. Free-radical chlorination of cyclopropane under mild conditions gives chlorocyclopropane and 1,1-dichlorocyclopropane. Free-radical halogenation of the higher cycloalkanes proceeds in a similar fashion. Ionic bromination of some polycycloalkanes occurs very readily at bridgehead positions. Thus, adamantane, diamantane,

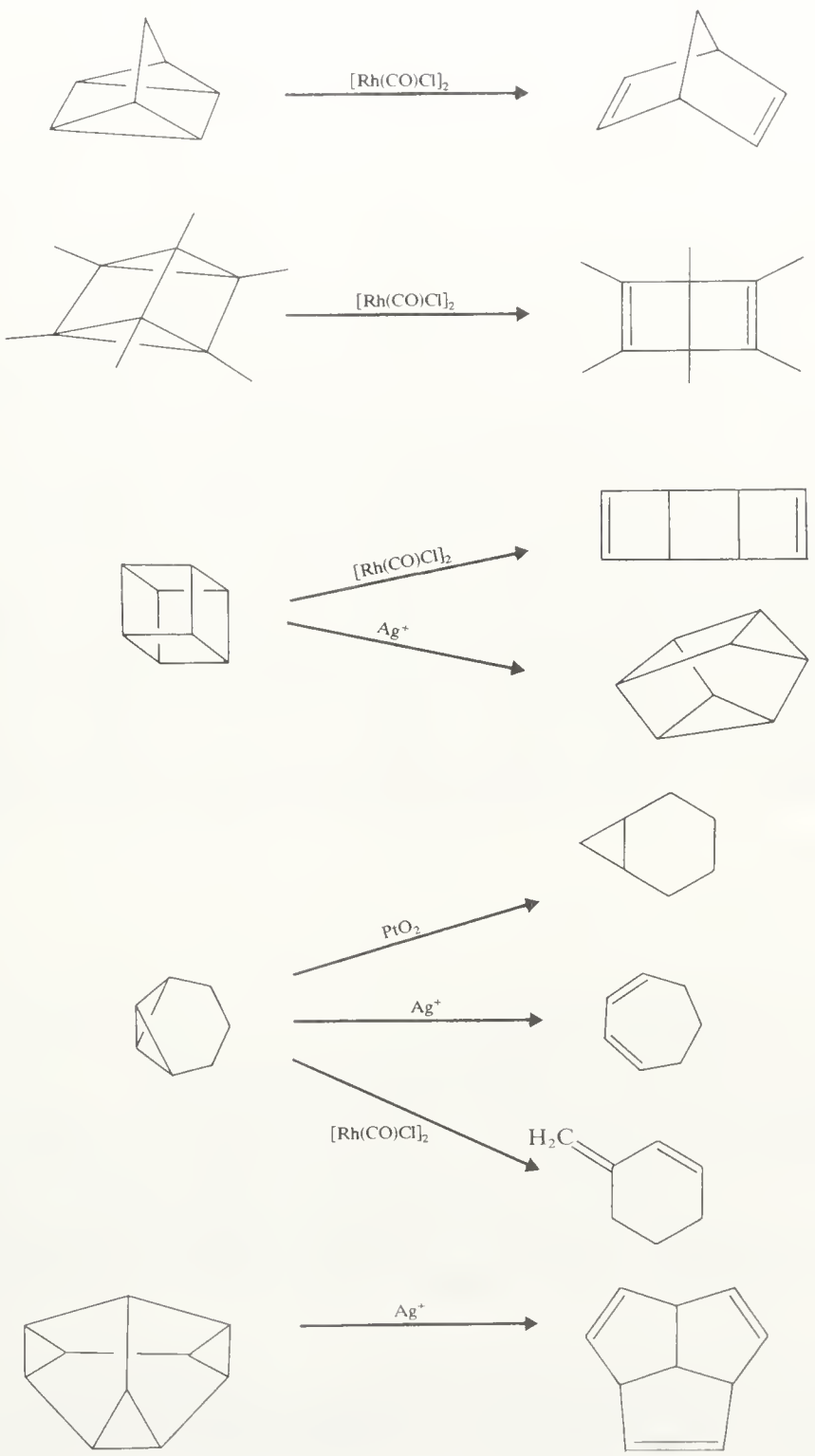


Figure 37 Catalysed isomerization of small-ring cycloalkanes

triamantane, and their alkyl derivatives react with liquid bromine, giving bridgehead bromides selectively.[134] With Lewis acid catalysts, polybromo derivatives are produced. Cycloalkanes and polycycloalkanes are selectively oxidized with ozone adsorbed on silica gel.[141] Alkylcyclopropanes react at the α-position, without ring opening, giving cyclopropyl alkyl ketones in high yield. For example, the tetraspirocyclopropane in Figure 36 reacts with ozone on silica gel to give the mono- and di-ketones shown. Other examples involving the use of ozone to functionalize cycloalkanes are given in Figure 36. Concentrated sulphuric acid has also been used to convert polycycloalkanes into ketones; the preparative utility of this reaction appears to be limited to the oxidation of adamantane and its derivatives.[134]

As with acyclic alkanes, there are numerous examples of isomerization and rearrangement reactions involving cyclic and polycyclic alkanes.[141,142] Lewis acid catalysts bring about ring contraction and expansion reactions *via* carbenium ion processes of the type discussed for the n-butane–isobutane isomerization. Five- and six-membered rings are usually favoured in cycloalkane equilibria. Three-, four-, seven-, and higher-membered rings can usually be considered absent at equilibrium; this is in accord with strain energy considerations. Thus cyclopentane does not form cyclopropanes or methylcyclobutane, and cycloheptane isomerizes to methylcyclohexane. In the five- and six-membered ring equilibria, the larger ring isomers are favoured at ordinary temperatures: with aluminium halide catalysis at 25 °C, methylcyclopentane and cyclohexane form an equilibrium mixture containing 88% of the latter isomer. Carbenium ion rearrangements of polycyclic alkanes can be of synthetic utility, a notable case being the production of the adamantanes shown in Figure 31 from strained polycyclic precursors in the presence of Lewis acid catalysts. Although such rearrangements are mechanistically complex, the high thermodynamic stability of the products provides a strong driving force for reaction.[145]

The severe angle strain in small ring polycycles provides the driving force for a number of recently discovered rearrangements and isomerizations brought about by catalysis with metal ions and metal complexes. Some examples are given in Figure 37. In some cases the type of isomerization or rearrangement observed is a function of the catalyst used. For example, with rhodium(I) complexes cubane gives cuneane whereas with silver ion a tricyclo-octadiene is produced. Although organometallic intermediates are believed to be involved in these reactions, the precise sequence of events are still not well understood; metallocarbenium ions, metallocarbene complexes, or oxidative addition of the metal into a strained carbon–carbon single bond have been proposed for these reaction mechanisms.[146]

References

1. For a comprehensive summary of the IUPAC nomenclature rules, see 'Nomenclature of Organic Chemistry', 2nd edn., Butterworths, London, 1971.
2. D. Ginsberg, *Accounts Chem. Res.*, 1972, **5**, 249.
3. U. Biethan, U. von Gizycki, and H. Musso, *Tetrahedron Letters*, 1965, 1477.
4. G. Schill, 'Catenanes, Rotaxanes, and Knots', Academic, New York, 1971.
5. For an excellent account of the early history of petroleum, see 'Chambers Encyclopaedia, Dictionary of Universal Knowledge', New Edition, London, 1895, volume 8, p. 98.
6. J. H. Gary and G. E. Handwerk, 'Petroleum Refining, Technology and Economics', Dekker, New York, 1975.
7. P. Wiseman, 'An introduction to Industrial Organic Chemistry', Applied Science, London, 1972.
8. For a more detailed analysis of petroleum constituents including the isolation of 91 pure hydrocarbons from a North American oil well, see F.D. Rossini, B. Mair, and G. Glasgow, *Record Chem. Prog.*, 1949, **10**, 121.
9. G. Egloff, *J. Chem. Educ.*, 1941, **18**, 582; see also Ref. 7.
10. H. Hendriks and T. M. Malingre, *Phytochemistry*, 1977, **16**, 719, and references therein.
11. H. E. Nordby and S. Nagy, *Phytochemistry*, 1977, **16**, 1393, and references therein.
12. G. Egloff, 'Physical Constants of Hydrocarbons', Reinhold, New York, 1939, vol. 1.
13. For a discussion of the melting point behaviour of the smaller cycloalkanes, see L. Ruzicka, P. A. Plattner, and H. Wild, *Helv. Chim. Acta*, 1937, **20**, 548.

14. The melting point behaviour of cycloalkanes containing 16-, 18-, 20-, 21-, 24-, 27-, 28-, 30-, 32-, 36-, 40-, 45-, and 54-membered rings has been discussed by F. Sondheimer, Y. Amiel, and R. Wolovsky, *J. Amer. Chem. Soc.*, 1959, **81**, 4600.
15. H. van Bekkum, A. van Veen, P. E. Verkade, and B. M. Wepster, *Rec. Trav. chim.*, 1961, **80**, 1310.
16. For an attempt to interpret the melting-transition temperature of some bridged-ring polycycloalkanes in terms of order–disorder effects, see T. Clark, M. A. McKervey, H. Mackle, and J. J. Rooney, *J.C.S. Faraday I*, 1974, **70**, 1279.
17. F. Hollowood and M. A. McKervey, unpublished results.
18. I. Hargittai and K. Hedberg, *Chem. Comm.*, 1971, 1499.
19. K. W. Cox, M. D. Harmony, G. Nelson, and K. B. Wiberg, *J. Chem. Phys.*, 1969, **50**, 1976.
20. C. S. Gibbons and J. Trotter, *Canad. J. Chem.*, 1973, **51**, 87.
21. General references: (a) E. L. Eliel, 'Stereochemistry of Carbon Compounds', McGraw-Hill, New York, 1962; (b) K. Mislow, 'Introduction to Stereochemistry', Benjamin, New York, 1965; (c) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, 'Conformational Analysis', McGraw-Hill, New York, 1968; (d) 'Steric Effects in Organic Chemistry', ed. M. S. Newman, Wiley, New York, 1956.
22. For applications of the concept of torsional angle to conformational descriptions, see R. Bucourt, *Topics Stereochem.*, 1974, **8**, 159.
23. J. M. Lehn, in 'Conformational Analysis', ed. G. Chiurdoglu, Academic, New York, 1971, p. 129; L. C. Allen, *Ann. Rev. Phys. Chem.*, 1969, **20**, 315; L. J. Oosterhoff, *Pure Appl. Chem.*, 1971, **25**, 563.
24. J. P. Lowe, *Prog. Phys. Org. Chem.*, 1968, **6**, 1.
25. A. von Baeyer, *Ber.*, 1885, **18**, 2269.
26. For a recent n.m.r. study see J. B. Lambert, J. J. Papay, S. A. Khan, K. A. Kappauf, and E. S. Magyar, *J. Amer. Chem. Soc.*, 1974, **96**, 6112.
27. H. Sasche, *Ber.*, 1890, **23**, 1363.
28. E. Mohr, *J. prakt. Chem.*, 1918, [2] **98**, 315; *Ber.*, 1922, **55**, 230.
29. For a historical survey, see D. H. R. Barton, O. Hassel, K. S. Pitzer, and V. Prelog, *Science*, 1954, **119**, 49; *Nature*, 1953, **172**, 1096.
30. D. H. R. Barton, *Experientia*, 1950, **6**, 316.
31. A comprehensive survey of the structure of cyclohexane has recently been published; see E. Osawa, J. B. Collins, and P. von R. Schleyer, *Tetrahedron*, 1977, **33**, 2667.
32. For a review of non-chair conformations of six-membered rings, see G. M. Kellie and F. G. Riddell, *Topics Stereochem.*, 1974, **8**, 225.
33. E. M. Engler, J. D. Andose, and P. von R. Schleyer, *J. Amer. Chem. Soc.*, 1973, **95**, 8005.
34. N. L. Allinger, M. T. Tribble, M. A. Miller, and D. H. Wertz, *J. Amer. Chem. Soc.*, 1971, **93**, 1637.
35. M. Squillacote, R. S. Sheridan, O. L. Chapman, and F. A. L. Anet, *J. Amer. Chem. Soc.*, 1975, **97**, 3244.
36. G. Binsch, *Topics Stereochem.*, 1968, **3**, 97.
37. O. A. Subbotin and N. M. Sergeyev, *J.C.S. Chem. Comm.*, 1976, 141.
38. D. Cremer, J. S. Binkley, and J. A. Pople, *J. Amer. Chem. Soc.*, 1976, **98**, 6836.
39. N. L. Allinger, J. A. Hirsch, M. A. Miller, I. J. Tyminski, and F. A. Van-Catledge, *J. Amer. Chem. Soc.*, 1968, **90**, 1199.
40. D. H. Wertz and N. L. Allinger, *Tetrahedron*, 1974, **30**, 1579.
41. N. L. Allinger and M. A. Miller, *J. Amer. Chem. Soc.*, 1961, **83**, 2145.
42. J. B. Hendrickson, *J. Amer. Chem. Soc.*, 1967, **89**, 7036.
43. J. B. Hendrickson, R. K. Boeckman, Jr., J. D. Glickson, and E. Grunwald, *J. Amer. Chem. Soc.*, 1973, **95**, 494.
44. For a general survey of the structures of medium-ring cycloalkanes, see J. D. Dunitz, *Perspect. Struct. Chem.*, 1968, **2**, 1.
45. J. E. Anderson, E. S. Glazer, D. L. Griffith, R. Knorr, and J. D. Roberts, *J. Amer. Chem. Soc.*, 1969, **91**, 1386.
46. F. A. L. Anet and M. St. Jacques, *J. Amer. Chem. Soc.*, 1966, **88**, 2585, 2586.
47. A. Almenningen, O. Bastiansen, and H. Jensen, *Acta Chem. Scand.*, 1966, **20**, 2689.
48. J. B. Hendrickson, *J. Amer. Chem. Soc.*, 1967, **89**, 7043, 7047.
49. R. L. Hilderbrandt, J. D. Wieser, and L. K. Montgomery, *J. Amer. Chem. Soc.*, 1973, **95**, 8598.
50. M. Saunders, *Tetrahedron*, 1967, **23**, 2105.
51. For a comprehensive review of medium-ring cycloalkane chemistry, see J. Sicher, *Prog. Stereochem.*, 1962, **3**, 202; see also A. C. Cope, M. M. Martin, and M. A. McKervey, *Quart. Rev.*, 1966, **20**, 119.
52. C. A. McAuliffe, 'The Hydrogen Economy', *Chem. Britain*, 1973, **9**, 559.
53. 'Experimental Thermochemistry', ed. F. D. Rossini, Interscience, New York, 1956, vol. 1; *ibid.*, ed. H. A. Skinner, 1962, vol. 2.
54. J. D. Cox and G. Pilcher, 'Thermochemistry of Organic and Organometallic Compounds', Academic, London, 1970.
55. D. R. Stull, E. F. Westrum, Jr., and G. C. Sinke, 'The Chemical Thermodynamics of Organic Compounds', Wiley, New York, 1969.
56. K. Fajans, *Ber.*, 1920, **53**, 643.
57. N. V. Sidgwick, 'The Covalent Link in Chemistry', Cornell University Press, 1933.
58. L. Pauling, 'The Nature of the Chemical Bond', 3rd edn., Cornell University Press, 1960.
59. C. T. Zahn, *J. Chem. Phys.*, 1934, **2**, 671.

60. K. J. Laidler, *Canad. J. Chem.*, 1956, **34,** 626.
61. T. L. Allen, *J. Chem. Phys.*, 1959, **31,** 1039.
62. H. A. Skinner, *J. Chem. Soc.*, 1962, 4396.
63. G. R. Somayajulu and B. J. Zwolinski, *Trans. Faraday Soc.*, 1966, **62,** 2327; *J.C.S. Faraday II*, 1972, **68,** 1971; *ibid.*, 1974, **70,** 967, 973.
64. G. S. Parks and H. M. Hiffman, 'Free Energies of Some Organic Compounds', American Chemical Society, No. 60, The Chemical Catalogue Co., New York, 1932.
65. S. W. Benson, and J. H. Buss, *J. Chem. Phys.*, 1958, **29,** 546; S. W. Benson, F. R. Cruickshank, D. M. Golden, G. R. Haugen, H. E. O'Neal, A. S. Rodgers, R. Shaw, and R. Walsh, *Chem. Rev.*, 1969, **69,** 279.
66. P. von R. Schleyer, J. E. Williams, and K. R. Blanchard, *J. Amer. Chem. Soc.*, 1970, **92,** 2377.
67. G. Mann, *Tetrahedron*, 1967, **23,** 3375; G. Mann, M. Muhlstadt, J. Braband, and E. Doring, *ibid.*, 1967, **23,** 3393.
68. F. H. Westheimer and J. E. Mayer, *J. Chem. Phys.*, 1946, **14,** 733; F. H. Westheimer, *ibid.*, 1947, **15,** 252; see also chapter by F. H. Westheimer in Ref. 21(d).
69. J. B. Hendrickson, *J. Amer. Chem. Soc.*, 1961, **83,** 4537; *ibid.*, 1962, **84,** 3355; *ibid.*, 1964, **86,** 4854; see also Ref. 42.
70. K. B. Wiberg, *J. Amer. Chem. Soc.*, 1965, **87,** 1070.
71. J. E. Williams, P. J. Stang, and P. von R. Schleyer, *Ann. Rev. Phys. Chem.*, 1968, **19,** 591.
72. N. L. Allinger, *Adv. Phys. Org. Chem.*, 1976, **13,** 1.
73. D. F. DeTar and C. J. Tenpas, *J. Org. Chem.*, 1976, **41,** 2009.
74. E. J. Jacob, H. B. Thompson, and L. S. Bartell, *J. Chem. Phys.*, 1967, **47,** 3736.
75. R. H. Boyd, *J. Chem. Phys.*, 1968, **49,** 2574; C. F. Shieh, D. McNally, and R. H. Boyd, *Tetrahedron*, 1969, **25**, 3653; R. H. Boyd, S. N. Sanwal, S. Shary-Tehrany, and D. McNally, *J. Phys. Chem.*, 1971, **75,** 1264; S. Chang, D. McNally, S. Shary-Tehrany, M. J. Hickey, and R. H. Boyd, *J. Amer. Chem. Soc.*, 1970, **92,** 3109.
76. N. L. Allinger, *J. Amer. Chem. Soc.*, 1977, **99,** 8127.
77. For an extensive review of strained molecules, including saturated hydrocarbons, see J. F. Liebman and A. Greenberg, *Chem. Rev.*, 1976, **76,** 311.
78. For a more detailed discussion, see P. George, M. Trachtman, C. W. Bock, and A. M. Brett, *Tetrahedron*, 1976, **32,** 317.
79. L. N. Ferguson, 'Highlights in Alicyclic Chemistry', Part I, Franklin, Palisades, New Jersey, 1973.
80. N. L. Bauld and J. Cessac, *J. Amer. Chem. Soc.*, 1977, **99,** 942.
81. (a) R. L. Augustine, 'Catalytic Hydrogenation', Dekker, New York, 1965; (b) P. Rylander, 'Catalytic Hydrogenation over Platinum Metals', Academic, New York, 1967; (c) H. O. House, 'Modern Synthetic Reactions', 2nd edn., Benjamin, New York, 1972; (d) M. Freifelder, 'Practical Catalytic Hydrogenation', Wiley-Interscience, New York, 1971.
82. H. C. Brown and C. A. Brown, *Tetrahedron, Suppl.*, 1966, **8** (1), 149; C. A. Brown, *J. Amer. Chem. Soc.*, 1969, **91,** 5901; *Chem. Comm.*, 1970, 139.
83. J. A. Osborn, F. H. Jardine, J. F. Young, and G. Wilkinson, *J. Chem. Soc. (A)*, 1966, 1711; for general reviews of homogeneous, catalytic hydrogenation see Ref. 81.
84. J. R. Morandi and H. B. Jensen, *J. Org. Chem.*, 1969, **34,** 1889.
85. E. E. van Tamelen, R. S. Dewey, and R. J. Timmons, *J. Amer. Chem. Soc.*, 1961, **83,** 3725; R. S. Dewey and E. E. van Tamelen, *ibid.*, 1961, **83,** 3729; E. E. van Tamelen, R. S. Dewey, M. F. Lease, and W. H. Pirkle, *ibid.*, 1961, **83,** 4302; M. Ohno and M. Okamoto, *Org. Synth.*, 1969, **49,** 30; W. Dürckheimer, *Annalen*, 1969, **721,** 240.
86. G. M. Whitesides and W. J. Ehmann, *J. Org. Chem.*, 1970, **35,** 3565.
87. For a general review of both chemical and catalytic reduction of olefins, see J. Zabicky, 'The Chemistry of Alkenes', ed. S. Patai, Interscience, New York, 1970, vol. 2, p. 175.
88. E. L. Martin, *Org. Reactions*, 1942, **1,** 155; D. Staschewski, *Angew. Chem.*, 1959, **71,** 726.
89. D. Todd, *Org. Reactions*, 1948, **4,** 378; H. H. Szmant, *Angew Chem. Internat. Edn.*, 1968, **7,** 120; 'Reduction', ed. W. Reuschin and R. L. Augustine, Dekker, New York, 1968, pp. 171–185; see also Ref. 81c.
90. D. J. Cram, M. R. V. Sahyun, and G. R. Knox, *J. Amer. Chem. Soc.*, 1962, **84,** 1734.
91. M. F. Grundon, H. B. Henbest, and M. D. Scott, *J. Chem. Soc.*, 1963, 1855.
92. L. Caglioti and M. Magi, *Tetrahedron*, 1963, **19,** 1127; R. O. Hutchins, B. E. Maryanoff, and C. A. Milewski, *J. Amer. Chem. Soc.*, 1971, **93,** 1793; L. Caglioti, *Tetrahedron*, 1966, **22,** 487.
93. G. R. Pettit and E. E. van Tamelen, *Org. Reactions*, 1962, **12,** 356; H. Hauptmann and W. F. Walter, *Chem. Rev.*, 1962, **62,** 347.
94. M. C. Baird, C. J. Nyman, and G. Wilkinson, *J. Chem. Soc. (A)*, 1968, 348; C. K. Brown and G. Wilkinson, *Tetrahedron Letters*, 1969, 1725; J. Tsugi and K. Ohno, *J. Amer. Chem. Soc.*, 1968, **90,** 94, 99.
95. J. E. Johnston, R. H. Blizzard, and H. W. Carhart, *J. Amer. Chem. Soc.*, 1948, **70,** 3664; R. O. Hutchins, D. Hoke, J. Keogh, and D. Koharski, *Tetrahedron Letters*, 1969, 3495.
96. H. C. Brown and S. Krishnamurthy, *J. Amer. Chem. Soc.*, 1973, **95,** 1669; H. C. Brown and S. Krishnamurthy, *J. Org. Chem.*, 1976, **41,** 3064.
97. H. M. Bell, C. W. Vanderslice, and A. Spehar, *J. Org. Chem.*, 1969, **34,** 3923.
98. R. O. Hutchins, C. A. Milewski and B. E. Maryanoff, *Org. Synth.*, 1973, **53,** 107.
99. A. C. Cope, R. K. Bly, E. P. Burrows, O. J. Ceder, E. Ciganek, B. T. Gillis, R. F. Porter, and H. E. Johnson, *J. Amer. Chem. Soc.*, 1962, **84,** 2170.

100. H. G. Kuivila, L. W. Menapace and C. R. Warner, *J. Amer. Chem. Soc.*, 1962, **84**, 3584; L. W. Menapace and H. G. Kuivila, *J. Amer. Chem. Soc.*, 1964, **86**, 3047.
101. C. R. Noller, *Org. Synth. Coll. Vol.* 2, 1943, 478.
102. P. A. Levene, *Org. Synth. Coll. Vol.* 2, 1943, 320.
103. G. Stallberg, S. Stallberg-Stenhagen, and E. Stenhagen, *Acta Chem. Scand.*, 1952, **6**, 313.
104. W. B. Smith, *J. Org. Chem.*, 1961, **26**, 4206.
105. M. Tamura and J. Kochi, *J. Amer. Chem. Soc.*, 1971, **93**, 1483; G. M. Whitesides, D. E. Bergbreiter, and P. E. Kendall, *ibid.*, 1974, **96**, 2806.
106. A. McKillop, L. F. Elsom, and E. C. Taylor, *J. Amer. Chem. Soc.*, 1968, **90**, 2423.
107. L. Meszaros, *Tetrahedron Letters*, 1967, 4951.
108. F. C. Whitmore and G. H. Fleming, *J. Amer. Chem. Soc.*, 1933, **55**, 3803.
109. E. J. Corey and G. H. Posner, *J. Amer. Chem. Soc.*, 1967, **89**, 3911; *ibid.*, 1968, **90**, 5615.
110. G. M. Whitesides, W. F. Fischer, Jr., J. San Filippo, Jr., R. W. Bashe, and H. O. House, *J. Amer. Chem. Soc.*, 1969, **91**, 4871 and references therein.
111. W. H. Mandeville and G. M. Whitesides, *J. Org. Chem.*, 1974, **39**, 400.
112. For comprehensive reviews of carbon–carbon bond formation *via* π-allylnickel compounds, see M. F. Semmelhack, *Org. Reactions*, 1972, **19**, 115, and P. Heimback, P. W. Jolly, and G. Wilke, *Adv. Organometallic Chem.*, 1970, **8**, 29.
113. H. C. Brown, N. C. Hébert, and C. H. Snyder, *J. Amer. Chem. Soc.*, 1961, **83**, 1001.
114. H. C. Brown, 'Hydroboration', Benjamin, New York, 1962.
115. For a comprehensive review of decarboxylation of acids, see R. A. Sheldon and J. K. Kochi, *Org. Reactions*, 1972, **19**, 279.
116. K. B. Wiberg, B. R. Lowry, and T. H. Colby, *J. Amer. Chem. Soc.*, 1961, **83**, 3998; P. E. Eaton and T. W. Cole, *ibid.*, 1964, **86**, 3157.
117. Recent developments in this reaction have been reviewed by L. Eberson in 'The Chemistry of Carboxylic Acids and Esters', ed. S. Patai, Interscience, New York, 1969; for a summary of synthetic applications see B. C. L. Weedon, *Quart. Rev.*, 1952, **6**, 380.
118. For a detailed account of the earlier examples of intramolecular Wurtz-type reactions, see E. E. Royals, 'Advanced Organic Chemistry', Prentice-Hall, New Jersey, 1954.
119. G. M. Whitesides and F. D. Gutowski, *J. Org. Chem.*, 1976, **41**, 2882.
120. E. J. Corey and E. K. W. Wat, *J. Amer. Chem. Soc.*, 1967, **89**, 2757; E. J. Corey and P. Helquist, *Tetrahedron Letters*, 1975, 4091; for a comprehensive survey of these reactions see Ref. 112.
121. L. Ruzicka, M. Stoll, and H. Schinz, *Helv. Chim. Acta*, 1926, **9**, 249; L. Ruzicka, W. Brugger, M. Pfeiffer, H. Schinz, and M. Stoll, *ibid.*, 1926, **9**, 499.
122. See also Ref. 51a.
123. For an extensive survey of both the Thorpe–Ziegler and Dieckmann cyclization reactions, see J. P. Schaefer and J. J. Bloomfield, *Org. Reactions*, 1967, **15**, 1.
124. For an extensive survey of the acyloin condensation, including the use of the bistrimethylsilyloxy intermediates, see J. J. Bloomfield, D. C. Owsley and J. M. Nelke, *Org. Reactions*, 1976, **23**, 259.
125. A. T. Blomquist and R. D. Spencer, *J. Amer. Chem. Soc.*, 1948, **70**, 30, 34, 36.
126. P. R. Story, B. Lee, C. E. Bishop, D. D. Denson, and P. Busch, *J. Org. Chem.*, 1970, **35**, 3059; P. Busch and P. R. Story, *Synthesis*, 1970, 181.
127. F. Sondheimer, Y. Amiel, and R. Wolovsky, *J. Amer. Chem. Soc.*, 1959, **81**, 4600.
128. For detailed accounts of synthetic aspects of the Diels–Alder reaction, see M. C. Kloetzel, *Org. Reactions*, 1948, **4**, 1; H. L. Holmes, *ibid.*, 1948, **4**, 60; A. S. Onishchenko, 'Diene Synthesis', Daniel Davey, New York, 1964; J. Sauer, *Angew. Chem. Internat. Edn.*, 1966, **5**, 211.
129. The synthesis of cyclobutanes from thermal cycloaddition reactions has been discussed in detail by J. D. Roberts and C. M. Sharts, *Org. Reactions*, 1962, **12**, 1.
130. P. de Mayo, *Accounts Chem. Res.*, 1971, **4**, 41.
131. R. B. Woodward and R. Hoffmann, 'The Conservation of Orbital Symmetry', Academic, New York, 1970; G. B. Gill, *Quart. Rev.*, 1968, **22**, 338.
132. H. E. Simmons and R. D. Smith, *J. Amer. Chem. Soc.*, 1958, **80**, 5323; *ibid.*, 1959, **81**, 4256; H. E. Simmons, T. L. Cairns, S. A. Vladuchick, and C. M. Hoiness, *Org. Reactions*, 1973, **20**, 1.
133. For details of general methods for generating carbenes, see 'Carbenes', ed. M. Jones, Jr., and R. A. Moss, Wiley, New York, 1973; W. Kirmse, 'Carbene Chemistry', Academic, New York, 1971; for the use of mercury-containing precursors, see D. Seyferth, *Accounts Chem. Res.*, 1972, **5**, 65.
134. For a comprehensive account of the chemistry of adamantane and related compounds, see R. C. Fort, Jr., 'Adamantane and the chemistry of Diamondoid Molecules', Dekker, New York, 1976.
135. For a survey of reactions of alkanes in super-acid media, see G. A. Olah, 'Carbocations and Electrophilic Reactions', Verlag Chemie, Weinheim, 1973.
136. N. F. Gol'dshleger, V. V. Es'kova, A. E. Shilov, and A. A. Shteinman, *Zhur. fiz. Khim.*, 1972, **46**, 1353.
137. For a concise introduction to alkane oxidation, see L. Reich and S. S. Stivala, 'Autoxidation of Hydrocarbons and Polyolefins', Dekker, New York, 1969; 'The Oxidation of Hydrocarbons in the Liquid Phase', ed. N. M. Emanuel, Pergamon, Oxford, 1965; 'Oxidation and Combustion Reviews', ed. S. Tipper, Elsevier, Amsterdam, 1965.
138. R. Stewart, 'Oxidation Mechanisms', Benjamin, New York, 1964.
139. 'Oxidation in Organic Chemistry', ed. K. B. Wiberg, Part A, Academic, New York, 1965.

140. K. B. Wiberg and G. Foster, *J. Amer. Chem. Soc.*, 1961, **83,** 423.
141. For an authoritative account of the mechanisms of isomerizations of alkanes, see C. D. Nenitzescu, in 'Carbonium Ions', ed. G. A. Olah and P. von R. Schleyer, Wiley-Interscience, New York, 1970, vol. 2, chapter 13.
142. L. Schmerling, in 'Friedel Crafts and Related Reactions', ed. G. A. Olah, Wiley-Interscience, New York, 1964, vol. 2, chapter 25.
143. J. K. A. Clarke and J. J. Rooney, *Adv. Catalysis*, 1976, **25,** 125.
144. Details of oxidation of alicyclic hydrocarbons with ozone on silica gel, including references to the earlier literature, are given by Z. Cohen, E. Keinan, Y. Mazur, and T. H. Varkony, *J. Org. Chem.*, 1975, **40,** 2141.
145. Recent synthetic, mechanistic, and thermodynamic aspects of rearrangements leading to diamondoid hydrocarbons are discussed by E. M. Engler and P. von R. Schleyer, in 'MTP International Review of Science, Organic Chemistry, Series One', Butterworths, 1973, vol. 5, p. 239, and M. A. McKervey, *Chem. Soc. Rev.*, 1974, **3,** 479; see also Ref. 134.
146. For a comprehensive survey of metal-catalysed rearrangements of small-ring polycycles, see K. C. Bishop III, *Chem. Rev.*, 1976, **76,** 461.

2.2

Olefinic and Acetylenic Hydrocarbons

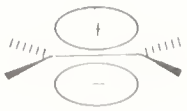
G. H. WHITHAM
University of Oxford

2.2.1 INTRODUCTION 121
2.2.2 PREPARATION OF OLEFINIC HYDROCARBONS 126
2.2.2.1 Eliminations of H—C_β—C_α—X systems 126
2.2.2.2 Eliminations on Y—C_β—C_α—X systems 128
2.2.2.3 Cycloeliminations 131
2.2.2.4 Partial reductions 133
2.2.2.5 Sulphonylhydrazone eliminations 134
2.2.2.6 Wittig and related reactions 136
2.2.2.7 Various coupling reactions 139
2.2.2.8 Electrocyclic reactions 140
2.2.2.9 Cyclo-oligomerizations 141
2.2.2.10 Coupling of allylic derivatives 142
2.2.2.11 Reactions of vinyl derivatives 143
2.2.3 REACTIONS OF OLEFINIC HYDROCARBONS 144
2.2.3.1 Electrophilic additions 144
2.2.3.2 Nucleophilic additions 154
2.2.3.3 Radical additions 155
2.2.3.4 Cycloadditions and related reactions 158
2.2.3.5 Oxidations 164
2.2.3.6 Reductions 166
2.2.3.7 Rearrangements 166
2.2.3.8 Photochemical reactions 167
2.2.3.9 Special features 168

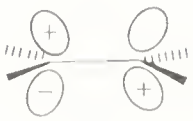
2.2.1 INTRODUCTION

The fundamental structural unit present in olefinic hydrocarbons is the carbon–carbon double bond, the prototype olefin being ethylene (ethene), C_2H_4. A convenient representation of the carbon–carbon double bond is constructed from two sp^2 hybridized carbons linked by a σ-bond, leaving two p-orbitals which constitute the basis orbitals of the filled, bonding (**1**) and the unfilled, antibonding (**2**) π-orbitals.

For simple olefins, the π-bond energy is of the order of 270 kJ mol^{-1}, which is the barrier to torsion about the double bond in 1,2-dideuterioethylene. The simple bonding model accommodates the planarity of ethylene; the bond angles only differ slightly from



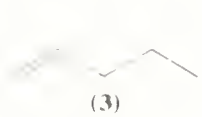
(1)



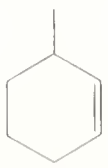
(2)

the idealized 120°. Increased C—C—C bond angles are found for substituted alkenes owing to C/C repulsion; thus the C—C—C bond angle for *trans*-but-2-ene is 124°.

Olefin nomenclature is derived by addition of the suffix 'ene' to the root of the name of the corresponding saturated hydrocarbon; numbers indicate the position of the double bond, *e.g.* pent-1-ene (**3**), 3-methylcyclohexene (**4**), *etc.* For acyclic olefins, and for medium and larger ring olefins, configurational isomers (diastereoisomers) exist owing to the high barrier to rotation about the double bond, *e.g. cis*- or (*Z*)- (**5**) and *trans*- or (*E*)-but-2-ene (**6**), *cis*- or (*Z*)- (**7**) and *trans*- or (*E*)-cyclo-octene (**8**), (*E*)-3-methylpent-2-ene (**9**), *etc.*



(3)

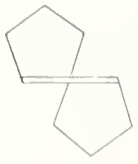


(4)

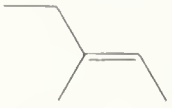
(5)

(6)

(7)



(8)

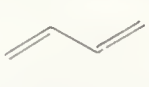


(9)

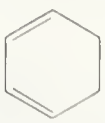
Acetylenic hydrocarbons are based on the triple bond unit, the parent compound being acetylene (ethyne), C_2H_2. The linear arrangement of atoms in acetylene is conveniently portrayed in terms of two *sp*-hybrid carbons joined by a σ-bond, the remaining four electrons being accommodated in two mutually orthogonal bonding π-orbitals. The overall π-bond energy of acetylene is *ca.* 185 kJ mol^{-1}, *i.e.* less than twice that of ethylene. Owing to the linearity of the system, configurational isomers do not exist. Naming is again straightforward, the suffix 'yne' being used as in hex-2-yne (**10**).

Clearly, several or many double or triple bonds may be present in a hydrocarbon skeleton, and such systems may be conjugated (alternating single and multiple bonds), *e.g.* buta-1,3-diene (**11**), cyclohexa-1,3-diene (**12**), but-1-en-3-yne (vinylacetylene) (**13**), *etc.* or unconjugated, *e.g.* penta-1,4-diene (**14**). Conjugated dienes like buta-1,3-diene exist predominantly in an extended coplanar conformation (**11**) often termed *transoid* (or s-*trans*). There is a minor contribution (*ca.* 0.5%) from a second conformation — the *cisoid* (or s-*cis*) (**15**) — for butadiene at room temperature. This is usually considered to be planar but there may be some torsion about the C-2—C-3 bond to relieve H/H interactions. Clearly, cyclic dienes such as (**12**) can only be *cisoid.*

(10)



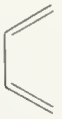
(11)



(12)

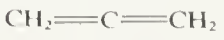
(13)

(14)



(15)

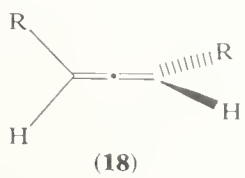
(16)



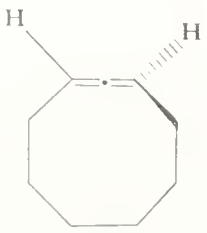
(17)

Systems possessing double bonds directly linked to one another are known as cumulenes, *e.g.* buta-1,2,3-triene (**16**). The parent compound, propa-1,2-diene (**17**),

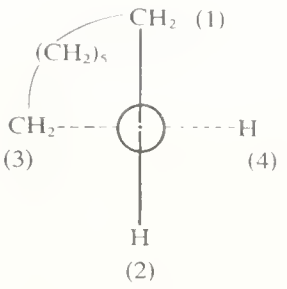
usually known as allene, has two contiguous double bonds. Allene can be represented in terms of two sp^2 carbons joined by a central *sp* carbon with two mutually orthogonal π-orbitals between C-1 and C-2, and C-2 and C-3, respectively. This accommodates the known geometry, the H—C-1—H plane being at right angles to the H—C-3—H plane. A stereochemical consequence of this geometry is that substituted allenes in which at *least* one hydrogen on C-1 and one on C-3 are replaced by another substituent (which *may* both be the same) have no reflection symmetry and are therefore chiral, *cf.* (**18**). Many optically active allenes are known,[1] a simple cyclic example being cyclonona-1,2-diene (**19**). Configurational nomenclature for optically active allenes in terms of the (*RS*) system is based on the sequence rule (see Section 1.4.3.1) together with the extra proximity rule that near groups precede far groups. Thus, projection formula (**20**) depicts (*R*)-(+)-cyclonona-1,2-diene. The (*R*) configuration is deduced since groups 1, 2, and 3 are oriented in a clockwise sense (*cf.* Section 1.4.3.1).



(**18**)



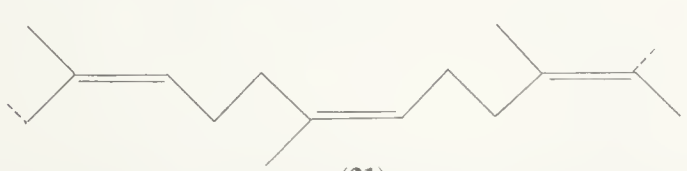
(**19**)



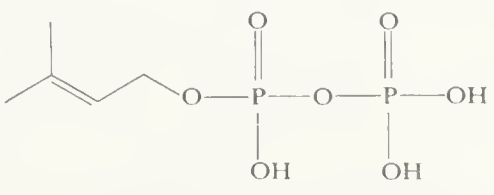
(**20**)

The most important simple olefins from the industrial point of view are ethylene, propylene (propene), and the butenes, all produced by the steam cracking of naphtha (petroleum fraction, b.p. 50–200 °C). Ethylene is used in the production of polyethylene, ethylene dihalides, ethylene oxide, ethanol, ethylbenzene, acetaldehyde, *etc.* Propylene is important as a source for polypropylene, isopropanol, acrylonitrile, phenol, and acetone (*via* isopropylbenzene), propylene oxide, allyl chloride, acrylic acid, *etc.* n-Butenes are used, amongst other things, in the production of butadiene, and isobutene is valuable as a precursor of butyl rubber (co-polymer with a small amount of isoprene). By far the most important aromatic olefinic hydrocarbon is styrene (1-phenylethylene), obtained by high-temperature dehydrogenation of ethylbenzene; it is used chiefly in the preparation of polystyrene and related co-polymers.

In industrial terms the most important conjugated diene is buta-1,3-diene, being one of the largest tonnage organic chemicals produced. Much effort has been expended in adjusting the conditions for steam cracking of naphtha to optimize the butadiene yield (*ca.* 5%). Alternatively, it is obtained by the dehydrogenation of butenes. Its predominant use is in the production of various synthetic rubbers *via* direct polymerization, *e.g.* using Ziegler catalysts, or copolymerization with styrene giving styrene–butadiene rubber (SBR), or with acrylonitrile giving nitrile rubber. The other important conjugated diene hydrocarbon is isoprene (2-methylbuta-1,3-diene) which is, however, relatively expensive to produce. Natural rubber (**21**) is effectively a polymer of isoprene and some synthetic rubber is produced by polymerization of isoprene using Ziegler-type catalysts.



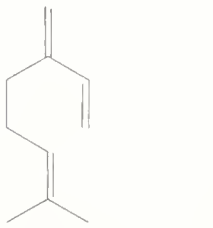
(**21**)



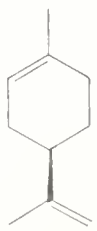
(**22**)

Many naturally occurring olefinic hydrocarbons are known. These are mostly terpenes, components of the essential oils in higher plants, which, like natural rubber, comprise C_5 'isoprene-units' linked together in more or less convoluted ways. This reflects a common

biogenctic origin. They are derived from the natural precursor isopentenyl pyrophosphate (**22**), Nature's isoprene unit. Details of this process are given in Chapter 29.2. It is sufficient to point out here that terpenes are classified as (i) monoterpenes, comprising two C_5 units, *e.g.* myrcene (**23**), (+)-limonene (**24**), (+)-α-pinene (**25**), (−)-camphene (**26**), (ii) sesquiterpenes, three C_5 units, *e.g.* β-farnesene (**27**), bisabolene (**28**), (−)-caryophyllene (**29**), (iii) diterpenes, four C_5 units, *e.g.* (+)-phyllocladene (**30**), and (iv) triterpenes, six C_5 units. Most triterpenes are not hydrocarbons, but squalene (**31**) is. It occupies a pivotal role in the biogenesis of the other triterpenes and steroids and is thereby of considerable importance. There is also a group of compounds based on two sets of four C_5 units linked head-to-head: the carotenoids. These C_{40} compounds are widespread as colouring matters in plants and animals; important hydrocarbon examples are β-carotene (**32**) from carrots and lycopene (**33**) which is responsible for the red colour of tomatoes.

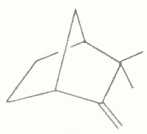


(**23**)

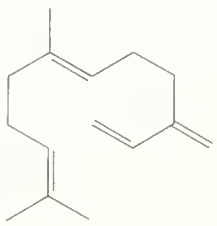


(**24**)

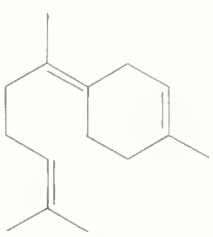
(**25**)



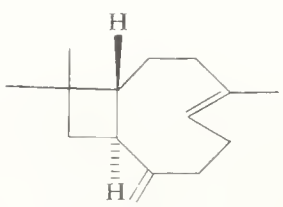
(**26**)



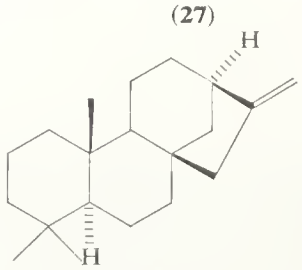
(**27**)



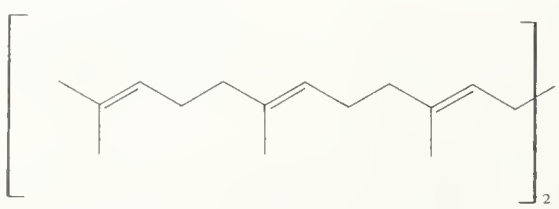
(**28**)



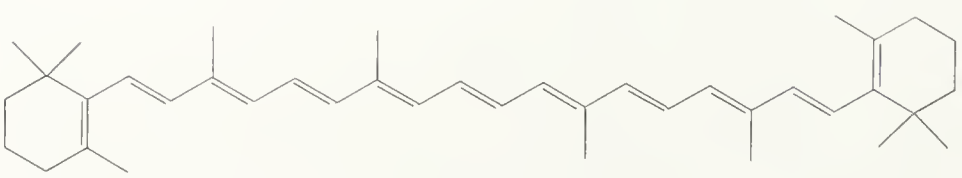
(**29**)



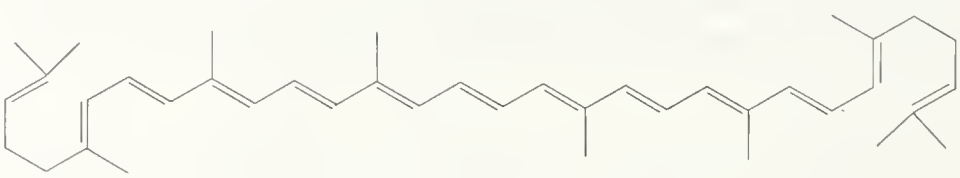
(**30**)



(**31**)



(**32**)

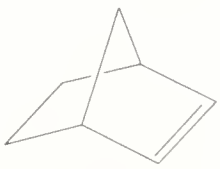


(**33**)

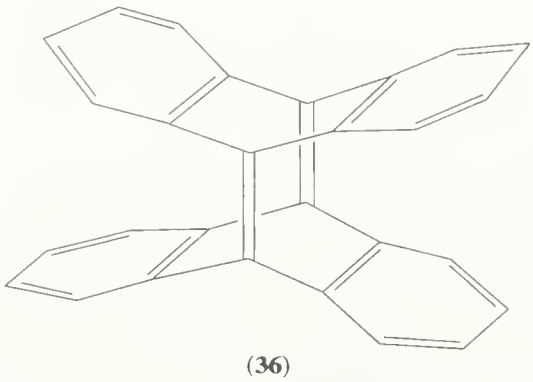
A number of examples of constitutionally unusual unsaturated hydrocarbons deserve special mention, a particularly interesting group being strained olefins.[2] Two types of strain can be recognized: (i) in-plane distortion leading to reduced C—C=C angles, *i.e.* 'σ-strain', and (ii) out-of-plane distortion, *i.e.* 'π-strain'. Cyclopropene (**34**) and norbornene (**35**) exemplify σ-strained olefins with strain energies of respectively 227 and

108 kJ mol^{-1}. Each shows high reactivity in additions where strain is relieved at the transition state. π-Strained olefins with distorted π-bonds leading to reduced π-bond energy are of several types. The remarkable compound (**36**) has all four substituents attached to the double bond tied back out of the olefinic plane (deviation 19.7°). More common are examples of torsional distortion due to either interaction between substituents, *e.g. cis*-di-t-butylethylene (strain energy 45 kJ mol^{-1}), or incorporation of a *trans* double bond into a medium sized ring, *e.g.* the isolable and resolvable *trans*-cyclo-octene (**37**) (strain energy 70 kJ mol^{-1}) and *trans*-cycloheptene (**38**) (estimated strain energy 112 kJ mol^{-1}), which has only been obtained and trapped as a transient species.

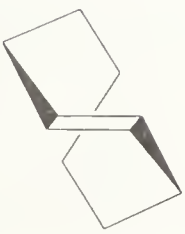
(**34**)



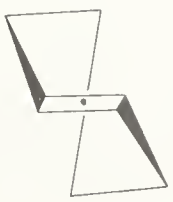
(**35**)



(**36**)

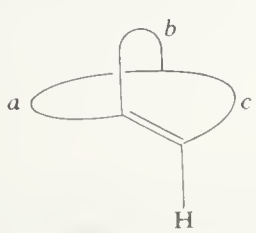


(**37**)

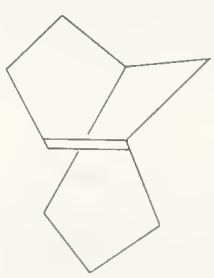


(**38**)

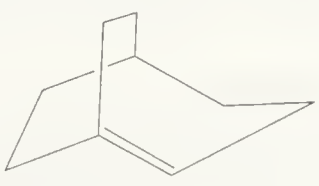
Related to the *trans*-cycloalkenes are those bicyclic olefins (*e.g.* **39**) containing a bridgehead double bond which are formally forbidden by Bredt's rule.[3] It is now clear that this rule is not so stringent as was originally thought and compounds of the type (**39**) have now been isolated even for relatively small sized bridges *a*, *b*, and *c*. Thus bicyclo[3,3,1]non-1-ene (**40**), clearly related to *trans*-cyclo-octene (**37**), is readily prepared and can be isolated. The bridgehead olefins (**41**) and (**42**), which are effectively *trans*-cycloheptenes, have been prepared transiently and trapped. Even evidence for the formal *trans*-cyclohexenes norborn-1-ene (**43**) and adamantene (**44**), as fleeting intermediates, has been obtained.



(**39**)

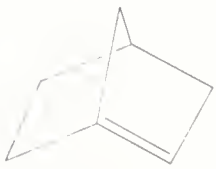


(**40**)

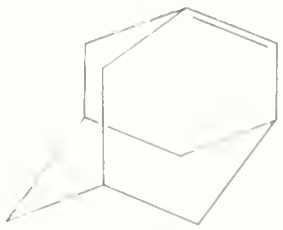


(**41**)

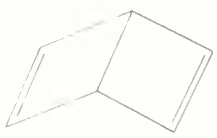
(42)



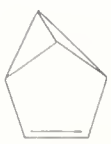
(43)



(44)



(45)



(46)

Although there are many other examples of unusually strained olefinic hydrocarbons which have exercized the imagination and taxed the synthetic prowess of chemists, two interesting cases which should be mentioned are the valence isomers of benzene: bicyclo[2,2,0]hexa-2,5-diene ('Dewar benzene') (**45**) and 'benzvalene' (**46**), strained to the tune of 117 and 143 kJ mol^{-1}, respectively.

Cyclic allenes and alkynes have also proved of interest as cyclic systems containing geometrically demanding structural units. The idealized C=C=C angle of 180° and 'torsional angle' of 90° would be expected to be acceptable only in relatively large rings. Cyclonona-1,2-diene (**19**) is readily isolable, cyclo-octa-1,2-diene has been demonstrated spectroscopically at low temperatures, while trapping evidence for even the seven- and six-membered ring species has been adduced. The allenic groups in the latter compounds are considered to be somewhat distorted by bending of the C=C=C fragment and twisting about the C-1—C-2 bond. Cycloalkynes[4] have also proved to be more accessible than naively might have been expected for compounds containing what is ideally a linear C_4 unit. Cyclo-octyne (strain energy 42 kJ mol^{-1}) is quite stable, and although cyclo-heptyne has only been trapped as a transient, the 3,3,7,7-tetramethyl analogue has been isolated. Evidence for cyclohexyne, cyclopentyne, and even for norborn-2-yne has been provided from trapping and labelling studies. Apparently bending of the formally linear acetylene system is not energetically prohibitive; thus the remarkable compound cyclo-octa-1,5-diyne has been shown to have a C—C≡C angle of 159.3° by X-ray crystallography.

2.2.2 PREPARATION OF OLEFINIC HYDROCARBONS

A very large number of methods has been developed for the synthesis of compounds containing double bonds.[5] We shall only be concerned here with those reactions which have been used for the synthesis of olefinic hydrocarbons. Particular attention will be paid to procedures which give control over the position and/or stereochemistry of the double bond. Two main classes can be discerned: (i) those reactions which lead to the introduction of a double bond into an existing carbon skeleton, and (ii) those which result in construction of the carbon skeleton with concomitant incorporation of the double bond.

The first class of reactions comprises mostly 1,2-eliminations of various types and it is convenient to subdivide the material.

2.2.2.1 Eliminations of H—C_β—C_α—X systems[6]

This subdivision includes many of the longest known ways of preparing olefins. However, they suffer from the fact that, in general, there will be more than one C_β—H bond suitably placed for elimination along with the leaving group (X), thereby leading to

only limited control over the position of the new double bond. Useful preparative goals may often be achieved where only one C_β atom is present in the reactant, where two or three C_β atoms are equivalent by symmetry, or where one of the possible olefins is appreciably more stable thermodynamically than the alternatives and the reaction is either equilibrium-controlled or the transition state is product-like in character (Saytzeff orientation). Sometimes a measure of stereochemical control may be achieved in that reactions are often either cleanly *anti* (H and X departing on opposite sides of the newly forming double bond) or *syn* (H and X depart on the same side) eliminations.

Elimination of alkyl halides or tosylates typify this reaction type. The choice of base is often crucial. In general, sterically hindered bases favour elimination over the possible competing reaction of substitution.[7] Thus, tertiary alkyl halides undergo elimination with a wide range of bases, secondary alkyl halides require a more discriminating base, and with primary alkyl halides only relatively few base/solvent systems, *e.g.* potassium t-butoxide in DMSO or ethyldi-isopropylamine (Hunig's base), give good yields of olefin. For example, n-octyl bromide affords oct-1-ene in 99% yield on treatment with Hunig's base at 180 °C. Bulky bases tend to give predominant formation of the less-stable olefin (Hofmann orientation) *via* the less-crowded transition state.

A further complication is that systems prone to rearrangement, *e.g.* bornyl tosylate, will often give rearranged olefins as products unless solvolysis is minimized by use of aprotic conditions, *e.g.* potassium t-butoxide complexed with 18-crown-6 in benzene. Other particularly good bases for favouring elimination *versus* substitution are the bicyclic amidines 1,5-diazabicyclo[4,3,0]non-5-ene and 1,5-diazabicyclo[5,4,0]undec-5-ene.[8]

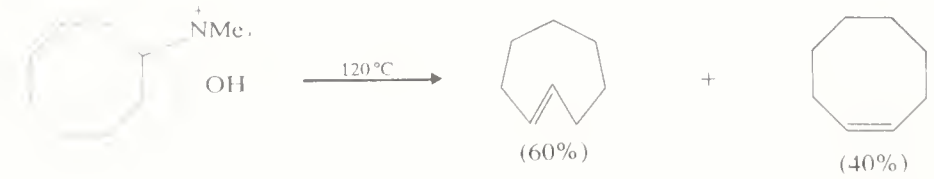
The dehydration of alcohols is another well-known route to olefins which also suffers from lack of constitutional control. It is often acid catalysed and this leads, in sensitive systems, to carbenium ion rearrangements. However, in favourable cases, *e.g.* (**47**) and (**48**), good yields can be obtained. Tertiary alcohols are more readily dehydrated than secondary, as expected for a carbenium ion reaction, and the dehydration of (**48**) can be performed using potassium bisulphate, or phosphorus oxychloride/pyridine, or even by heating in the presence of a trace of iodine.

(**47**)

(**48**)

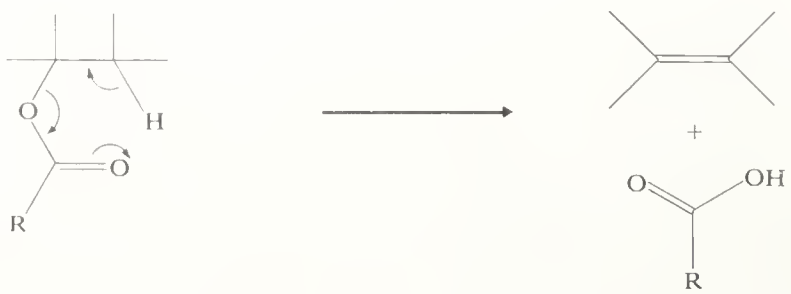
Pyrolytic elimination of tertiary amines from quaternary ammonium hydroxides tends to give the less-substituted olefin[9] — the paradigm of Hofmann orientation, *e.g.* (**49**) → (**50**), unless a more substituted C_β—H is activated by, for example, an aromatic ring. In general, Hofmann elimination occurs by an *anti* process although, in medium-sized rings, *trans*-olefin is obtained *via* a *syn* elimination,[10] *cf.* equation (1). This remarkable example, in which the much more strained olefin is formed predominantly, provides a dramatic illustration that the transition state for Hofmann elimination can have little product-like character.

(**49**) (**50**)



(1)

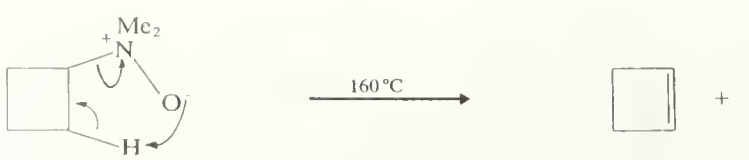
Another category of elimination in this subdivision is the pyrolysis of carboxylate esters and related derivatives of alcohols.[11] The reaction is a *syn* elimination, *i.e.* equation (2), and thus a degree of constitutional control can sometimes be achieved by appropriate choice of stereochemistry of substrate, *e.g.* equation (3). In more complex cases, rearrangements have been observed but these can be minimized by use of xanthate esters (dithiocarbonates) which also undergo elimination at lower temperatures than carboxylate esters.[12] The pyrolysis of phenylurethanes of secondary and tertiary alcohols has also found preparative use.



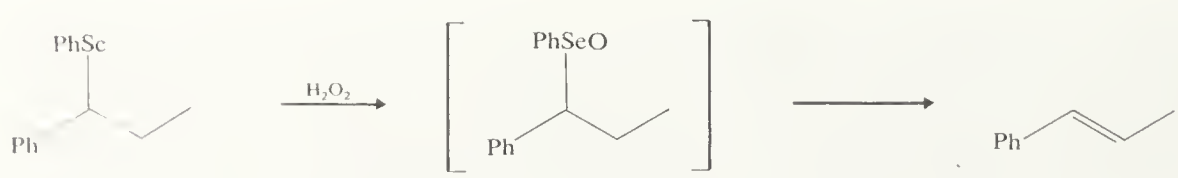
(2)

(3)

A range of related *syn* eliminations involving a five-membered cyclic transition state can be illustrated by the pyrolysis of amine oxides (Cope elimination)[9] (equation 4). Similar eliminations of sulphoxides and selenoxides have recently come into vogue for olefin synthesis. Selenoxide eliminations occur under remarkably mild conditions, at or a little above room temperature, and usually oxidation of a selenide leads directly to elimination products,[13] *e.g.* equation (5).



(4)

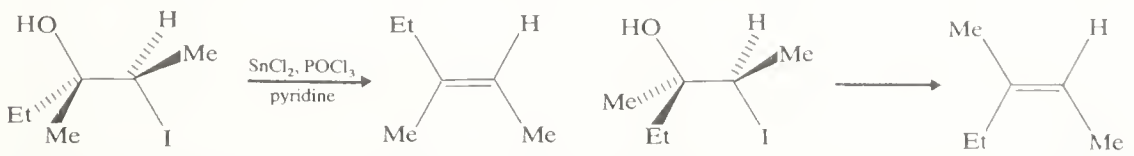


(5)

2.2.2.2 Eliminations on Y—C_β—C_α—X systems

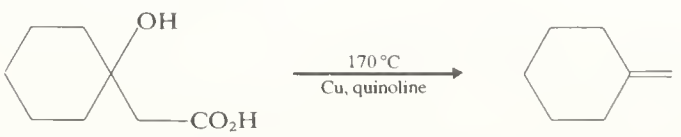
In recent years, elimination of XY from such systems where Y is an electrofugal group — able formally to depart as a positively charged species — other than hydrogen have been extensively investigated since they give control over double bond position. In addition, stereospecificity is sometimes also possible if the precursor can be obtained diastereoisomerically pure.

One of the longest known examples is the reductive elimination of 1,2-dihalides, halohydrins, haloethers, *etc.* Zinc is usually employed as reducing agent, although lithium aluminium hydride and potassium iodide have also been used. Fairly high stereospecificity is sometimes found, *e.g.* (±)-2,3-dibromobutane with zinc gives but-2-ene as >96% *cis*-isomer, indicative of an *anti* elimination process. However, (±)-1,2-dibromo-1,2-diphenylethane with zinc/ethanol gives a *cis*- to *trans*-stilbene ratio of 0.12 and many examples of non-stereospecific reduction are known. A careful study of reaction conditions can often lead to better stereochemical control, an important illustration being the reduction of iodohydrins in the last stage of Cornforth's olefin synthesis,[14] *cf.* equation (6). The iodohydrin precursors are obtained by epoxide opening.



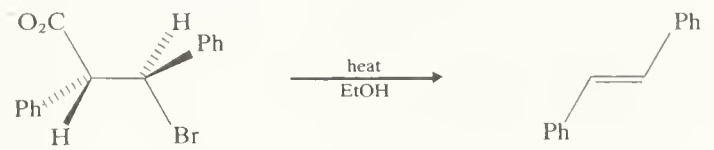
(6)

The decarboxylation–dehydration of β-hydroxycarboxylic acids has been fairly frequently used as a constitution-specific olefin synthesis, particularly for terminal alkenes owing to the availability of the precursors *via* the Reformatsky and analogous reactions. Typical conditions involve pyrolysis in the presence of copper and quinoline, *e.g.* equation (7). In a recent milder modification, the hydroxy acid is heated with the dimethyl acetal of *N*,*N*-dimethylformamide in chloroform.[15]

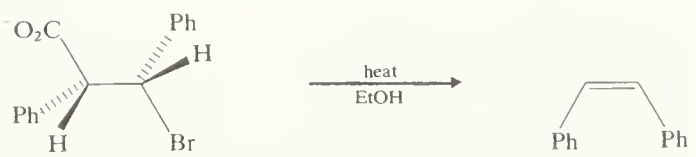


(7)

Closely related is the decarboxylation–elimination of β-halocarboxylates. In some instances, β-lactones are known to be intermediates (see later), although a clean *anti* elimination of CO_2 and Br^- is believed to occur in others, *e.g.* equations (8) and (9). In better ionizing solvents, low stereospecificity is observed and this is attributed to a solvolytic mechanism *via* the β-carbenium ion.

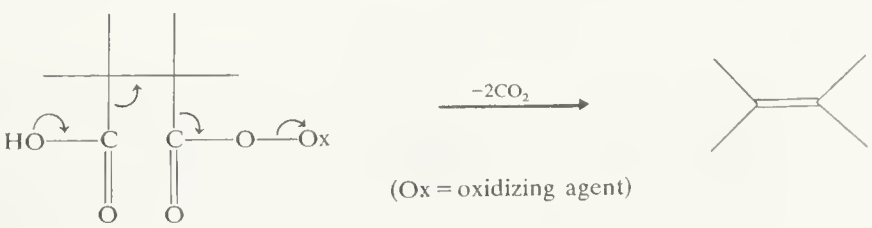


(8)

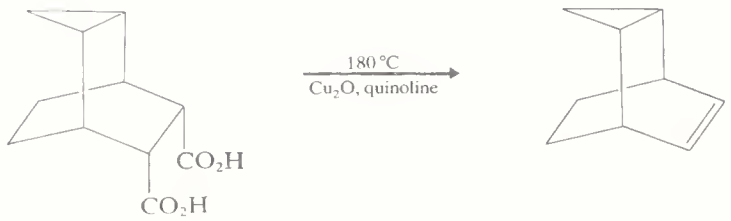


(9)

A useful constitution-specific route to olefins in this category of elimination is the oxidative decarboxylation of 1,2-dicarboxylic acids, the general process being schematically represented in equation (10). It has been carried out using lead tetra-acetate (Grob), electrolytically, and, more recently, with cuprous oxide in quinoline.[16] The reaction is not stereospecific; however, it affords a convenient route to cyclic olefins where, in the case of normal-sized rings, stereochemistry is not a problem since only *cis* double bonds are accessible. Appropriate precursors are often available *via* Diels–Alder synthesis, *e.g.* equation (11).

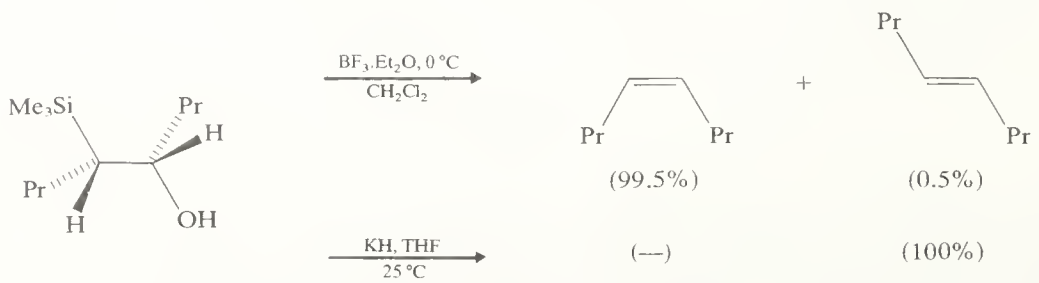


(10)

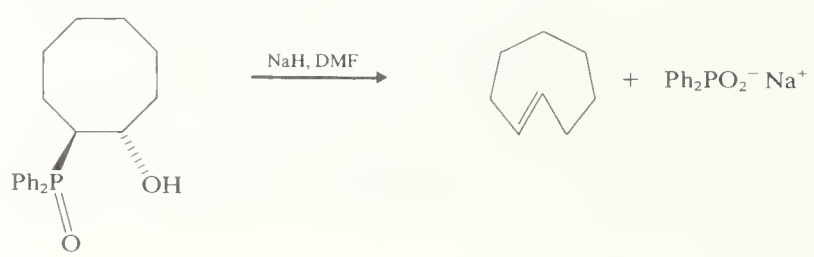


(11)

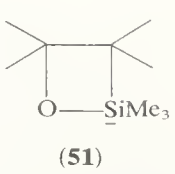
One of the more versatile β-elimination-based olefin syntheses is one involving β-hydroxysilanes.[17] Here, by appropriate choice of conditions, either an *anti* elimination of 'Me_3SiOH' (promoted by acid catalysis or after conversion of hydroxyl into a respectable leaving group, *e.g.* with $MeSO_2Cl$) or a *syn* elimination (base-induced 'Peterson elimination') can be achieved. Thus, either of a pair of diastereoisomeric olefins can be obtained from a given precursor in favourable cases (equation 12). A number of ways are available for making β-hydroxysilanes.[18] Another example of a base-induced stereospecific *syn* elimination is provided by the elimination of phosphinate from the anion of a β-hydroxyphosphine oxide, *e.g.* equation (13).[19] *syn* Elimination of these types probably proceed through four-membered ring intermediates, *e.g.* (**51**) for the Peterson reaction and (**52**) in the case of β-hydroxyphosphine oxides. Such intermediates are analogous to those postulated in the Wittig reaction (see Section 2.2.2.6).



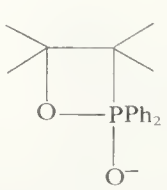
(12)



(13)

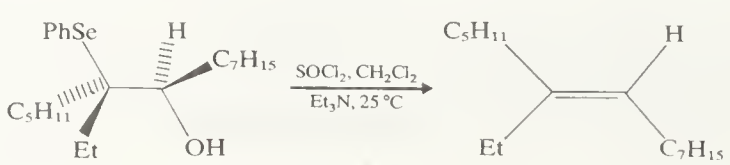


(**51**)

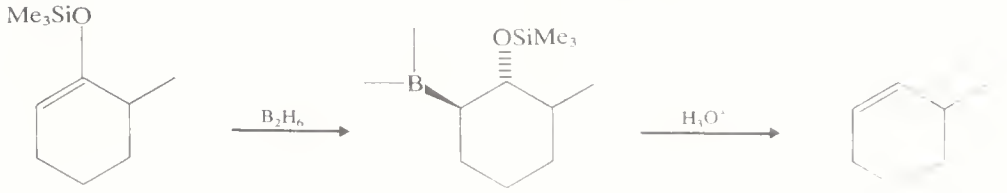


(**52**)

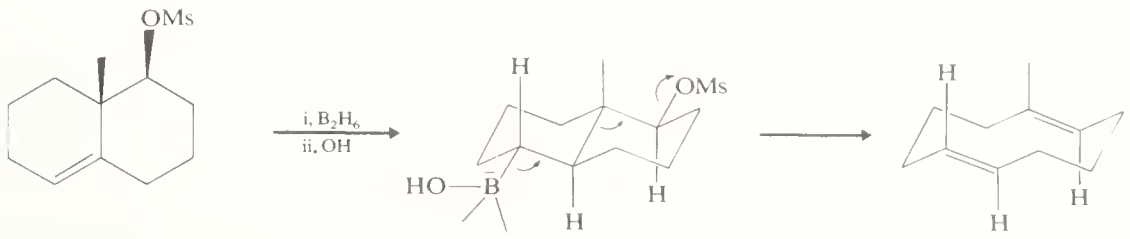
It is not possible in limited space to do justice to all the X—C—C—Y systems which have been utilized as precursors to olefins in recently developed syntheses. Further examples of substrates which undergo *anti* eliminations include β-hydroxyselenides (which can be obtained stereospecifically *via* epoxide opening), *e.g.* equation (14),[20] and β-alkoxyboranes, derived by hydroboration, *e.g.* equation (15).[21] Borane eliminations have also been extended to embrace more complex fragmentation reactions leading, for example, to medium-sized ring olefins (equation 16).[22]



(14)



(15)



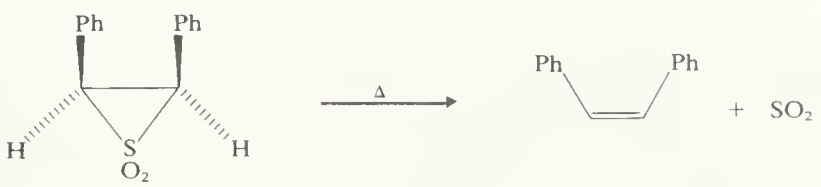
(16)

A number of β-eliminations of the general type under discussion are involved as the second stage of some overall carbonyl olefination reactions. Some of these are dealt with later.

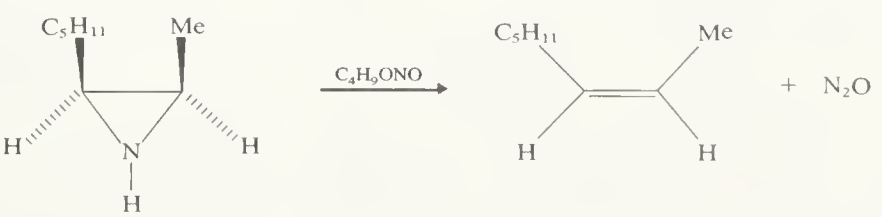
2.2.2.3 Cycloeliminations

A number of ring systems, mostly heterocyclic, undergo cycloelimination under appropriate conditions with formation of olefins. These reactions have found use in synthesis. One advantage of this type of reaction is that the leaving fragment usually departs suprafacially (*syn* elimination) and thus control over both position and stereochemistry of the resulting double bond is possible.

Examples involving three-membered rings are provided by the cheletropic extrusion of sulphur dioxide from episulphones, which is a key step in the Ramberg–Bäcklund reaction (equation 17), and the deamination of aziridines induced by nitrosation (equation 18).[23] Related reactions are (i) the desulphurization of episulphides, which occurs spontaneously in some cases where the product is a conjugated olefin, and in others on treatment with thiophiles, *e.g.* triphenylphosphine, and (ii) the deselenation of episelenides formed, for example, *in situ* on treatment of epoxides with trialkylphosphine selenides.

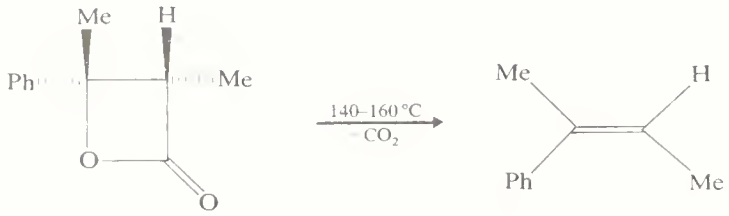


(17)



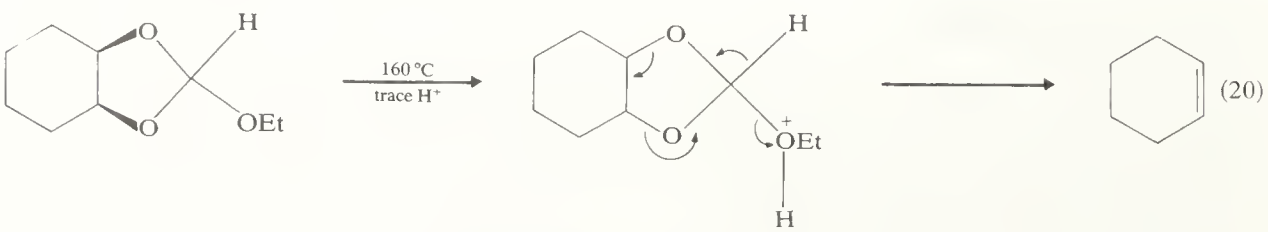
(18)

Heterocyclic four-membered ring fragmentations are very probably involved in the olefin forming step of the Wittig, Peterson, and related reactions, but since the intermediates are not generally isolable or even directly demonstrable they will not be considered here. A more clear-cut example is provided by the thermal decomposition of β-lactones formed, for example, from β-halocarboxylic acids, *e.g.* equation (19).[24]

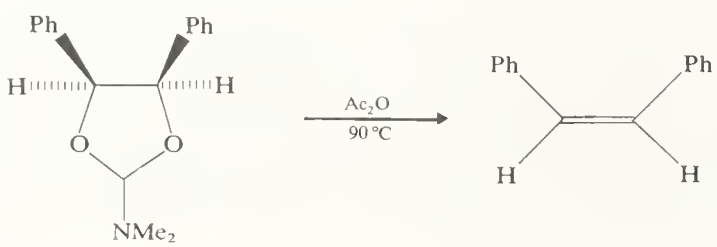


(19)

Cycloeliminations of five-membered heterocyclic systems are more prevalent. Examples include the fragmentation of cyclic orthoesters (equation 20), and of the corresponding 2-dimethylamino derivatives (equation 21),[25] which occur under essentially cationic conditions and provide stereospecific routes to olefins from 1,2-diols. Cyclic thionocarbonates, also derived from 1,2-diols, undergo cycloelimination with abstraction of sulphur on treatment with trialkyl phosphites to afford olefins stereospecifically, *e.g.* equation (22). A similar process occurs with cyclic trithiocarbonates.[26] Related anionic reactions are found for 2-phenyl-1,3-dioxolans on treatment with alkyl-lithium reagents (equation 22), and the metallation–fragmentation of 2-phenyl-1,3-oxathiolans (equation 23). The latter two reactions[27] comprise six-electron cycloeliminations, the effective reverse of 1,3-dipolar cycloadditions. A variation on the theme is provided by the sulphoximine pyrolysis illustrated in equation (24).[28] Here the precursor, derived ultimately from an epoxide, is the cyclic *N*-aminourethane shown.

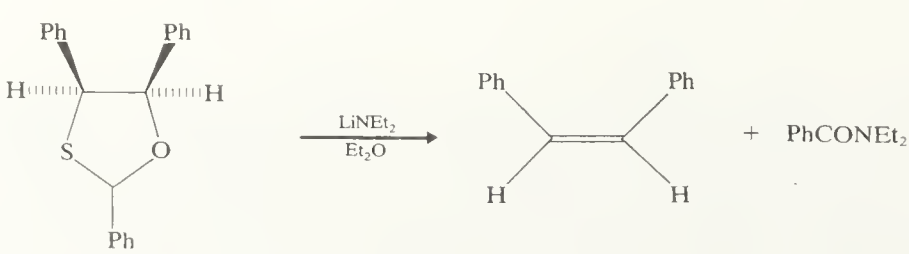


(20)

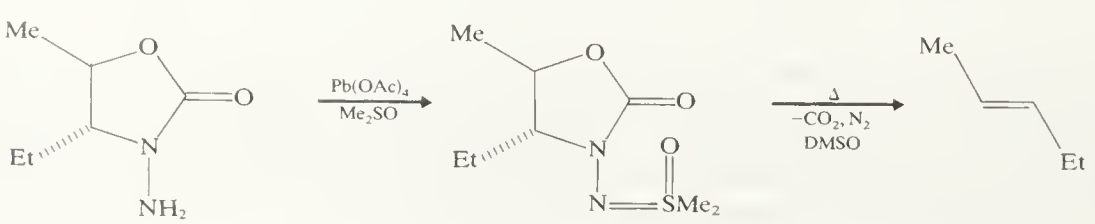


(21)

(22)

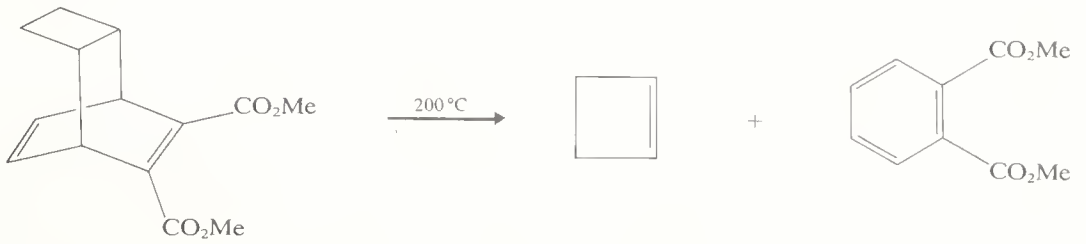


(23)



(24)

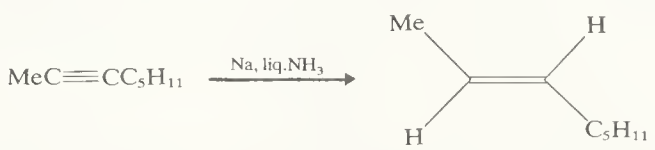
Six-membered ring cycloeliminations of the retro-Diels–Alder type, although feasible, have not been much used for olefin synthesis. For a purely carbocyclic ring, the retro-process will only occur if one of the products is particularly stable, *e.g.* aromatic, as in the cyclobutene synthesis shown (equation 25).



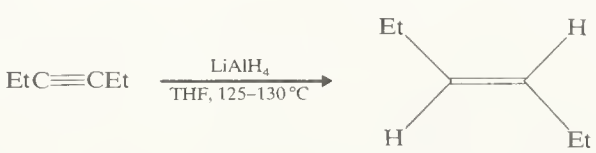
(25)

2.2.2.4 Partial reductions

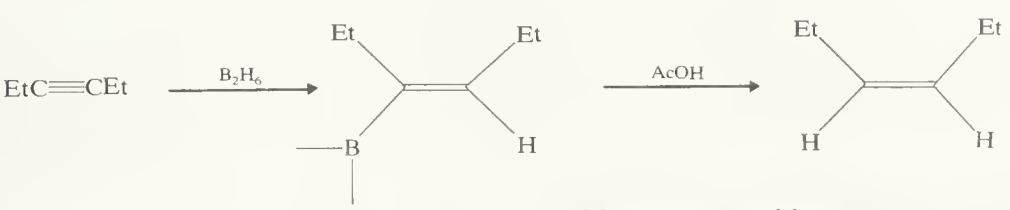
A long-known group of olefin syntheses consists of the partial reduction of more highly unsaturated precursors or other derivatives. The most important examples comprise the reduction of acetylenes, which, in general, affords control over both the position and the stereochemistry of the double bond. Some features are very familiar and will not be discussed in any detail. Equations (26)–(29) illustrate the main points. Disubstituted acetylenes can be reduced with fairly high stereoselectivity to *trans*-olefins by sodium in liquid ammonia (equation 26), or less familiarly by heating to 125–130 °C with lithium aluminium hydride in an ethereal solvent (equation 27).[29] Conversion of disubstituted acetylenes into *cis*-olefins can be effected either by hydroboration followed by protonolysis (equation 28) (analogous results have been obtained using hydroalumination), or by selective catalytic hydrogenation,[30] *e.g.* equation (29). The catalyst *par excellence* for the latter is that due to Lindlar (palladium–calcium carbonate modified by treatment with lead tetra-acetate) which works well even in complex molecules containing other unsaturated groupings; the homogenous catalyst $(Ph_3P)_3RuCl_2$ has also been used.[31]



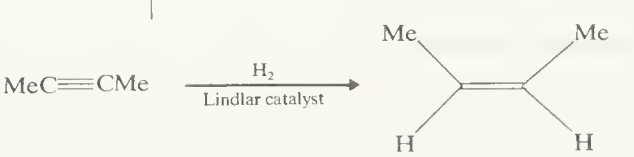
(26)



(27)

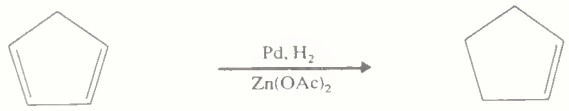


(28)

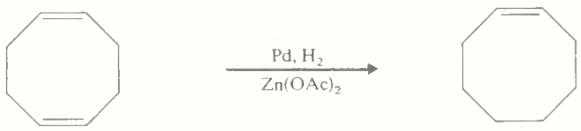


(29)

The partial reduction of conjugated dienes or higher polyenes suffers from problems of constitution control particularly in the case of dissolving metal reductions, owing to the possibility of 1,2- *versus* 1,4-addition. However, in certain situations useful preparations are possible, *e.g.* equation (30). The partial reduction of non-conjugated dienes is also occasionally useful, *cf.* equation (31).

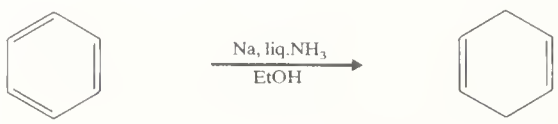


(30)

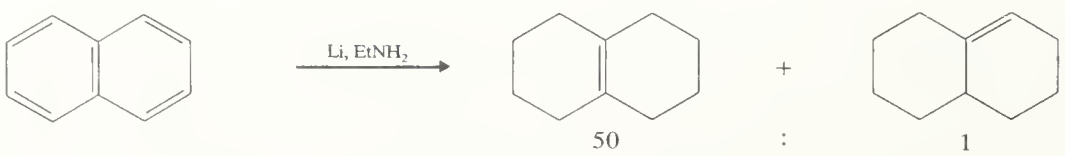


(31)

The reduction of aromatic hydrocarbons using alkali metal–liquid ammonia (Birch reduction)[32] or lithium in ethylamine (Benkeser reduction)[33] offers ways of preparing six-membered mono- and poly-cyclic olefinic hydrocarbons. In particular, the Birch reduction makes cyclohexa-1,4-diene and derivatives readily available, *cf.* equation (32). Lithium–ethylamine reductions usually result in reduction to mono-olefins, presumably because the first-formed dihydroaromatic compounds are isomerized under the basic conditions of the reaction to conjugated dienes which then suffer further reduction, *e.g.* equation (33).

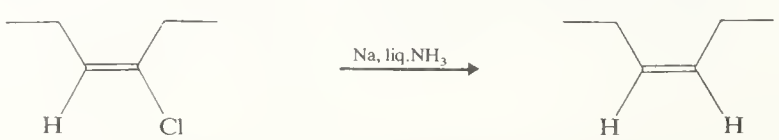


(32)

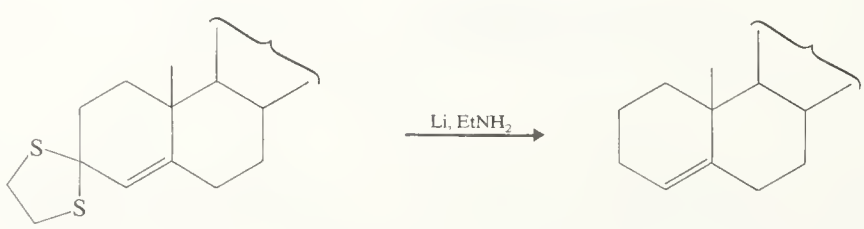


(33)

The reduction of other olefinic derivatives is sometimes preparatively useful, *e.g.* the stereospecific reductions of vinyl halides using sodium in liquid ammonia (equation 34). Suitable allylic derivatives can also be cleaved by dissolving metal reductions, exemplified by the transformation in equation (35), which represents a constitutionally specific preparation of olefins from α,β-unsaturated ketones *via* dithioacetals.



(34)

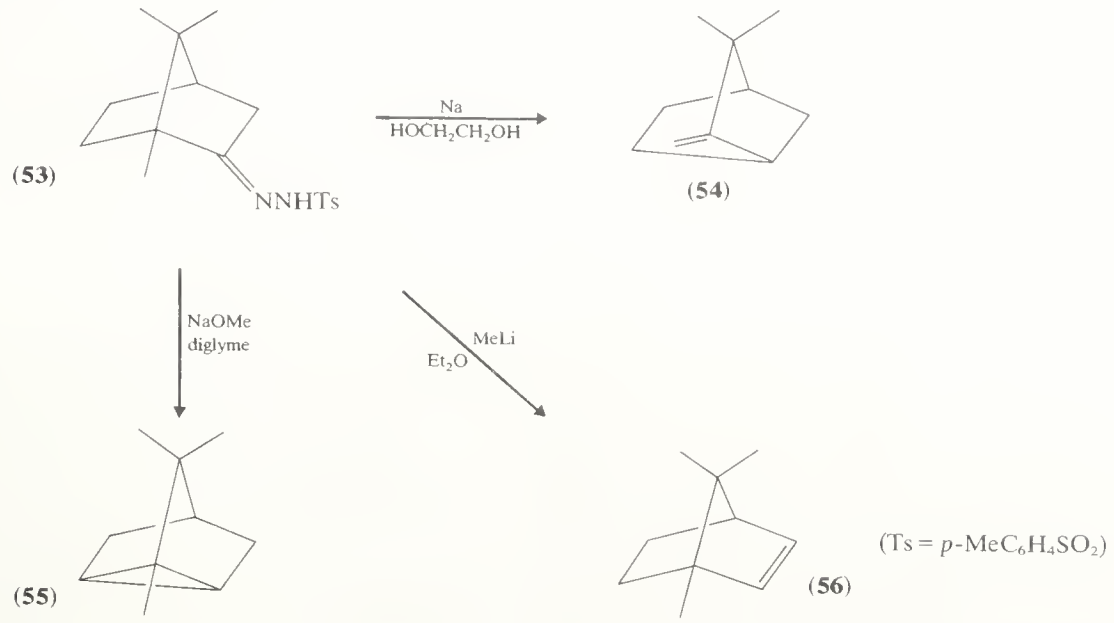


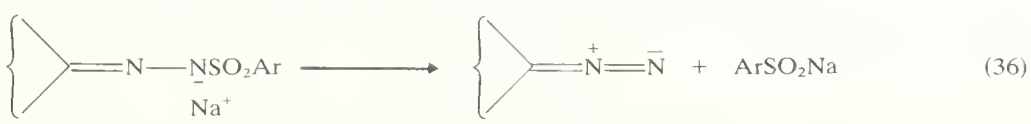
(35)

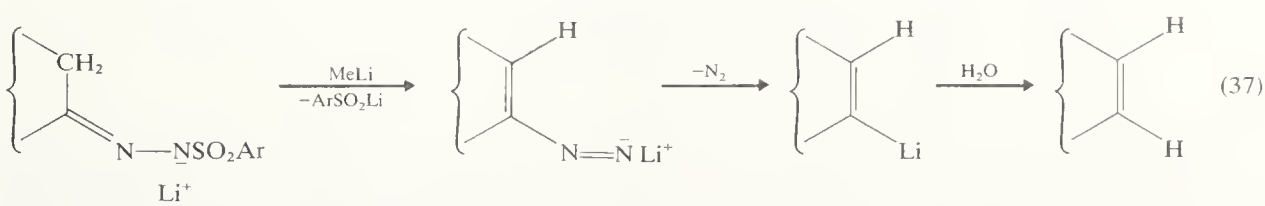
2.2.2.5 Sulphonylhydrazone eliminations

A fairly recently developed group of olefin-forming reactions are those based on the decomposition of ketone or aldehyde sulphonylhydrazones. There are three main pathways for the elimination of sulphinate ion from the alkali metal salts of sulphonylhydrazones which can be illustrated using camphor *p*-toluenesulphonylhydrazone (**53**) as an example. In the formation of camphene (**54**) and tricyclene (**55**) it is considered that the corresponding diazoalkane is first formed (equation 36). In a protic solvent like ethylene glycol, protonation to give the diazonium ion, followed by loss of nitrogen with rearrangement, gives camphene (**54**). On the other hand, thermal decomposition of the

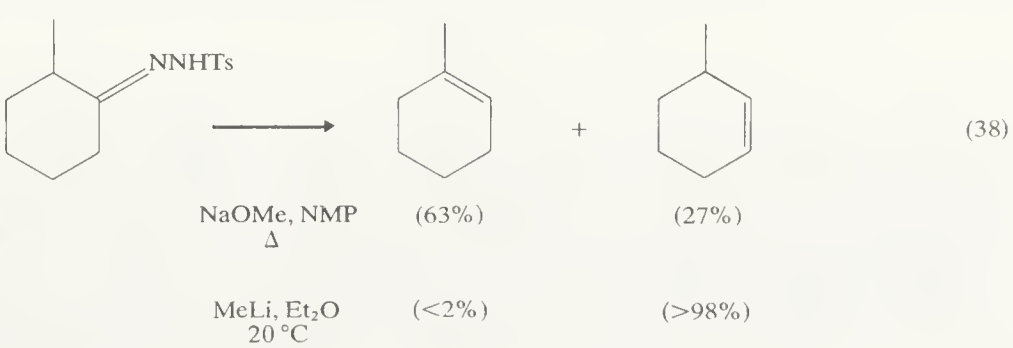
diazoalkane in the aprotic solvent diglyme leads to formation of a carbene which promptly inserts into a C—H bond to give tricyclene (**55**). The reaction leading to bornylene (**56**), which occurs at much lower temperatures, is postulated to involve abstraction of an enolizable proton followed by loss of nitrogen, *etc.* as in equation (37). In its later stages, this scheme has affinities to the mechanism of the Wolff–Kishner reduction of ketones.







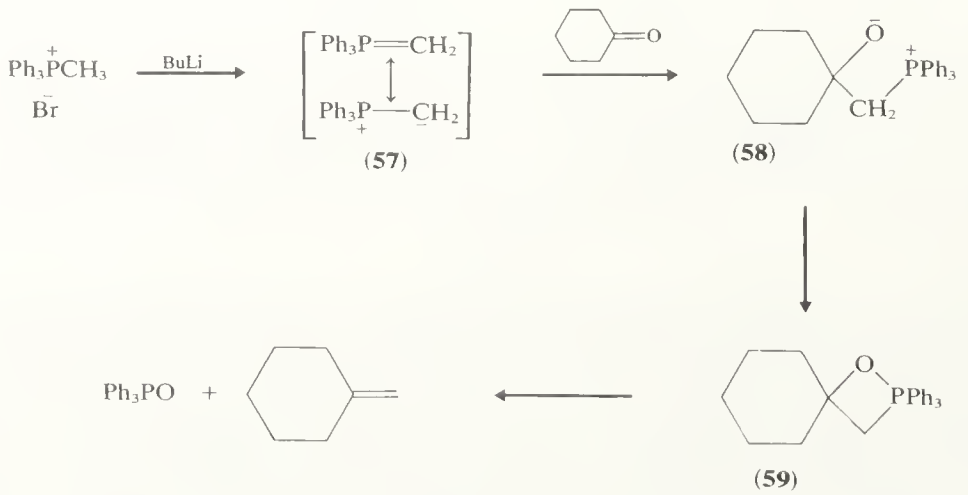
This reaction of arylsulphonylhydrazones with two equivalents of alkyl-lithium reagent constitutes a useful olefin synthesis from ketones.[34] From constitutionally symmetrical ketones there is no specificity problem, and, in acyclic cases, there is an additional bonus in that stereoselective formation of *cis*-olefin is sometimes observed. In cases like camphor, where only one enolizable position is available, ambiguity about double bond position does not arise, and even with constitutionally unsymmetrical ketones very significant selectivity can be achieved where kinetic control leads to more rapid proton loss from one side. An example of the latter, which also illustrates the advantages of the alkyl-lithium induced process compared with the carbenoid type decomposition, is provided by equation (38).



Having dealt with various methods whereby a double bond can be introduced into an existing carbon skeleton, we now need to consider the second class of olefin-forming reactions in which the carbon framework is built up with concomitant incorporation of the double bond. Such reactions sometimes proceed in two discrete steps, an addition followed by an elimination, and to the extent that the second step can be carried out separately from the first there will obviously be some overlap with the first class of reactions. Although addition–elimination processes have long been known for the preparation of certain olefin derivatives, *e.g.* α,β-unsaturated carbonyl compounds from carbonyl condensation reactions, it was really the development of the Wittig reaction in the mid-1950s which sparked off interest in this type of reaction for olefin synthesis in general.

2.2.2.6 Wittig and related reactions

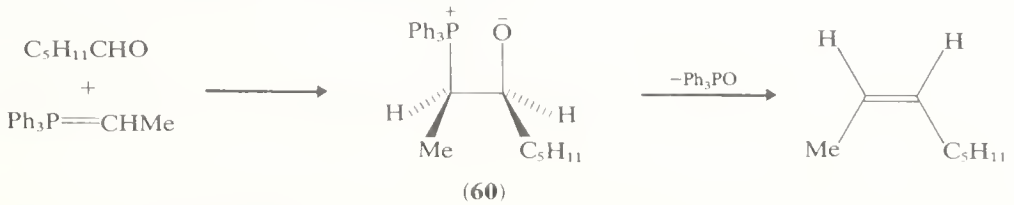
In the classical Wittig reaction, an alkylidenephosphorane (ylide), *e.g.* (**57**), generated *in situ* by treatment of a phosphonium salt with strong base (usually alkyl-lithium), is treated with a carbonyl compound to give an olefin. A typical example is shown in equation (39) and the probable mechanism, involving a betaine, *e.g.* (**58**), and an intermediate oxaphosphetan, *e.g.* (**59**), which undergoes cycloelimination of phosphine oxide with formation of olefin, is indicated. A more complex example in which intramolecular reaction occurs is presented in equation (40) and gives some idea of the potential of the reaction for synthesizing strained olefins. The high degree of control over double bond position is evident and this undoubtedly is the reason for the popularity of the reaction which has been extensively studied.[35] (See Chapter 10.6 for further examples of its use in natural product synthesis.)



Stereochemical problems arise, for example, in the reaction of aldehydes (RCHO) with substituted ylides ($R^1CH{=}PPh_3$) and much work has been carried out in order to understand the mechanism so as to achieve control of stereochemistry. The following discussion is a rather drastic simplification and Schlosser's review[36] should be consulted for further details.

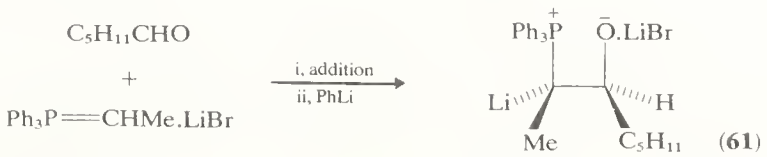
Firstly, if the phosphorane is formed under salt-free conditions, *e.g.* no lithium salts should be present, reaction with the aldehyde gives predominantly *erythro*-betaine, *e.g.*

(**60**), which then undergoes elimination to give the *cis*-alkene (equation 41). However, high stereoselectivity is only found where R^1 and R^2 are relatively small alkyl groups. If R^1 and R^2 are aryl or other groups which can conjugatively stabilize a double bond, or if they are secondary or tertiary alkyl groups, increasing amounts of *trans*-olefins are formed. Secondly, in the presence of lithium salts, equilibration between the diastereoisomeric betaines occurs. This equilibration is accelerated when alkyl-lithium reagents are added owing to formation of the α-metallated betaines, *e.g.* (**61**) and (**62**), and the sterically-favoured *threo*-isomer (**62**) predominates. Protonation followed by elimination then leads to formation of the *trans*-olefin (equation 42).



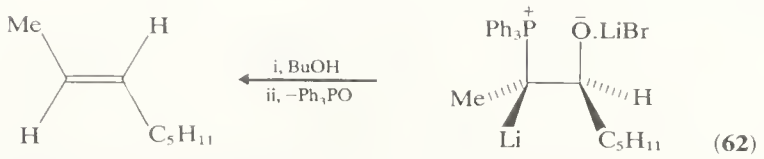
(41)

(**60**)



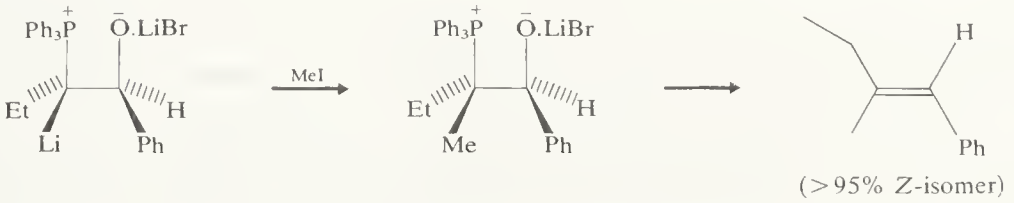
(**61**)

(42)



(**62**)

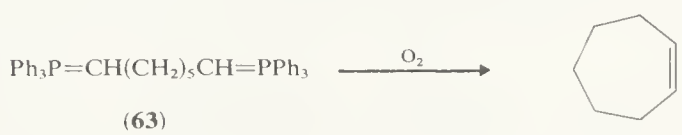
α-Metallated betaine intermediates of the above type have also found further application in that they may be alkylated or treated with other electrophiles,[37] thereby leading stereoselectively to trisubstituted olefins, *e.g.* equation (43).



(43)

(>95% *Z*-isomer)

An example of another variant on the intramolecular Wittig reaction is provided by the autoxidation of the bisphosphorane (**63**). Here, reaction of one ylide moiety with oxygen to give a carbonyl compound plus phosphine oxide is followed by cyclization (equation 44).

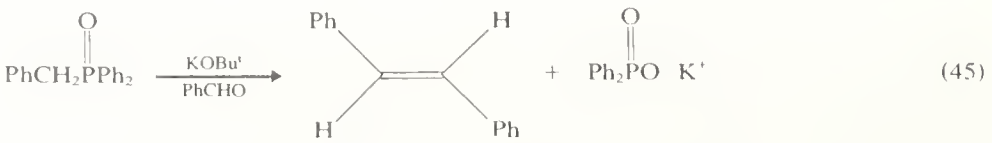


(**63**)

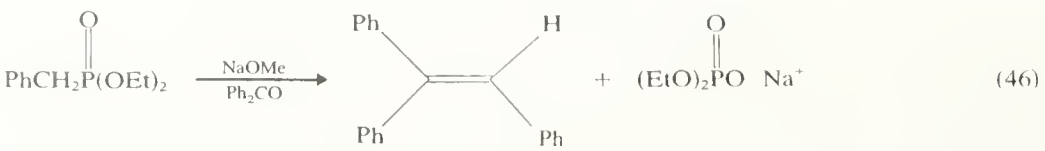
(44)

There are a number of olefin-forming reactions more or less related to the Wittig reaction in which an effective carbanion α to phosphorus or sulphur undergoes addition to a carbonyl group, followed by an elimination to give olefin. Examples include the 'PO-activated olefination' discovered by Horner for phosphine oxides,[38] *e.g.* equation (45), and

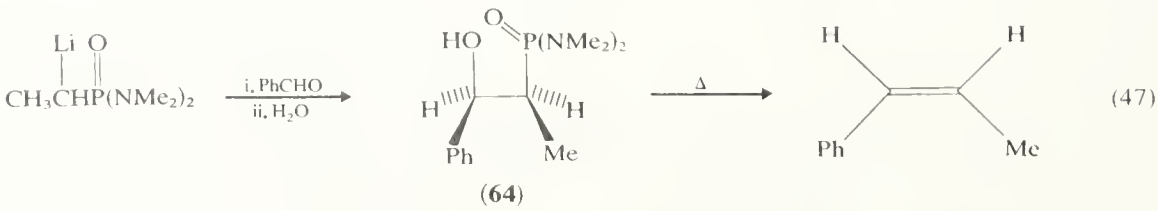
phosphonates,[39] *e.g.* equation (46). As originally developed and as exemplified here, the phosphine oxide and phosphonate syntheses work best where substituents are present which conjugatively stabilize the olefinic product, and the more stable olefin predominates in cases where *cis*- and *trans*-isomers are possible, probably as a result of equilibration of the diastereoisomeric adducts. More recently, it has been shown that in the phosphine oxide method, use of α-lithiated phosphine oxides allows the intermediate adducts to be isolated as β-hydroxyphosphine oxides, after quenching, and the latter can be subsequently fragmented stereospecifically to olefins,[40] *cf.* equation (13) above. Analogous reactions of phosphonamides,[41] *e.g.* equation (47) in which the predominant intermediate (**64**) was purified by crystallization, and sulphinamides,[42] *e.g.* equation (48), have been developed by Corey but they have not been widely applied. In the phosphonamide case, this is probably due to the relatively high temperatures required for the elimination step; in the sulphinamide reaction, substituted alkyl sulphinamides could not be metallated in good yield.



(45)

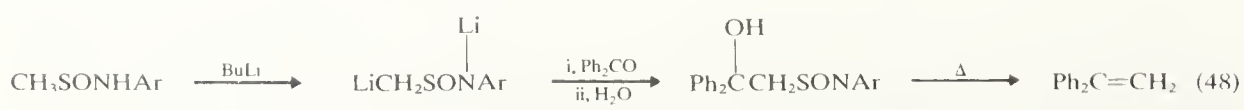


(46)



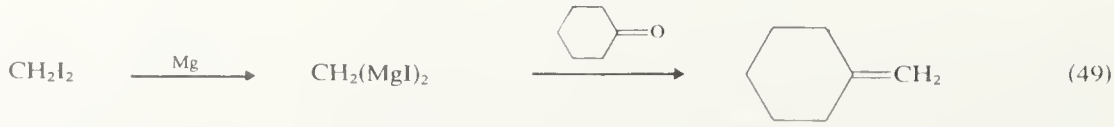
(47)

(**64**)

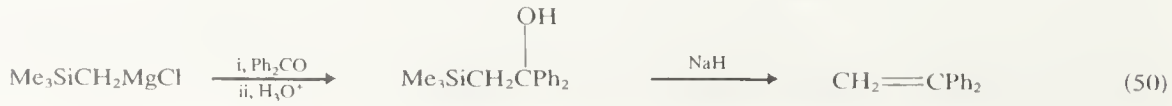


(48)

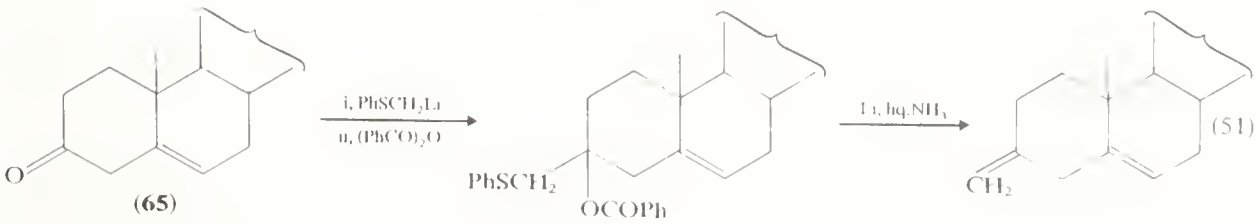
Variations on the addition–elimination theme which have been developed into useful olefin syntheses include the following: (i) the methylenation of ketones on treatment with the intermediate *gem*-dimetallated speices derived from methylene di-iodide and magnesium,[43] *e.g.* equation (49); (ii) the reaction of α-metallated silanes with carbonyl compounds followed by elimination [Peterson reaction,[17] *cf.* equation (12)], *e.g.* equation (50); and (iii) the sequence introduced by Coates[44] for conversion of ketones prone to isomerization such as (**65**) into their methylene analogues (equation 51). This latter transformation cannot be carried out by the Wittig reaction since the methylenephosphorane is sufficiently basic to induce prototropic isomerization of (**65**) to the α,β-unsaturated ketone. A process starting from α-metallated sulphones, which has been used for synthesis of tetrasubstituted olefins, may also be mentioned here,[45] *e.g.* equation (52).



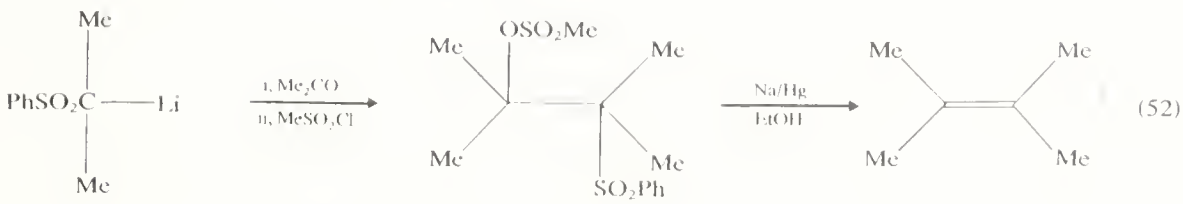
(49)



(50)



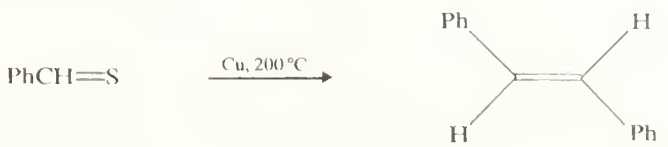
(51)



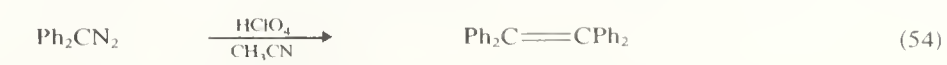
(52)

2.2.2.7 Various coupling reactions

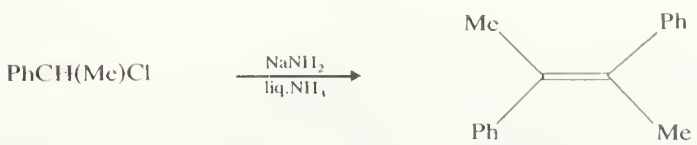
Under this heading we shall consider a number of reactions in which an olefinic double bond is created by coupling together of two sub-units but which do not come under the heading of carbanion component plus carbonyl component which is the essence of the Wittig-type processes. Some of these reactions are fairly old and restricted in their application, *e.g.* equations (53)–(55).



(53)

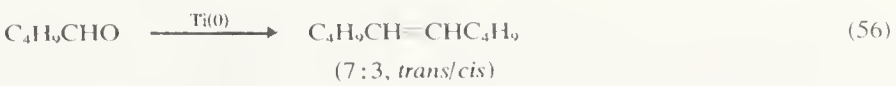


(54)

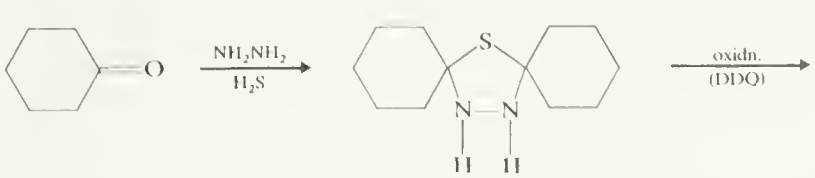


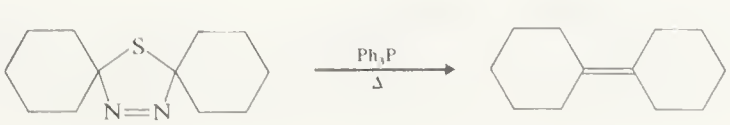
(55)

More recent illustrations are provided by a reaction developed by McMurry[46] involving reductive coupling of aldehydes or ketones with Ti(0), *e.g.* equation (56), and Barton's double extrusion reactions.[47] Two examples of the latter (equations 57 and 58) show the use of different types of precursors. Thiirans have been identified as intermediates in some cases, being isolable in the absence of triphenylphosphine and converted into the olefin on treatment with the reagent. These methods are clearly valuable for the synthesis of sterically congested olefins possessing large substituents. However, tetra-t-butylethylene has not so far succumbed to this or any other procedure.

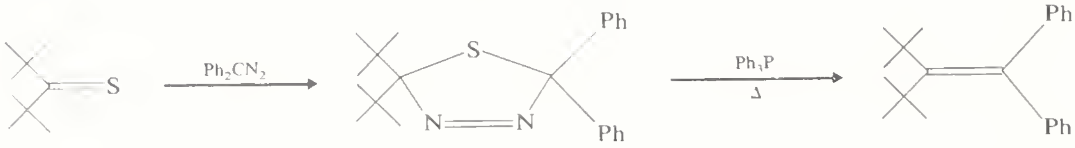


(56)



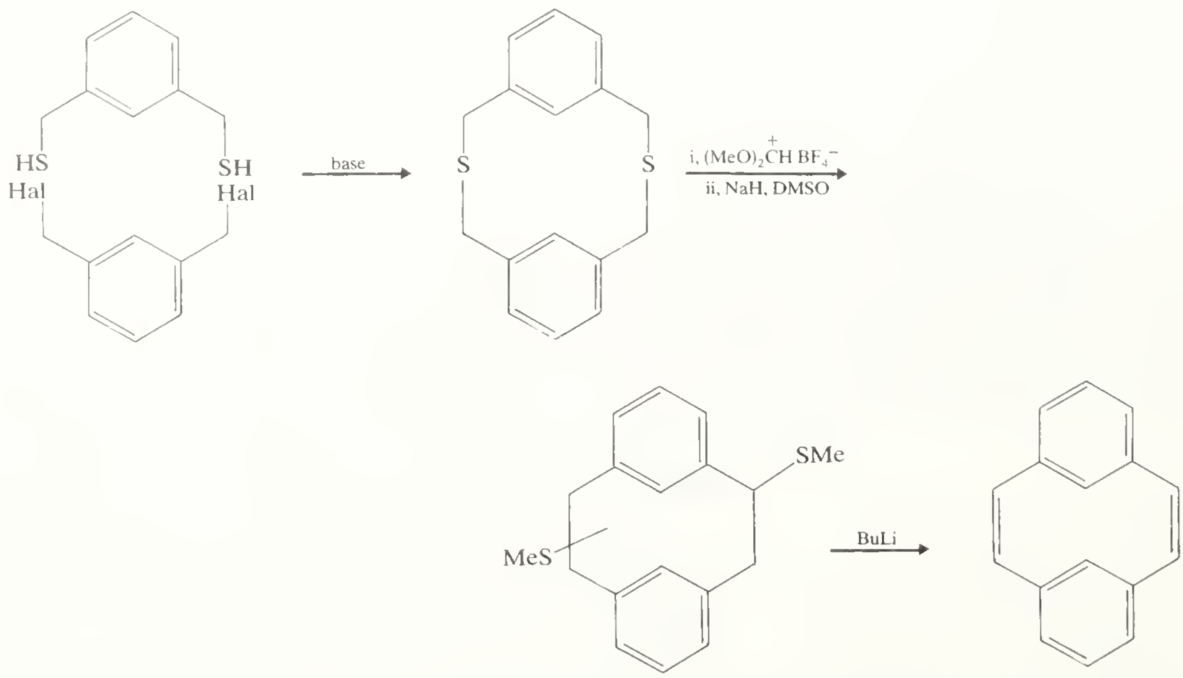


(57)



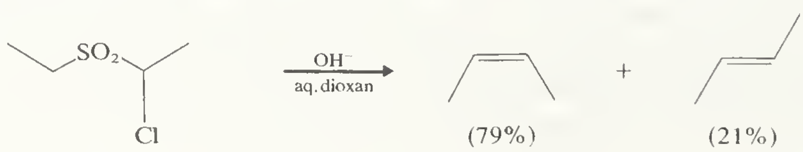
(58)

Within this category of olefin syntheses it is convenient to deal with those approaches in which the two 'components' of the olefin are assembled at a heteroatom followed by subsequent elimination of the heteroatom. A good example is provided by the synthesis of the metacyclophane shown in equation (59), where assembly at sulphur is followed by Stevens rearrangement and then elimination.

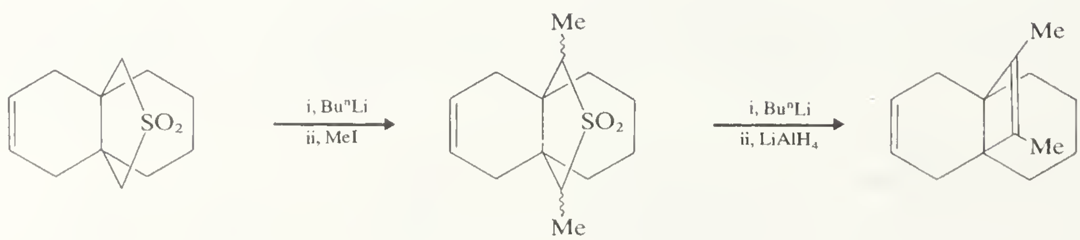


(59)

The same approach can be applied in the case of the Ramberg–Bäcklund reaction[48] (*cf.* equation 17) since the precursor sulphone is derivable from a thiol which is then alkylated with the second component and the ensuing thioether is oxidized to the sulphone. In its classic form, the Ramberg–Bäcklund reaction involves initial formation of the α-halosulphone followed by base-catalysed elimination, olefin being formed *via* decomposition of an intermediate episulphone, *e.g.* equation (60). Recent variants not involving halosulphone have been developed and may be exemplified by the sequence in equation (61)[49] which incorporates additional alkylation steps at the sulphone stage.



(60)



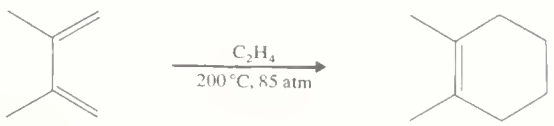
(61)

2.2.2.8 Electrocyclic reactions

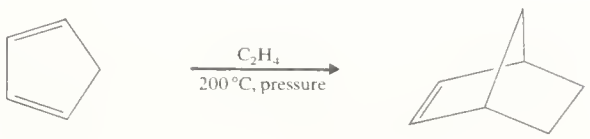
Carbon skeleton construction *via* electrocyclic reaction (*cf.* Section 2.2.3.4) can often be accompanied by constitutionally specific placement of a double bond. In most cases

such reactions, particularly Diels–Alder additions and Claisen rearrangements, are employed in the synthesis of functionalized derivatives rather than olefinic hydrocarbons themselves. However, a number of hydrocarbon examples are known and may be illustrated by: (i) Diels–Alder additions, *e.g.* equations (62) and (63); (ii) Cope rearrangements, *e.g.* equation (64); and (iii) 1,5-sigmatropic shifts, *e.g.* equations (65) and (66).

Closely related is the olefin metathesis process which will be dealt with in Section 2.2.3.4.

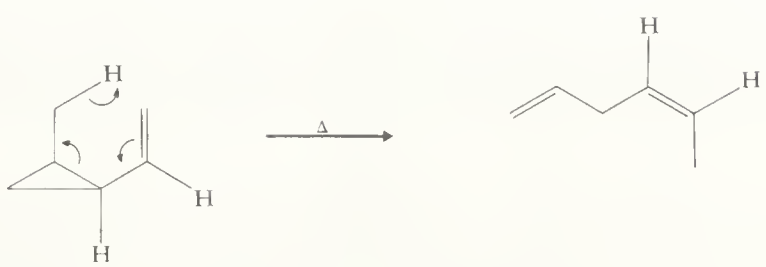


(62)

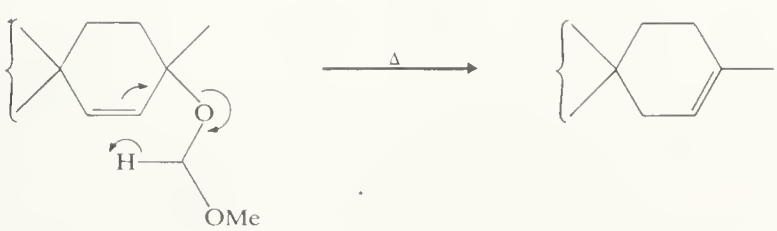


(63)

(64)



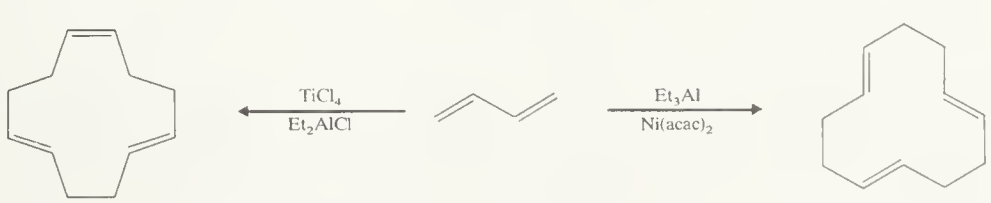
(65)



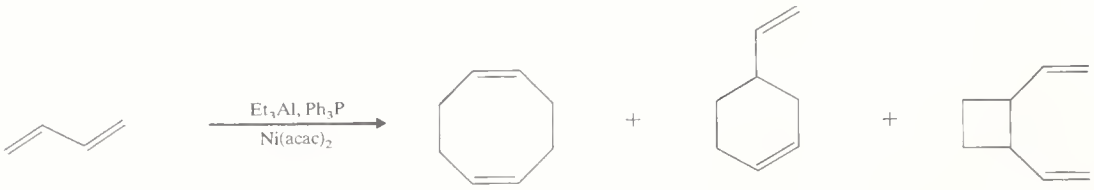
(66)

2.2.2.9 Cyclo-oligomerizations

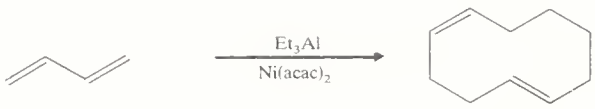
An important set of reactions has been developed by Wilke and co-workers[50] in which buta-1,3-diene and similar dienes are converted into cyclopolyolefins. Since cyclization with placement of double bond occurs, the reactions have synthetic affinities with electrocyclic processes, although organometallic intermediates are involved and there is no mechanistic analogy. Typical examples are given in equations (67)–(69), which show the marked dependence of product type on the nature of the catalyst. Despite this, yields are often very high.



(67)



(68)

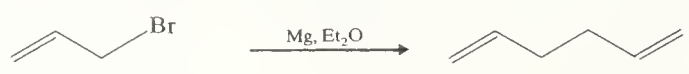


(69)

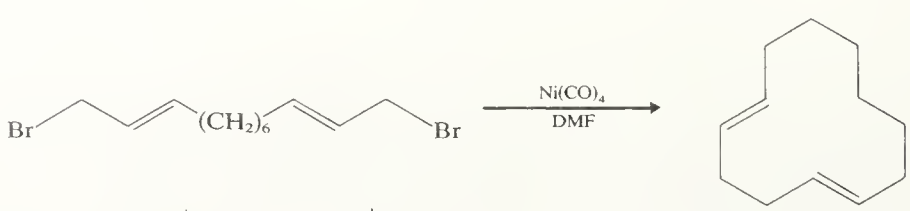
In addition to the above two large classes of olefin syntheses in which the double bond forming reaction is an integral part of the process, there is clearly another class of reaction in which compounds already containing an olefinic group are elaborated into more complex products. We shall not deal with those reactions in which a remote functional group in an unsaturated compound is transformed so as to make the corresponding olefin, since this type of example is obviously trivial as an olefin synthesis. However, there are some reactions of allyl and vinyl derivatives in which the double bond is formally retained which clearly deserve to be called olefin syntheses.

2.2.2.10 Coupling of allylic derivatives

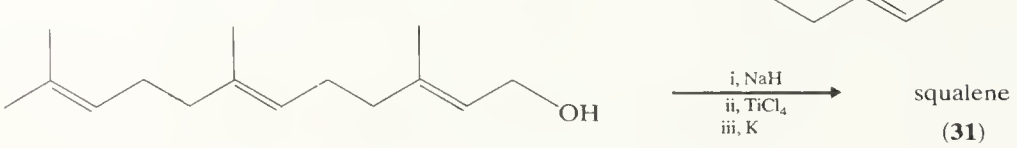
Other than reductive cleavage which has already been mentioned (see Section 2.2.2.4), the main reaction type requiring comment is 'Wurtz-type' coupling to give 1,5-dienes. The reaction has been known for a long time and examples range from simple instances, *e.g.* equation (70), through more complex couplings using nickel carbonyl and π-allylnickel complexes,[51] *e.g.* equation (71), to a synthesis of squalene from farnesol (equation 72).[52]



(70)



(71)

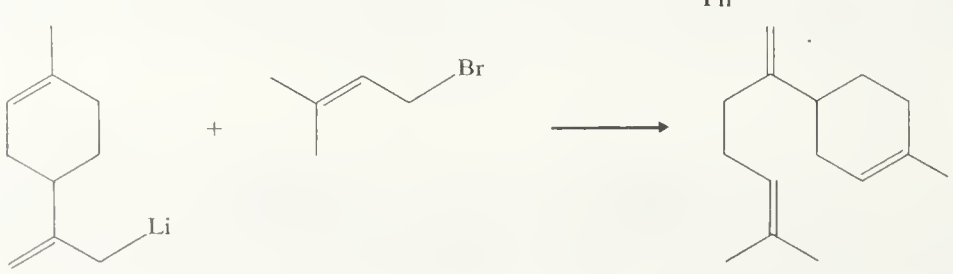


(72)

'Mixed couplings,' in which allylic halides, *etc.* are treated with organometallic reagents, have found widespread application and only a few examples are quoted (equations 73–75). Related reactions of π-allylnickel compounds show considerable synthetic potential.[51]

(73)

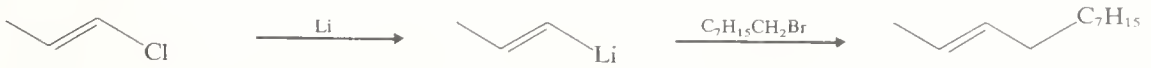
(74)



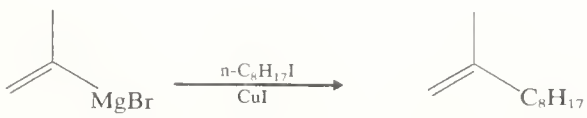
(75)

2.2.2.11 Reactions of vinyl derivatives

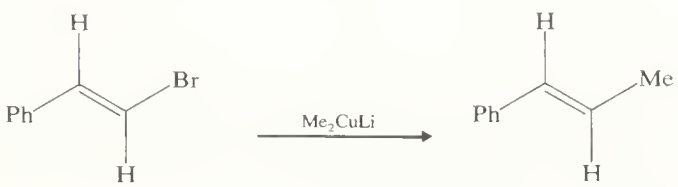
Reduction of vinyl halides to olefins has already been mentioned, *e.g.* equation (34) above. More important are 'Wurtz-type' couplings which lead to the construction of a new carbon skeleton, *e.g.* equations (76) and (77). In recent years, organocopper compounds have proved to be particularly useful and popular reagents for this kind of reaction,[53] *e.g.* equations (78) and (79).



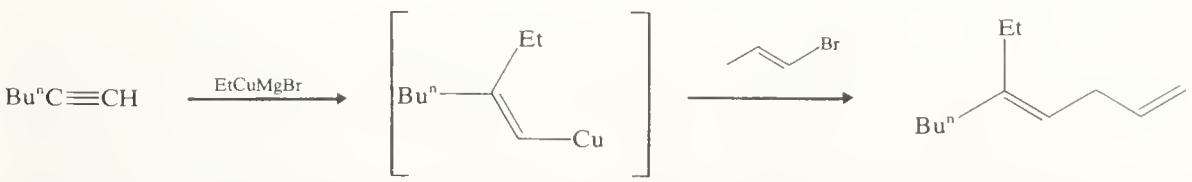
(76)



(77)

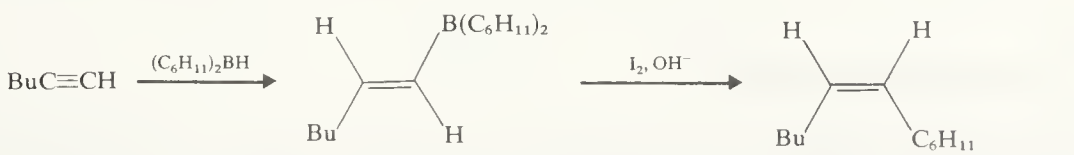


(78)

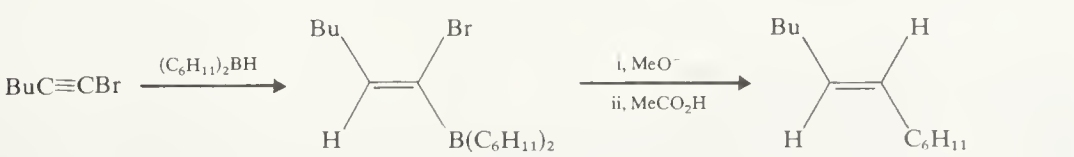


(79)

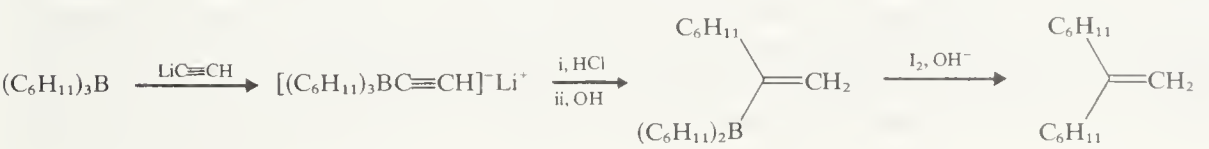
Vinylboranes and vinylboronate complexes have recently found application in the synthesis of olefins.[54] Since the precursors are fairly readily obtainable from appropriate acetylenes by hydroboration, these reactions have considerable potential. The following examples give some idea of the scope: (i) a synthesis of *cis*-1,2-disubstituted alkenes from alk-1-ynes (equation 80); (ii) preparation of *trans*-alkenes from 1-bromoalkynes (equation 81); and (iii) the preparation–protonation of alkenylboranes from alkynylboronates (equations 82 and 83). In each case, an alkyl migration from boron to the adjacent electron-deficient carbon is involved. Thus, the last step in equation (80) can be interpreted in terms of the transformation (**66**) followed by (**67**). Related reactions of vinyl-alanes and -alanates are also known (see Ref. 55 for leading references.)



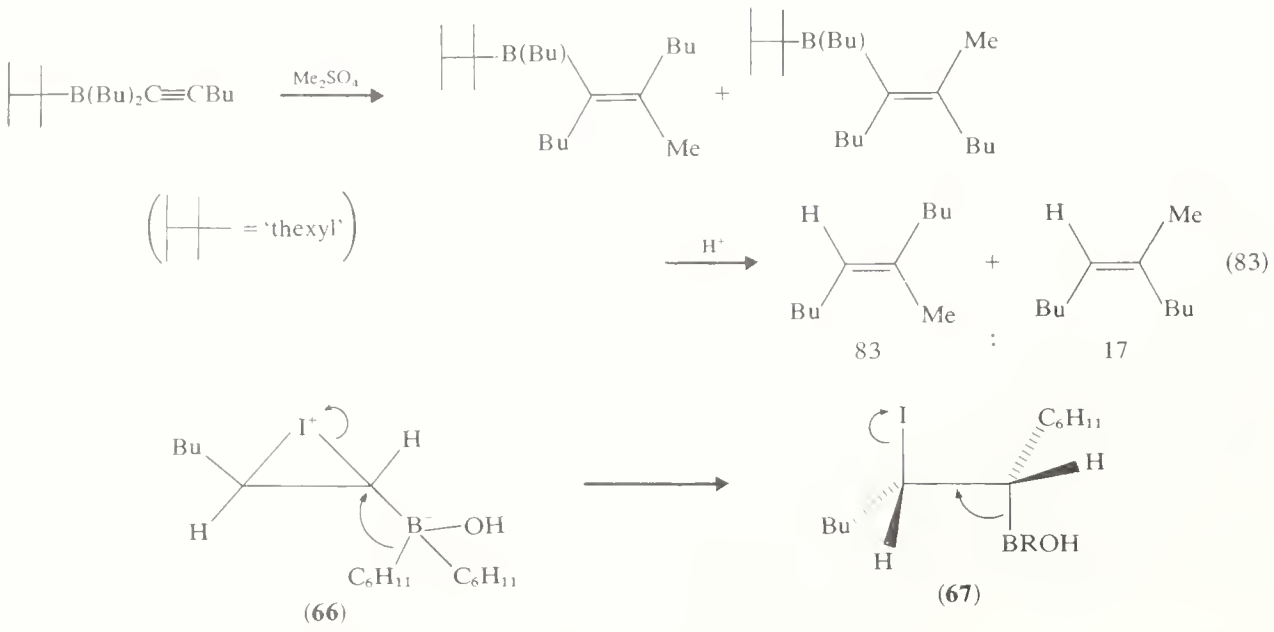
(80)



(81)



(82)



Vinylsilanes can be stereospecifically proto-desilylated with retention of configuration, *e.g.* equation (84),[56] and since vinylsilanes can be often stereospecifically prepared the reaction is considered to be synthetically useful.

In concluding this section on olefin syntheses, it should be pointed out that isomerizations can sometimes be preparatively useful when one isomer is appreciably more stable than the others. Olefin isomerizations are dealt with in Section 2.2.3.7.

2.2.3 REACTIONS OF OLEFINIC HYDROCARBONS

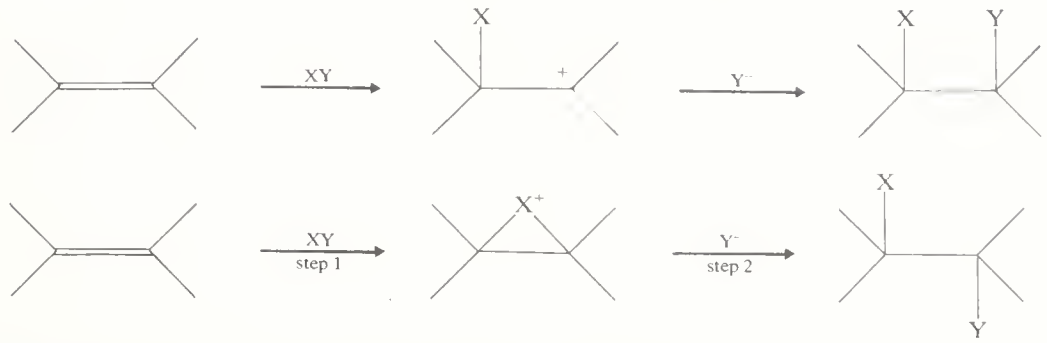
Owing to the importance of olefins and the wide range of their reactions, their chemistry has been studied extensively. The material in this section must necessarily be truncated and often sketchy in order to include some of the more recent developments along with well-established features. The preparation and properties of transition metal–olefin complexes will not be included since they are covered in Chapter 15.6.

2.2.3.1 Electrophilic additions[57]

The majority of additions of reagents XY to simple olefins are electrophilic in nature (the generalized reagent X—Y is treated as polarized in the sense $X^{\delta+}$—$Y^{\delta-}$ with Y more electronegative than X). That is, the effect of change of substituents is such as to indicate development of partial positive charge at the olefinic carbon(s) in the transition state of the rate-determining stage.

Most electrophilic additions to olefins are believed to occur by the so-called Ad_E2 (addition, electrophilic, bimolecular) mechanism, *i.e.* an actual cationic intermediate is formed. A pervading theme is whether this intermediate is a carbenium ion (*cf.* equation 85) or a bridged ion (equation 86). As is often the case, it seems that a spectrum of behaviour occurs depending on the particular reagent and substrate.

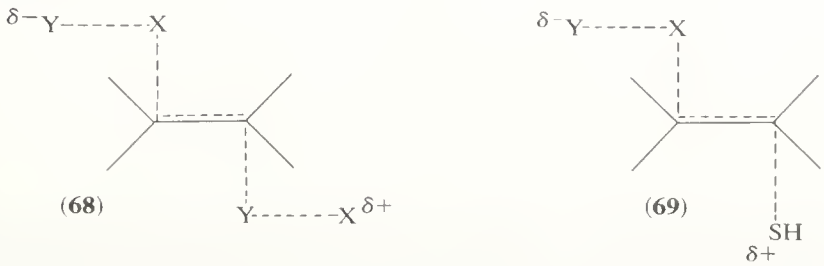
Another mechanistic possibility which is sometimes postulated is the Ad_E3 process in which the rate-determining transition state contains a third species, either another



(85)

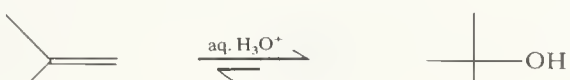
(86)

molecule of reagent (**68**) or a solvent molecule SH (**69**). Such a transition state could either be reached directly, or by way of a bridged ion (*cf.* equation 86) with step 1 rapid and reversible and step 2 slow.



In the light of the above preamble it is instructive to consider two types of electrophilic addition to olefins: (i) acid-catalysed hydration and (ii) addition of sulphenyl halides, which illustrate the two extremes of the Ad_E2 mechanism.

The hydration of olefins[58] is an acid-catalysed reaction, the equilibrium normally being significantly in favour of the alcohol, *e.g.* equation (87). Markownikov orientation is observed (*i.e.* proton addition occurring in general at the less-substituted olefinic carbon to give the more-stable carbenium ion) — $\log k$ for hydration of substituted styrenes correlates nicely with σ^+ giving a highly negative ρ (where k is the apparent first-order rate constant and σ^+ and ρ, the relevant Hammett constants) — and carbenium ion type rearrangements occur in susceptible systems. In addition, the rate of hydration varies in the sequence: $CH_2{=}CH_2 \ll MeCH{=}CH_2 \approx MeCH{=}CHMe \ll Me_2C{=}CH_2 \approx Me_2C{=}CMe_2$. Clearly, a carbenium ion mechanism is indicated and an open carbenium ion rather than a bridged ion most readily accommodates the similarity in rate between $MeCH{=}CH_2$ and $MeCH{=}CHMe$. Furthermore, general acid catalysis in the hydration of strained olefins has been demonstrated. The evidence is consistent with the simple mechanism shown in equation (88) for the hydration of all but highly deactivated olefins.

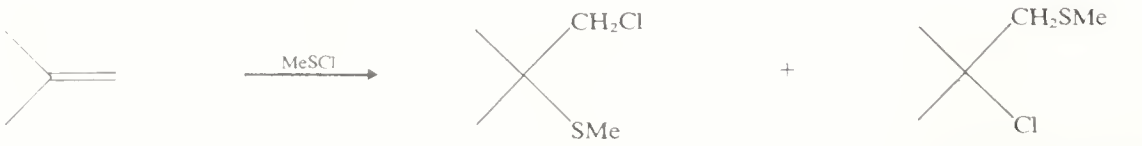


(87)

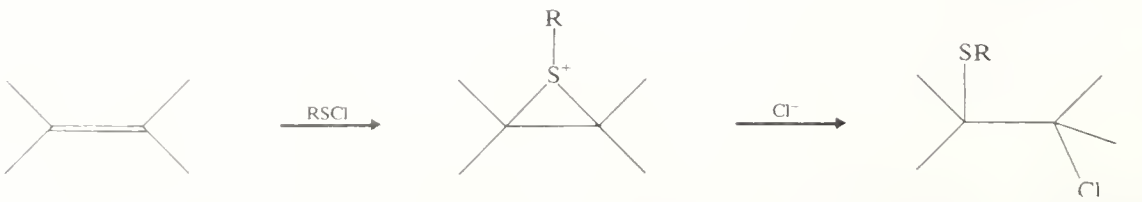
(88)

Addition of sulphenyl halides to olefins[59] stands in sharp contrast to hydration. Addition, under conditions of kinetic control, is often 'anti-Markownikov' in that the product from attachment of halogen (the more electronegative species) to the less-substituted carbon predominates (equation 89). Only small substituent effects for increasing alkylation of olefin are observed, *e.g.* the following relative rates: for addition of methanesulphenyl chloride, $CH_3CH_2CH{=}CH_2$ (1.0); *cis*-$CH_3CH{=}CHCH_3$ (13.0); *trans*-$CH_3CH{=}CHCH_3$ (0.72); $(CH_3)_2C{=}CH_2$ (0.75); $(CH_3)_2C{=}CHCH_3$ (8.26); $(CH_3)_2C{=}C(CH_3)_2$ (12.9). Even for aryl-substituted olefins, clean *anti*-addition

stereochemistry is found. The above and other evidence points to an Ad_E2 mechanism involving a bridged intermediate (episulphonium ion) with little cationic character on the olefinic carbon atoms in the transition state (equation 90). The product-determining step, opening of episulphonium ion, is influenced by steric effects which can account for the anti-Markownikov orientation.



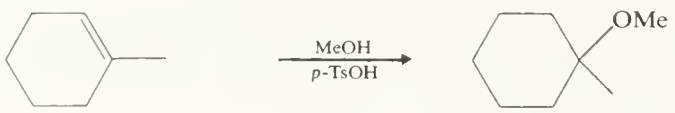
(89)



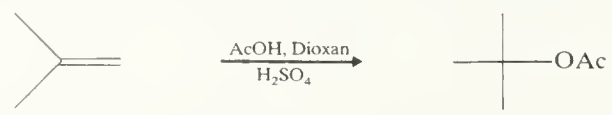
(90)

The above two reaction types represent mechanistic extremes for which a fairly clear-cut consensus has emerged. In many other examples of electrophilic addition it is often a vexed question whether or not a bridged intermediate is involved. It remains now to consider some of the more important reactions of this category.

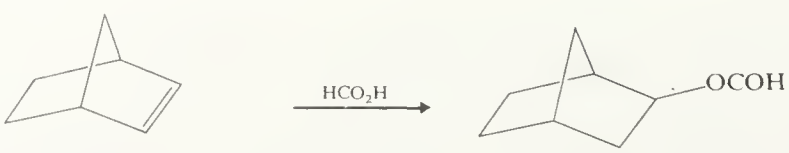
In the addition of reagents containing an O—H bond to olefins, Markownikov orientation (O becoming attached to the more substituted carbon) is observed, presumably reflecting a carbenium ion mechanism. If the hydroxylic compound is a weak acid such as water, or an alcohol, acid or Lewis acid, catalysis is required (*cf.* hydration) but stronger acids act as their own proton source. Further, alkyl substitution in the olefin (greater stability of the incipient carbenium ion) and olefin strain lead to increased reactivity. The classical method, originally used industrially, for hydration of simple olefins is the addition of sulphuric acid to give an alkyl hydrogen sulphate, followed by hydrolysis. Otherwise, addition of hydroxylic compounds to olefinic hydrocarbons is not greatly used in synthesis, presumably because of the likelihood of carbenium ion rearrangements in more complex systems. Some examples are given in equations (91)–(93).



(91)



(92)



(93)

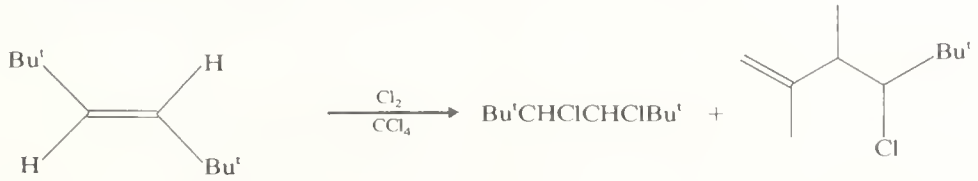
Addition of hydrogen halides to olefins[60] is another time-honoured electrophilic reaction of olefins giving Markownikov orientation (halogen attached to the more substituted carbon) under polar conditions. The reaction is used preparatively for adducts of simple olefins but not so much used with complex systems owing to rearrangement. Extensive mechanistic and stereochemical studies have been carried out. For non-conjugated olefins, *e.g.* addition of hydrogen chloride or hydrogen bromide in acetic acid to cyclohexene, the evidence favours an Ad_E3 mechanism, thereby accounting for the *anti* addition which is

observed. Conjugated olefins such as acenaphthylene, indene, *etc.* undergo predominant *syn* addition (observable with deuterium bromide) explained in terms of an intermediate carbenium–halide ion pair favoured by the conjugating substituent(s) which stabilize the carbenium ion.

Addition of halogens is probably the most typical of olefin reactions and it has been intensively investigated, preparatively and mechanistically.[61]

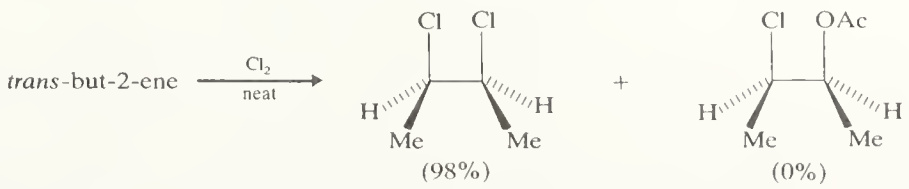
There is some evidence that at −78 °C electrophilic addition of fluorine to simple olefins can occur. There is a tendency for *syn* addition with aryl-substituted olefins, but bridged ions are neither expected nor is there any evidence for them.

Heterolytic addition of chlorine to olefins is found, provided precautions (absence of light, presence of radical inhibitors) are taken to avoid radical-chain addition. Results of kinetic studies, and substituent effects in particular, are consistent with a bimolecular electrophilic mechanism. In suitably susceptible systems, carbenium ion intermediates are signified by the formation of rearranged products, *e.g.* equation (94).

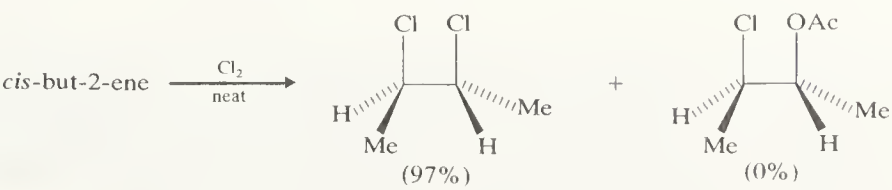


(94)

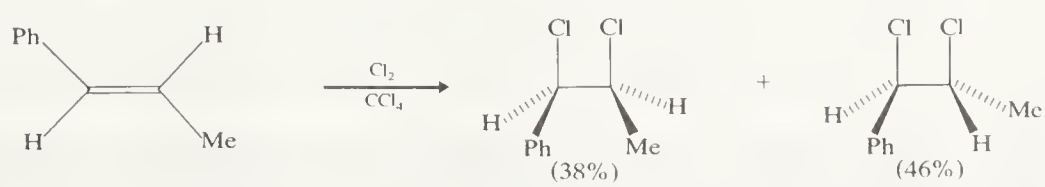
Stereochemical results suggest that simple alkenes undergo *anti* addition of chlorine *via* an Ad_E2 mechanism involving a bridged ion, while for aryl-substituted olefins, where benzylic stabilization of a carbenium ion is possible, an open ion is implicated. In either case, chlorination in the presence of a nucleophilic solvent leads to products of solvent capture. A number of the above points are illustrated in equations (95)–(98). In the 1-phenylprop-1-ene reactions, some substitution products are also formed. The excess of *syn* addition is ascribed to a carbenium–chloride ion pair process.



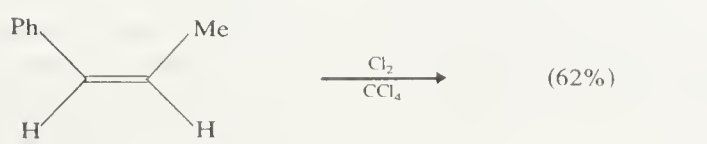
(95)



(96)



(97)



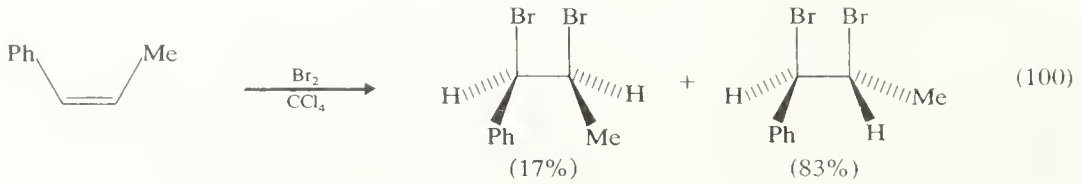
(98)

Electrophilic bromination of olefins has been shown to follow the rather complex rate law given in equation (99) where [E] represents olefin concentration and the rate constants are experimentally determined second (k_2) and third (k_3 and k_3') order terms. For bromination in non-polar solvents, where Br^- ions are not normally present, the first and second terms are the most important. In hydroxylic solvents, the first and third terms are the most significant.

$$-d[Br_2]/dt = k_2[Br_2][E] + k_3[Br_2]^2[E] + k_3'[Br_2][Br^-][E] \quad (99)$$

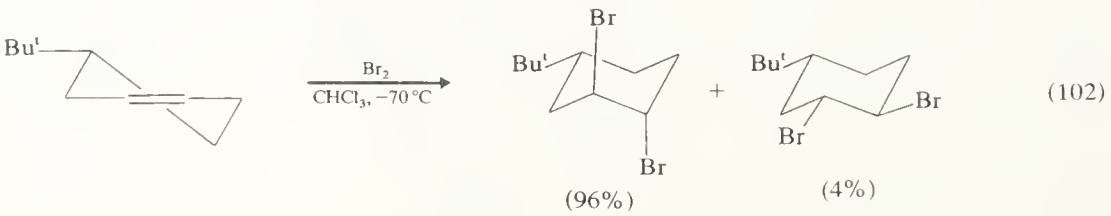
Compared to chlorination, it appears that the tendency for involvement of bridged ions is greater for bromination. *anti* Addition *via* a bromonium ion, *cf.* (**70**), seems well established, and in special cases they have been 'observed' spectroscopically. Weakly bridged bromonium ions (**71**) are postulated for some aryl-substituted alkenes. Thus, addition of bromine in carbon tetrachloride to *cis*- and *trans*-1-phenylprop-1-ene is not completely *anti* stereospecific (equations 100 and 101) (compare the chlorination results above). Bromination of *p*-methoxy-*trans*-1-phenylprop-1-ene, where a more stable cation can be formed, is non-stereospecific.

(**70**) (**71**)



(17%) (83%) (100)

(88%) (12%) (101)

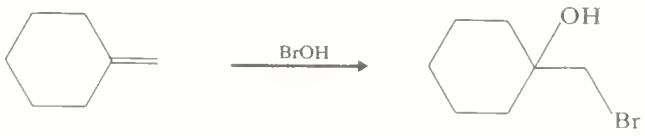


(96%) (4%) (102)

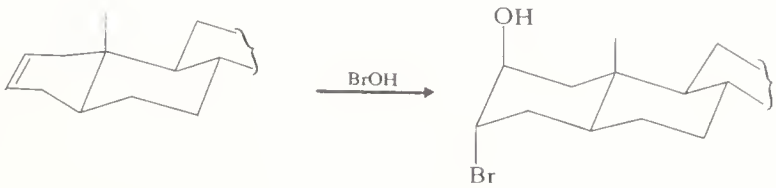
An important consequence of the Ad_E2 mechanism for bromination of conformationally biased unconjugated olefins is that the diaxial adduct is obtained, presumably because of stereoelectronic constraints on the opening of the bromonium ion (equation 102). There is some evidence that bromonium ion formation is at least partially reversible for bromination in the presence of pyridine and other tertiary bases.

Iodination is not in general a useful process for simple olefins since the equilibrium constant for addition is low. However, electrophilic attack of iodine is important for a number of interhalogens and pseudohalogens (see below) and in many cases there is good stereochemical evidence to implicate bridged iodonium ion intermediates. Thus, the expected trend of an increased tendency for bridging along the series $F < Cl < Br < I$ is vindicated.

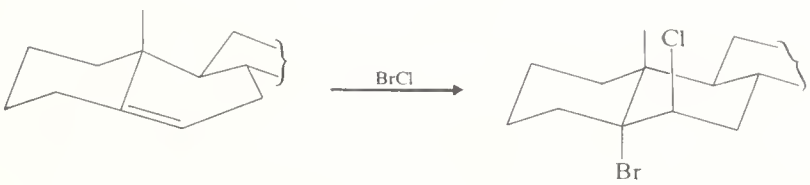
Addition of 'mixed' reagents such as interhalogens and pseudohalogens to olefins has been widely studied[62] and a number of preparatively useful reactions have been developed. Little more need be said regarding mechanism. A number of examples are given in equations (103)–(111) which illustrate a variety of points. For simple olefins, unsymmetrical reagents of this type give adducts in which the more electronegative atom becomes attached to the carbon atom better able to sustain a positive charge (extended



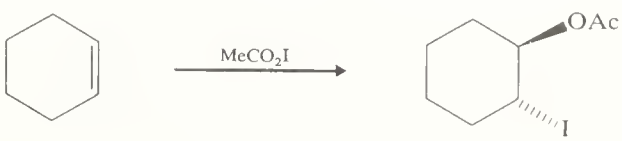
(103)



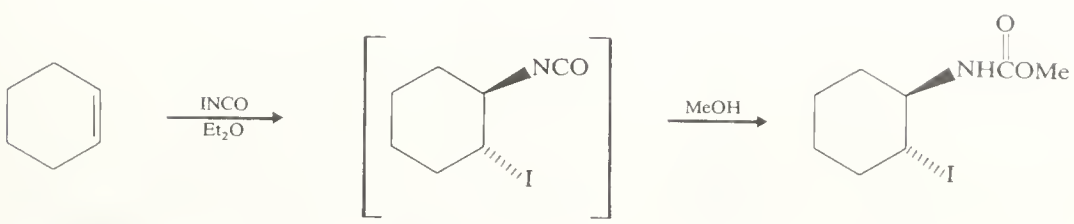
(104)



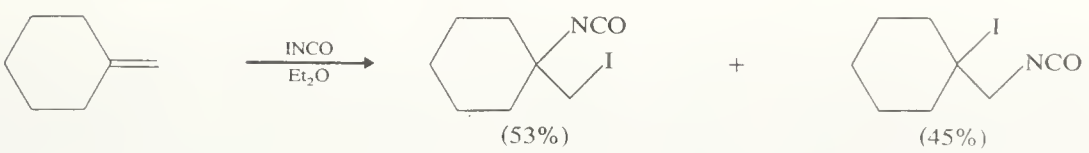
(105)



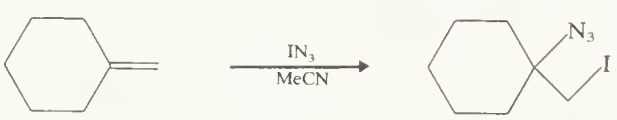
(106)



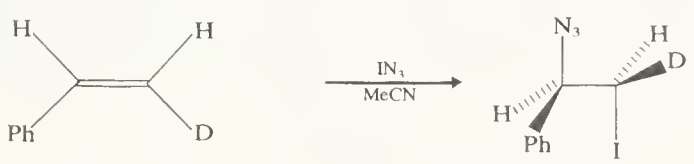
(107)



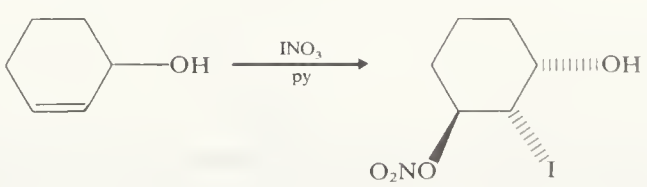
(108)



(109)



(110)



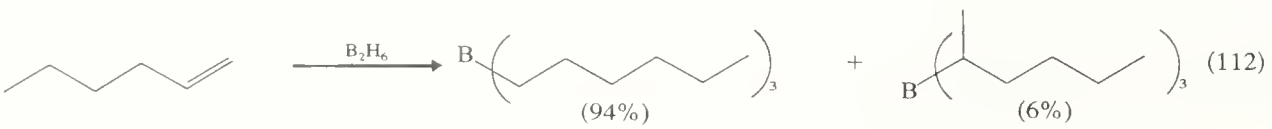
(111)

Markownikov rule). For more complex cyclic systems, *e.g.* equation (105), diaxial opening of a first-formed α-bromonium ion seems the most likely explanation of the observed orientation. Some of the 'positive iodine' reagents, usually generated from appropriate silver salts and iodine, are exemplified in equations (106)–(111); orientation can depend on the precise nature of the reagent (equations 108 and 109). Iodine azide shows a marked tendency for *anti* addition, even with aryl-substituted olefins, *e.g.* equation (110),

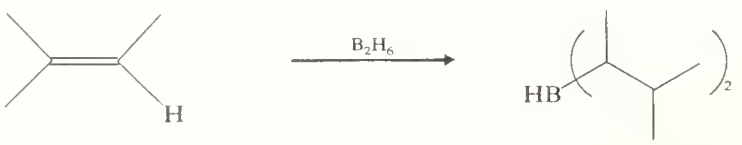
which presumably implies an iodonium ion intermediate. Reversible iodonium ion formation could account for the stereoselectivity shown in equation (111), and there is evidence for such iodonium equilibration in other cases.

Addition of sulphenyl halides to olefins has already been considered as the prototype of electrophilic addition to olefins involving a bridged ion and will not be discussed further.

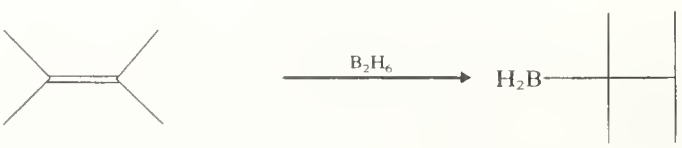
The hydroboration of olefins by diborane and by mono- or di-alkylboranes[63] is an essentially electrophilic addition which differs in many features from the reactions considered so far. Overall *syn* addition is found and the predominant product is that with boron attached to the less-substituted carbon atom (equation 112). All but the most highly hindered olefins react, but with trimethylethylene and tetramethylethylene, addition proceeds rapidly only as far as the dialkylborane or monoalkylborane, respectively (equations 113 and 114).



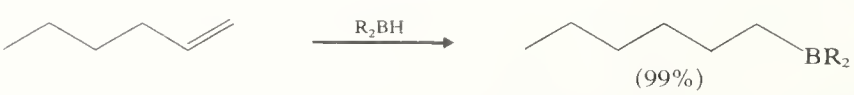
(112)



(113)

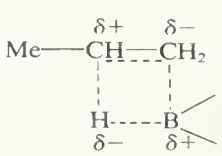


(114)



(R=CHMeCMe$_2$) (115)

The importance of the hydroboration reaction lies in the wealth of further reactions available to the alkylboranes,[64] *e.g.* oxidation to alcohols by alkaline hydrogen peroxide. The relative rates of hydroboration of olefins do not show the expected substituent dependence for an electrophilic addition: *e.g.* hex-1-ene (1.00), 2-methylbut-2-ene (0.50), cyclohexene (0.30), and 2,3-dimethylbut-2-ene (0.07). Presumably these results reflect a fairly early transition state in which small steric and electronic effects are fairly evenly balanced. Steric effects become dominant for hydroboration using substituted boranes, *e.g.* equation (115), which clearly has useful synthetic implications. Although a really clear view of the transition state for hydroboration has yet to materialize, the four-centre representation (**72**) provides a convenient working hypothesis which explains orientation, stereochemistry, *etc.*

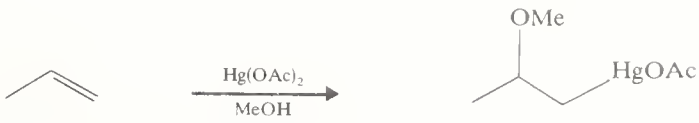


(**72**)

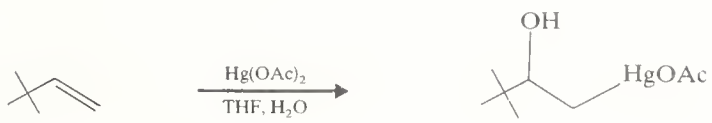
Another type of electrophilic addition to olefins is that of metal salts MX_n, often in the presence of a hydroxylic solvent, to give an oxymetallation adduct (equation 116). The adducts can sometimes be isolated as such, *e.g.* Hg(II), or else undergo further transformation to form products of overall oxidation of the olefin, *e.g.* Tl(III) and Pb(IV).

Examples of oxymercuration are given in equations (117)–(120) and illustrate: (i) high Markownikov orientation (equation 117), (ii) little tendency to rearrangement with susceptible systems (equation 118), (iii) *anti* stereospecificity for normal olefins, leading to diaxial addition with conformationally biased olefins (equation 119), but (iv) *syn* addition

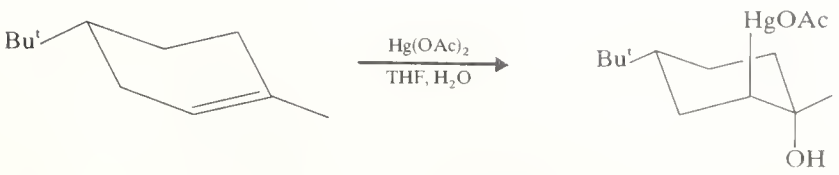
(116)



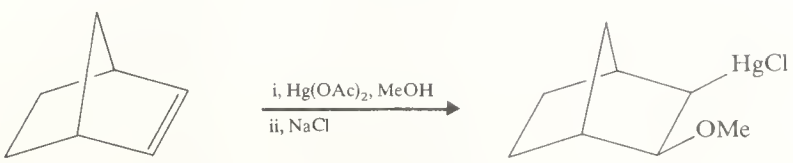
(117)



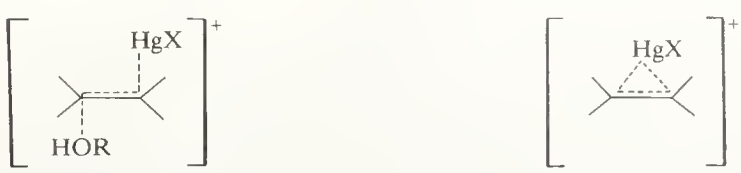
(118)



(119)



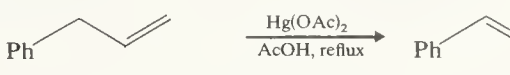
(120)



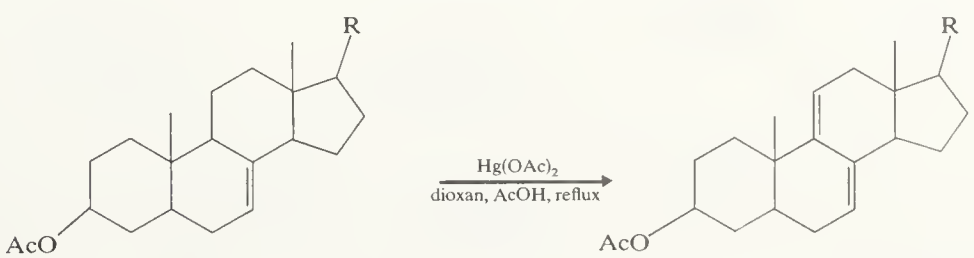
(73) (74)

to norbornene where *anti* coplanar addition is not readily achieved (equation 120). An Ad_E3 mechanism with a product and rate-determining transition state akin to (**73**) is probable for simple olefins. Whether this is preceded by pre-equilibrium formation of a bridged 'mercurinium ion' (**74**) is uncertain,[65] although there is spectroscopic evidence that such a species is formed in super-acid media in the absence of nucleophiles.

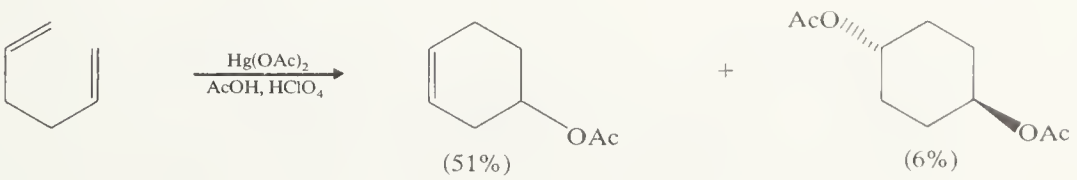
Under more vigorous reaction conditions, simple oxymercuration adducts are not isolated, and overall oxidation products are formed,[66] *e.g.* equations (121)–(123), which can be rationalized as further transformation products of initial oxymercuration adducts, *cf.* equation (124).



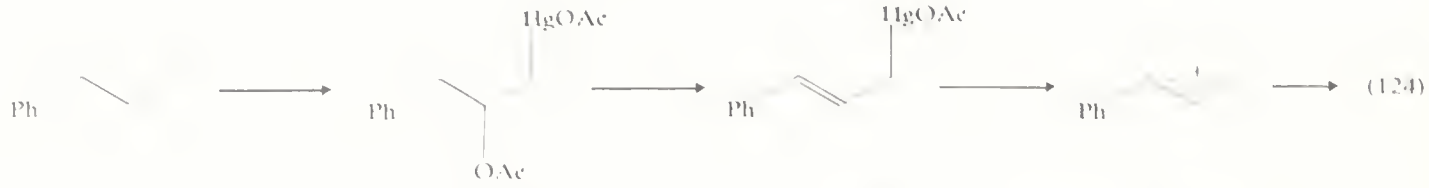
(121)



(122)

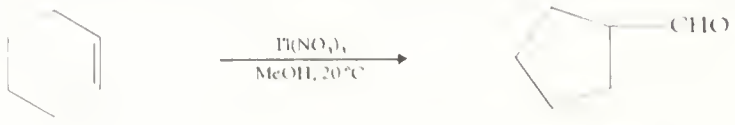


(123)

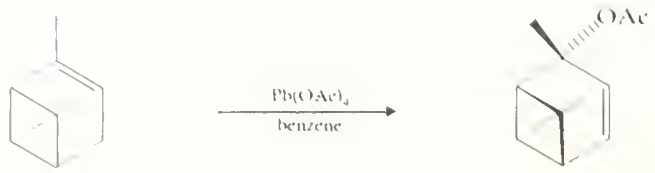


(124)

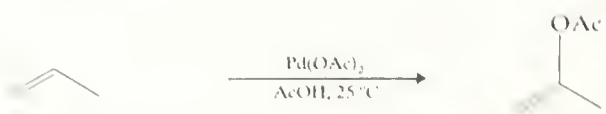
Formation of the manifold oxidation products that have been obtained by treatment of olefins with salts of Tl(III), Pb(IV), Pd(II), *etc.*[67] can be interpreted in similar vein. A few illustrative examples are given in equations (125)–(127). The precise prediction of the particular products obtainable from a given olefin and metal salt is difficult since the reactions are very sensitive to conditions and the nature of the substrate.



(125)

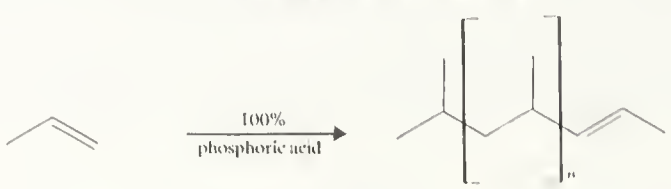


(126)

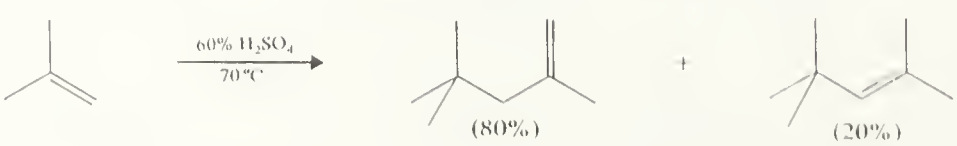


(127)

Given the propensity of olefins to undergo electrophilic addition, it might be expected that there would be a large group of synthetically important reactions initiated by carbenium ion attack. In fact this possibility is limited by the polymerization of simple olefins on treatment with proton acids, Friedel–Crafts catalysts (Lewis acids), *etc.*, *e.g.* equation (128). Because of the stability of the intermediate carbenium ions, polymerization occurs the more readily with more highly substituted (particularly aryl-substituted) alkenes. Thus styrene polymerizes readily with cationic catalysts. In special cases, however, careful choice of conditions allows simple reactions to predominate, *e.g.* equations (129)–(131). These reactions are readily interpretable in terms of carbenium ion attack on the olefin followed by proton loss, nucleophile capture, *etc.*



(128)

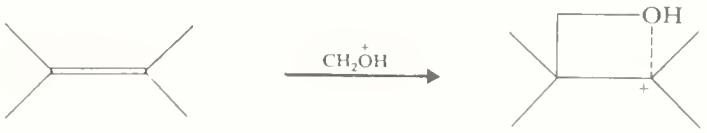


(129)

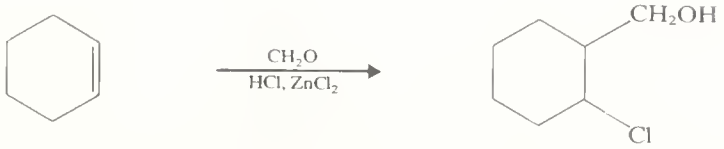
(130)

(131)

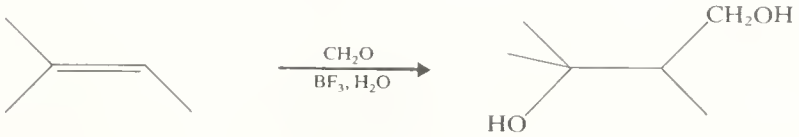
A more generally useful process of this type is the Prins reaction[68] where the attacking species is a hydroxycarbenium ion (protonated aldehyde or ketone). It may be that one reason for the greater efficacy here is that the intermediate carbenium ion derives greater stability from the neighbouring hydroxyl and is therefore not so prone to initiate polymerization, *cf.* equation (132). Some examples of the Prins reaction are given in equations (133)–(135). In each case, completion of addition occurs by attack of nucleophile, chloride ion, water, and acetic acid, respectively.



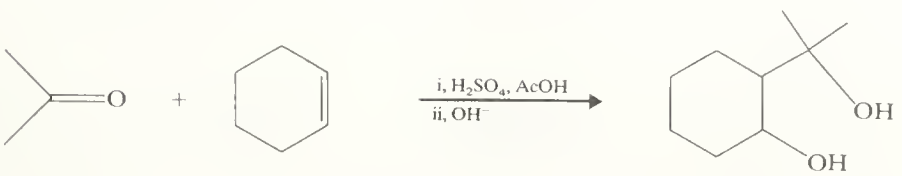
(132)



(133)

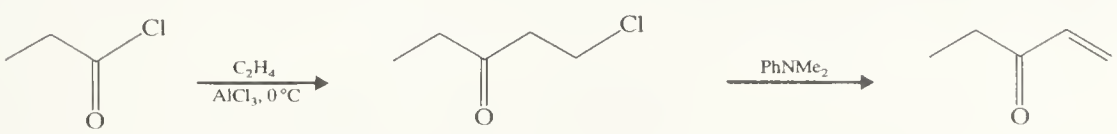


(134)

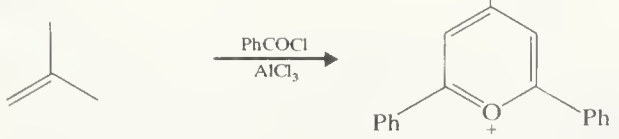


(135)

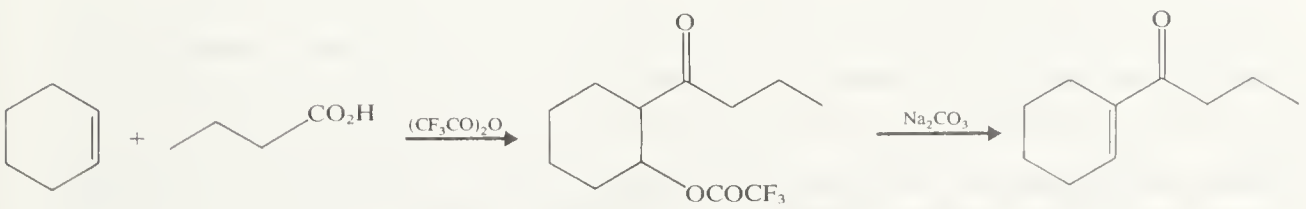
As with alkylation, efficient cationic acylations of olefins[69] are not very common for the same sort of reasons. However, the lower reactivity of ethylene enables simple adducts to be isolated and the adducts are useful precursors of vinyl ketones, *e.g.* equation (136). Branched olefins with excess of acyl halides and Friedel–Crafts catalysts lead to pyrylium salts as further transformation products of the initial adducts, *e.g.* equation (137). Apparently, clean formation of simple acylated adducts is achieved by the use of mixed anhydrides. Again, unsaturated ketones may be derived by further transformation (equation 138).



(136)

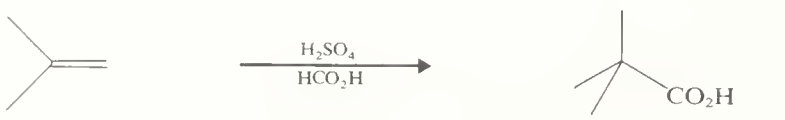


(137)

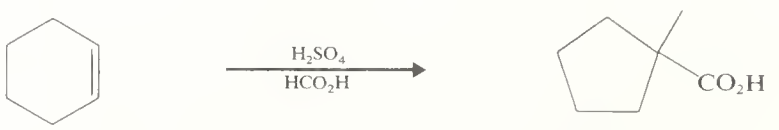


(138)

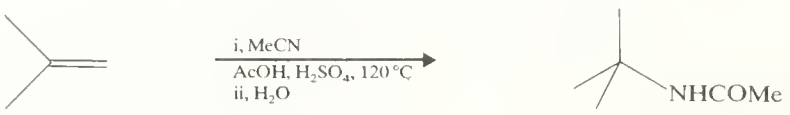
Before leaving this section on electrophilic additions to olefins, it should be pointed out that there are a number of reactions in which protonation to give a carbenium ion is followed by attack of a nucleophile. Since these reactions are not only typical of olefins, the intermediate carbenium ion being obtainable from other precursors, they will only be mentioned briefly. Examples include: (i) the alkylation of carbon monoxide (derived from formic acid), the Koch–Haaf carboxylation,[70] *e.g.* equations (139) and (140); (ii) the alkylation of a nitrile to give an amide, the Ritter reaction,[71] *e.g.* equation (141); (iii) alkylation of a thiol, *e.g.* equation (142); and (iv) hydride transfer from a silyl hydride leading to overall reduction,[72] *e.g.* equation (143). As indicated in equation (140), however, such carbenium ion processes are prone to rearrangement.



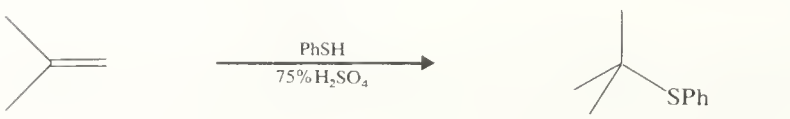
(139)



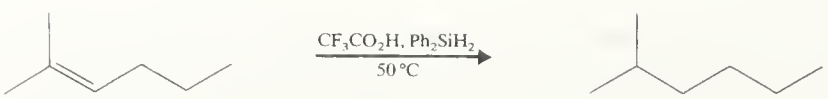
(140)



(141)

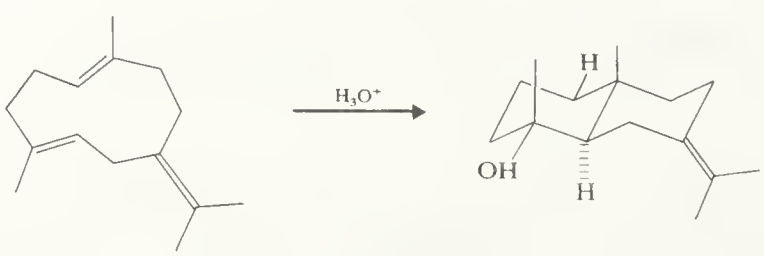


(142)



(143)

In polyenes the generation of a carbenium ion by protonation of one double bond is sometimes followed by intramolecular addition to another. This sort of reaction is the prototype of biogenetic cyclizations leading to terpenes, *etc.* (see Chapter 29.2). A nice example which illustrates the preferred formation of a six-membered ring with equatorial entry of proton and nucleophile (*anti* addition) is the acid-catalysed cyclization of the sesquiterpene hydrocarbon germacrene (equation 144).



(144)

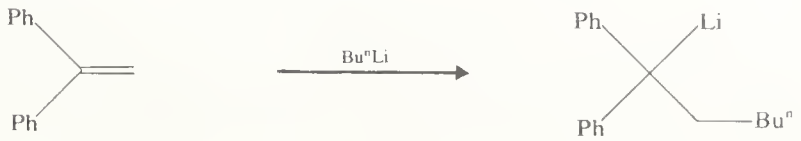
2.2.3.2 Nucleophilic additions

In contrast to the propensity of olefinic hydrocarbons to be attacked by electrophiles, the addition of simple nucleophiles does not generally occur. Only when attachment of electron-withdrawing groups renders the double bond electron deficient are such additions found (*e.g.* Michael addition to unsaturated ketones), but such substrates are not relevant here.

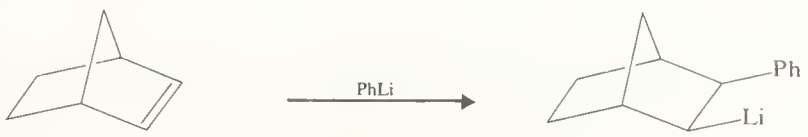
Reactive organometallic reagents such as metal alkyls, *etc.*, however, do undergo effective nucleophilic addition to olefinic hydrocarbons. Addition may be a single stage

leading to a 1 : 1 adduct (equation 145; $n = 1$) or multi-stage leading to polymerization (n large). An example is the addition of alkyl-lithium reagents (RLi) to olefins. Reactivity increases along the series R = primary < secondary < tertiary. n-Butyl-lithium adds to ethylene only under high pressure and polymerization occurs since the initial adduct is also a primary alkyl lithium and it reacts further with the ethylene. In contrast, t-butyl-lithium gives a 1 : 1 adduct with ethylene owing to the lower reactivity of product than reagent. Addition of alkyl-lithium to aryl-conjugated olefins occurs readily since the incipient carbanion is stabilized by virtue of its benzylic character, *e.g.* equation (146). Strain in the olefin also leads to enhanced reactivity, allowing simple adducts to be isolated, *e.g.* norbornene (equation 147) and cyclopropene (equation 148).

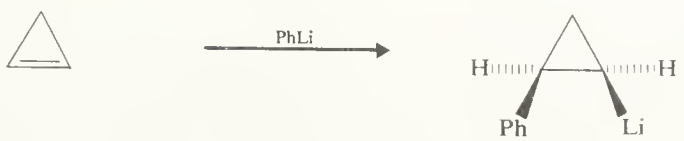
(145)



(146)

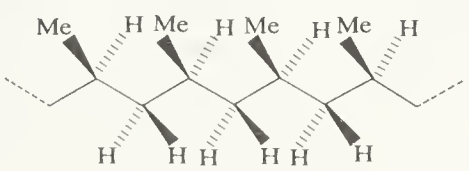


(147)



(148)

The whole subject of anionic polymerization[73] (equation 145) is too specialized to be discussed in detail. The Ziegler–Natta process is the most important. Here the active catalyst is derived from an aluminium trialkyl and a Group IV–VI transition metal compound, *e.g.* titanium tetrachloride or molybdenum pentachloride. Polypropylene produced by this process is a stereoregular *isotactic* polymer (**75**). This is highly crystalline and has one of the highest tensile strengths and lowest densities of all commercial plastics.

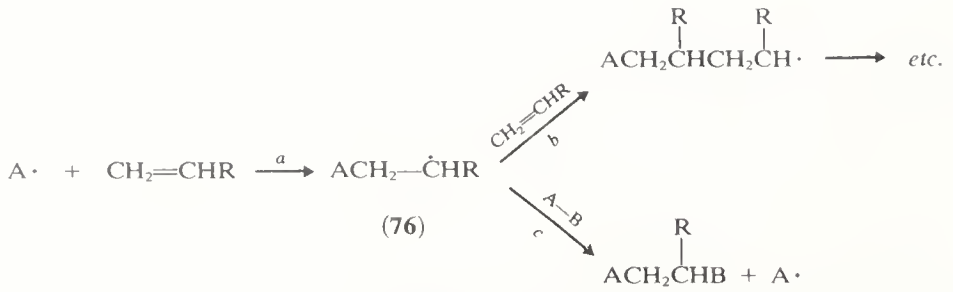


(**75**)

2.2.3.3 Radical additions

Addition of a free radical A· to an olefin will give a new radical (**76**) which may either undergo addition to a second molecule of olefin (step *b*) resulting, after repeated addition, in telomerization or polymerization, or the new radical (**76**) may interact with a substrate A—B by abstraction of B (step *c*, the transfer step). The repetitive combination of steps *a* and *c* constitutes the radical chain mechanism for addition of the addendum A—B to the olefin (equation 149).

The balance between polymerization and 1 : 1 adduct formation depends critically on the nature of the olefin and the addendum. Space does not permit a detailed discussion of the thermodynamic factors involved (*cf.* Section 2.8.1) and the following is an over-simplified summary. Path *b* is favoured for more reactive olefins, particularly those for which the adduct radical (**76**) is stabilized, *e.g.* styrene (benzylic radical produced) or



(149)

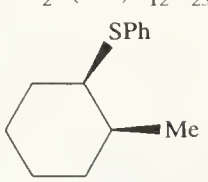
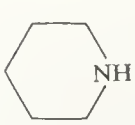
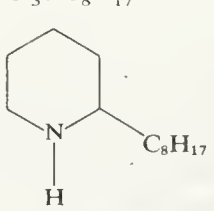
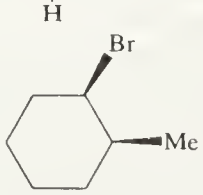
butadiene (allylic radical produced). On the other hand, path *c* is favoured if the A—B bond energy is low and if the new bond to B, formed in the transfer step, is relatively strong so that this step is exothermic.

The topic of radical-initiated polymerization has been extensively reviewed[74] and will not be discussed in any detail, particularly since it is a topic not confined to olefinic hydrocarbons. However, it is noteworthy that enormous quantities of polystyrene and styrene–butadiene copolymer (SB-R) are produced in this way. In these cases the radicals required in the initiating step *a* in equation (149) are derived either by decomposition of acyl peroxides, *e.g.* dibenzoyl peroxide, or, in emulsion polymerization, by heating persulphates. Clearly these conditions favour polymerization because of the absence of efficient chain transfer agents A—B.

Many different addenda (A—B) have been added to olefins under radical chain conditions to give useful yields of 1:1 adducts.[75] Such additions are favoured by non-polar solvents or gas-phase conditions, and are accelerated by light, radical initiators, or heat. Most addenda are either of the A—H type or the A—Hal type for which A· is a relatively stable free radical. The demands of the transfer step (*c*), which is effectively a radical displacement by (**76**) on A—B at B, require that B must be a simple species like hydrogen or halogen. Clearly another factor which will favour 1:1 adduct formation over polymerization is the presence of excess of addendum. Table 1 gives some examples of 1:1 adduct formation featuring typical addenda. A number of points can be made. Firstly,

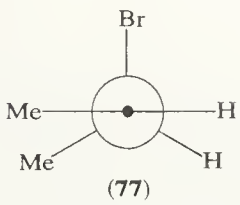
TABLE 1

Radical Additions to Olefins

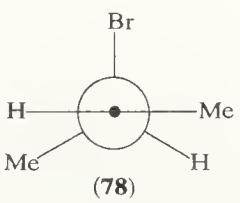
Addendum	*Olefin*	*Initiator*	*Adduct*
(1) CCl_4	hept-1-ene	Bz_2O_2	$Cl_3CCH_2CHClC_5H_{11}$
(2) CBr_4	styrene	$h\nu$	$Br_3CCH_2CHBrPh$
(3) $CH_2(CO_2Et)_2$	oct-1-ene	$(Bu^tO)_2$	$(EtO_2C)_2CHC_8H_{17}$
(4) MeCH(OH)Me	dodec-1-ene	$(Bu^tO)_2$	$Me_2C(OH)C_{12}H_{25}$
(5) PhSH	1-methylcyclohexene	$h\nu$	
(6) Cl_3SiH	oct-1-ene	Ac_2O_2	$Cl_3SiC_8H_{17}$
(7) 	oct-1-ene	$(Bu^tO)_2$	
(8) HBr	1-methylcyclohexene	Bz_2O_2	

as regards orientation of addition to constitutionally unsymmetrical olefins, in step *a* addition of A· usually occurs at the less-substituted carbon. The classical example is the so-called 'anti-Markownikov' addition of hydrogen bromide to olefins in the presence of peroxides discovered by Kharasch and Mayo in 1933, *e.g.* Table 1 entry (8). Conventional explanations of this orientation pattern give a dominant role to the formation of the more stable — generally more substituted — of the two possible radicals in step *a*, though this view has been disputed.[76] Secondly, radical addition of alcohols and amines to olefins occurs with α-C—C bond formation (Table 1 entries 4 and 7). This contrasts with ionic addition where C—O and C—N bonding would be expected and is a consequence of high O—H and N—H bond energies combined with the relative stability of a radical α to oxygen or nitrogen.

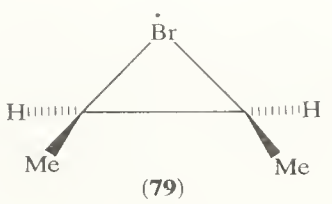
The stereochemistry of radical addition also merits some comment. In favourable cases, *e.g.* Table 1, entries (5) and (8), fairly clear-cut *anti* addition of A—B is found, while in others, *e.g.* peroxide-catalysed addition of DBr to *cis*- and *trans*-but-2-ene, although *anti* addition predominates at −70 °C, non-stereospecific addition is found at higher temperatures. It is possible that these results reflect conformational equilibration between the intermediate radicals (**77**) and (**78**), the former being the immediate species from *cis*- and the latter from *trans*-butene, which becomes more important the higher the temperature. The transfer step *c* presumably occurs from the side opposite to the bulky Br atom already present. An alternative view favoured by some authorities is that a bridged radical, *e.g.* (**79**), controls the overall *anti* addition and that interconversion with 'open' radicals leads to loss of stereospecificity at elevated temperatures.



(**77**)

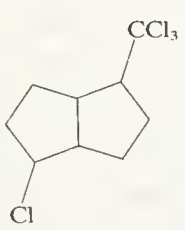


(**78**)

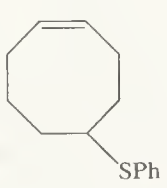


(**79**)

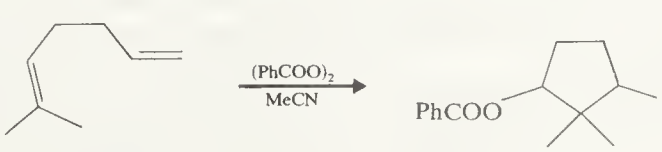
Intramolecular radical additions[77] to non-conjugated dienes sometimes lead to cyclization, *e.g.* benzoyl peroxide catalysed addition of carbon tetrachloride to cyclo-octa-1,5-diene gives the bicyclic derivative (**80**). In contrast, radical chain addition of thiophenol to the same diene gives the monocyclic adduct (**81**). Apparently thiophenol is a more efficient transfer agent and it traps the monocyclic radical intermediate prior to cyclization. An interesting feature of the radical-promoted cyclization of acyclic 1,5-dienes is the propensity for cyclopentane ring formation, *e.g.* equation (150). This result may be contrasted with the cationic cyclization of similar dienes in which six-membered ring formation predominates (see equation 144 above).



(**80**)



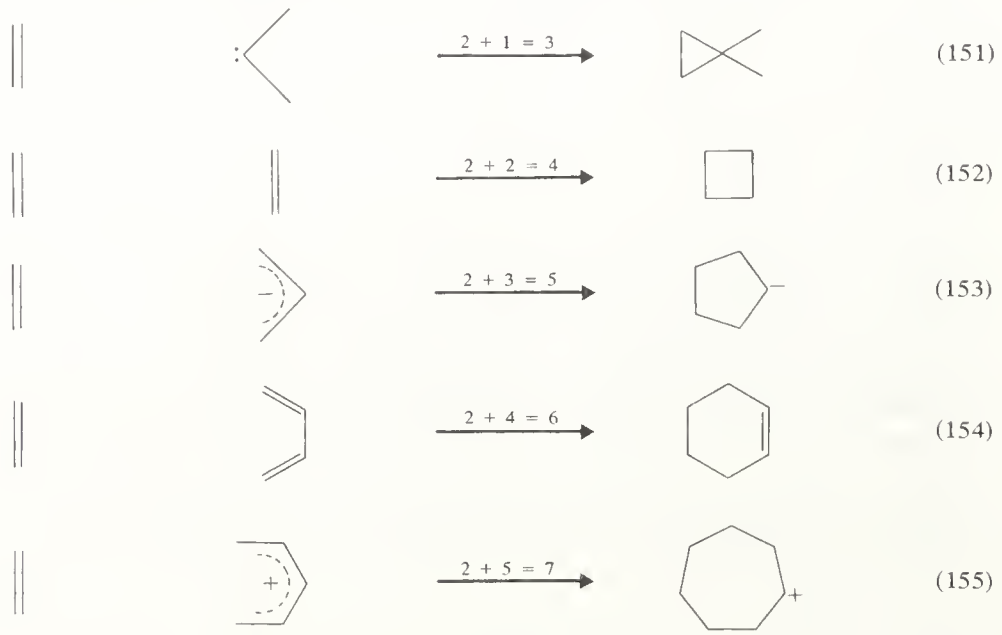
(**81**)



(150)

2.2.3.4 Cycloadditions and related reactions

Virtually all the additions of olefins discussed so far have been stepwise processes. We need to consider now a class of reactions in which an addendum adds in a more or less concerted fashion to an olefin with formation of two new σ-bonds. The main types of such cycloadditions are summarized in schematic form in equations (151)–(155).



(151)

(152)

(153)

(154)

(155)

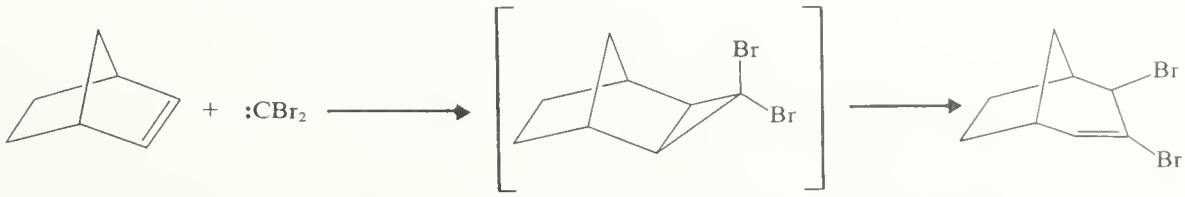
These reaction types are designated in terms of the number of reacting atoms in the two substrate molecules and the size of the ring formed, *e.g.* $2+1=3$ indicates addition of a carbene or its equivalent to an olefin with the formation of a three-membered ring. Many reactions of the types shown in equations (151)–(155) can be characterized as pericyclic, *i.e.* 'reactions in which all first-order changes in bonding relationships take place in concert on a closed curve', and as such may be treated in terms of orbital symmetry according to the Woodward–Hoffmann and related rules. This is not the place to describe these rules in detail, extensive reviews being available.[78] A simplified treatment applicable to the cycloadditions under consideration may be made by observing that since only small and normal rings are involved, addition of the two components must be *syn* to each other (suprafacial in Woodward–Hoffmann terminology). Suprafacial cycloadditions are allowed thermally if the total number of participating electrons is $4q+2$ (where q is 0, 1, 2, . . .) while they are forbidden in the ground state but allowed in the excited state for $4q$ electrons. These rules are of course an extension of aromaticity concepts to transition states (see Section 2.4.6).

Addition of a carbene to an olefin to give a cyclopropane ($2+1=3$) is thus allowed thermally provided that overlap in the transition state is between the π-orbitals of the olefin and the vacant orbital of a singlet carbene ('non-linear cheletropic process'). Addition of two olefinic systems to give a cyclobutane (four participating electrons) does not in general occur thermally — and then presumably by a stepwise process to which rules for concerted additions do not apply — but is well known photochemically. Addition of an allyl anion to an olefin (equation 153) ($4q+2$ where $q=1$) does not, as such, have many simple examples, but as we shall see a number of heterocyclic ring-forming reactions conform to this description and should be allowed thermally. The conjugated diene plus olefin reaction has of course the Diels–Alder reaction as its prototype and the $2+5=7$ process, although rare, is included for completeness. Both are thermally allowed, having six participating electrons. With this background, we shall consider some examples of olefin cycloadditions.

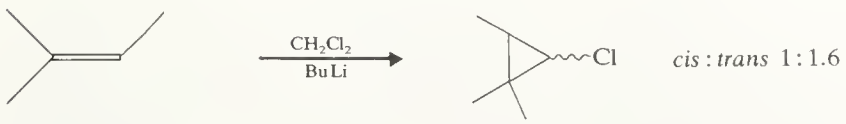
An enormous amount of preparative and mechanistic work has been done on the addition of carbenes and related species to olefins to form cyclopropane derivatives[79] (see

Section 2.8.2). Two extreme types of behaviour may be discerned, one being addition of a free carbene presumably under orbital symmetry control, and the other involving attack of an organometallic intermediate, 'carbenoid'. The former is illustrated by the addition of a dihalogenocarbene (derived by base elimination of hydrogen halide from a haloform) to an olefin to give a dihalogenocyclopropane, *e.g.* equation (156). The latter is exemplified by addition of iodomethylzinc iodide (Simmons–Smith reagent,[80] derived from methylene di-iodide and zinc–copper couple) to an olefin to give a cyclopropane with expulsion of zinc iodide, *e.g.* equation (163). Equations (156)–(164) give some idea of the scope of carbene and carbenoid reactions. Also included is an example of the related addition of a nitrene (equation 165).

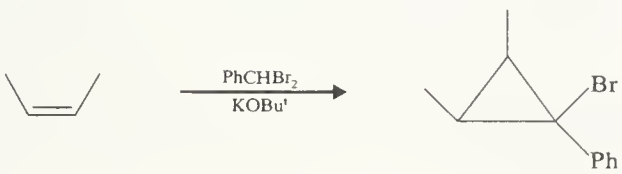
(156)



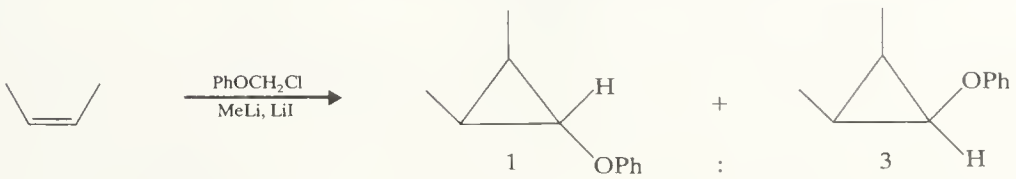
(157)



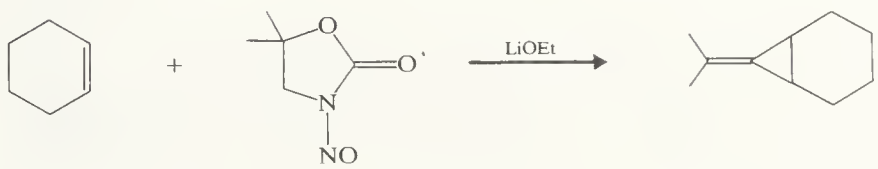
(158)



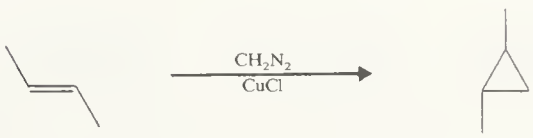
(159)



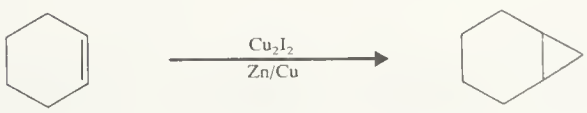
(160)



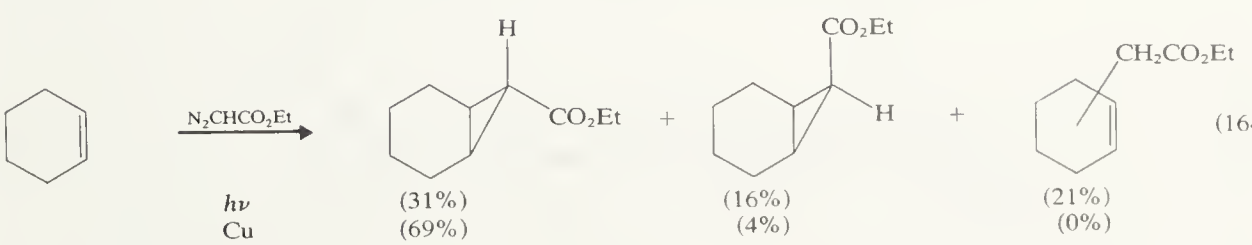
(161)



(162)



(163)



(164)

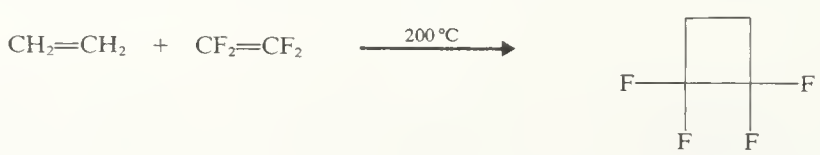
(165)

Equation (157) provides an example where the first-formed adduct undergoes a further reaction owing to its instability. Equations (158)–(160) and (162) show some features relating to stereospecificity of addition and stereochemistry of adduct from unsymmetrical carbenes and carbenoids. Equation (164) illustrates the differing selectivity of a photochemically generated carbene (triplet) as opposed to a copper-complexed one. Finally, in equation (165), the ethoxycarbonylnitrene may be generated either by thermolysis of ethyl azidoformate or by base-induced decomposition of p-$O_2NC_6H_4SO_2NHCO_2Et$.

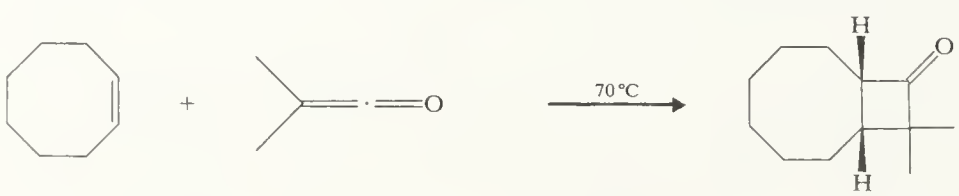
Formally related to the $2+1=3$ reaction type is epoxidation of olefins, which will be discussed later under oxidations (see Section 2.2.3.5).

The formation of cyclobutanes by [2+2] processes in which one component is an olefin[81] can be divided into two categories: (i) those in which the other component is a fluoro-olefin, keten, isocyanate, or other compound with an activated double bond; and (ii) those in which the other component is a photoexcited π-bond system such as a carbonyl or conjugated olefin, *etc.*[82] In the first category the orbital symmetry barrier to cycloaddition is avoided either by adoption of a stepwise mechanism, or, in the case of ketenes, *etc.* addition may be antarafacial (*anti*) to the second component, thereby constituting an overall allowed $[_\pi 2_s + _\pi 2_a]$ process.[78] The photochemical category may well be excited state reactions which, since they involve $4q$ electrons ($q=1$), would be allowed. Examples of both categories are given in equations (166)–(174). Addition to simple olefins of stable ketens only occurs at elevated temperatures (equation 167), but the more reactive species containing electron-withdrawing groups react more readily [equations (168)–(170)].

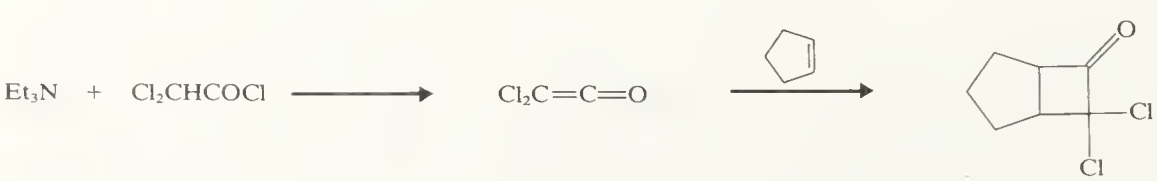
One instance is given of the addition of photoexcited carbonyl to an olefin to give an oxetan: the Paterno–Büchi reaction[83] (equation 174).



(166)



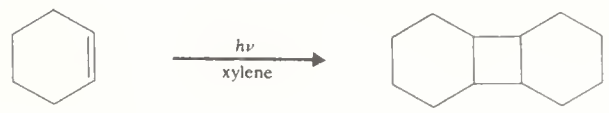
(167)



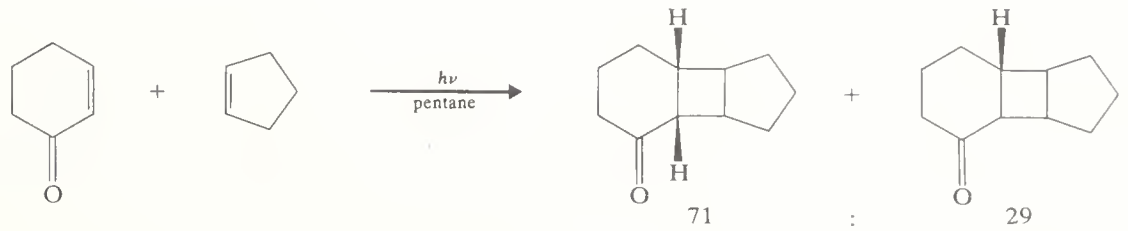
(168)

(169)

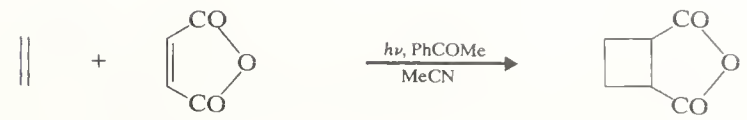
(170)



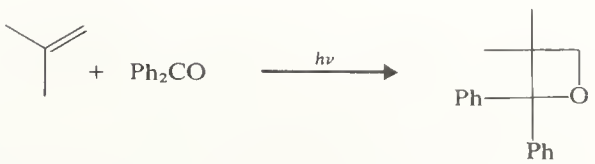
3 stereoisomers (171)



(172)

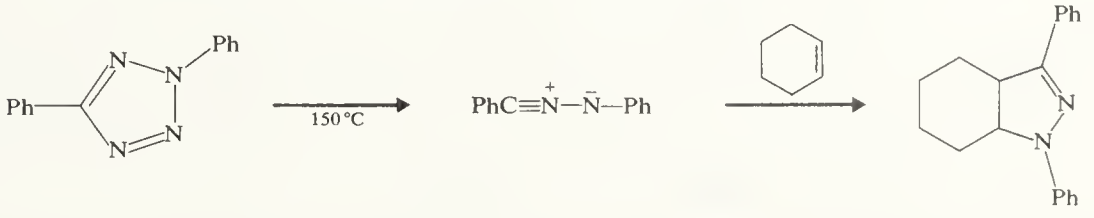


(173)

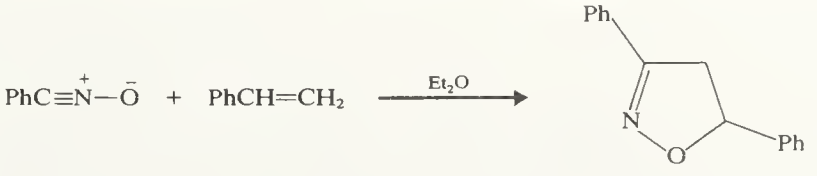


(174)

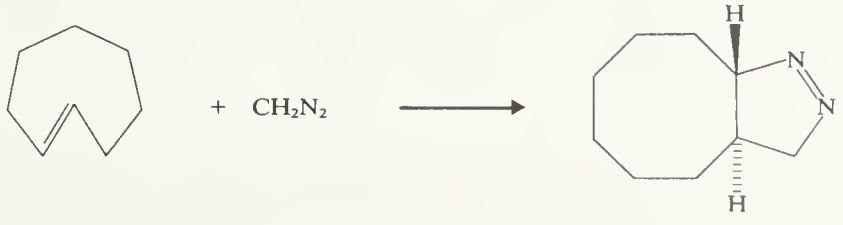
The 2+3=5 cycloaddition[84] has been extensively studied for three-atom components $\overset{+}{a}$=b—$\bar{c}$ (1,3-dipole with double bond in the sextet form) and $\overset{+}{a}$—b—$\bar{c}$ (1,3-dipole without double bond in the sextet form). Many heterocyclic systems (see Volume 4) have been synthesized and examples where olefinic hydrocarbons act as the dipolarophile are given in equations (175)–(181). Only strained reactive olefins readily form adducts with less-reactive dipoles such as diazomethane and azides, *e.g.* equations (177) and (178). Simple olefins often require more forcing conditions and the first-formed 1:1 adducts then undergo further transformations (equations 180 and 181).



(175)

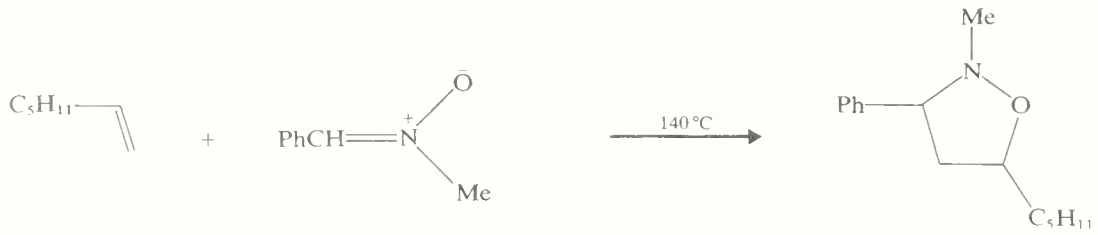


(176)



(177)

(178)

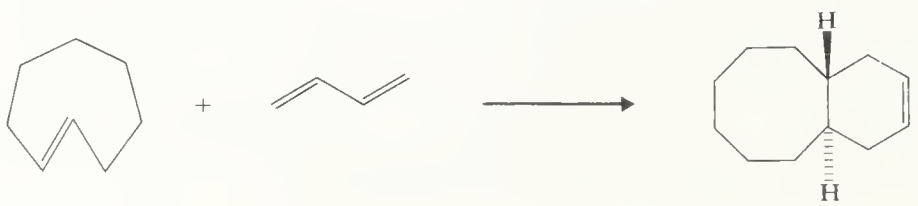


(179)

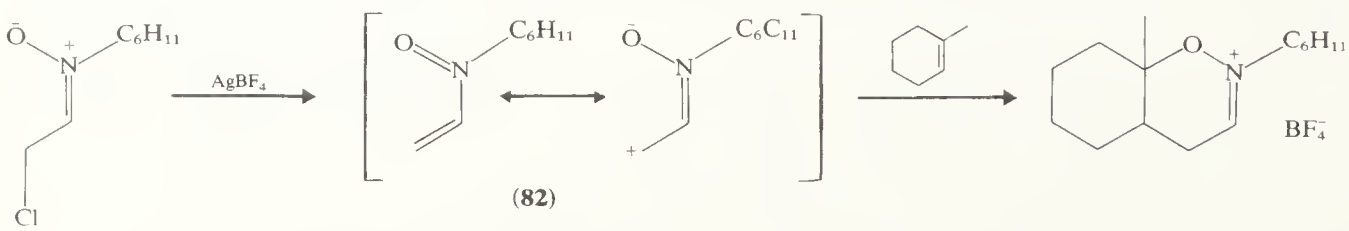
(180)

(181)

Cycloadditions of the 2+4=6 class are chiefly of the Diels–Alder type (see Section 2.3.2.4) and need little further comment here except to reiterate that only reactive dienes such as cyclopentadiene add to simple olefins. Highly strained olefins like norbornene and *trans*-cyclo-octene do give adducts with simple dienes, *e.g.* equation (182). A recent development has been the *in situ* generation of the heterodiene equivalent (**82**) from an α-chloronitrone and its addition to olefins, *e.g.* equation (183). The resulting adducts are useful synthetic intermediates.[85]



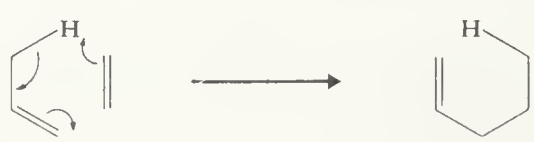
(182)



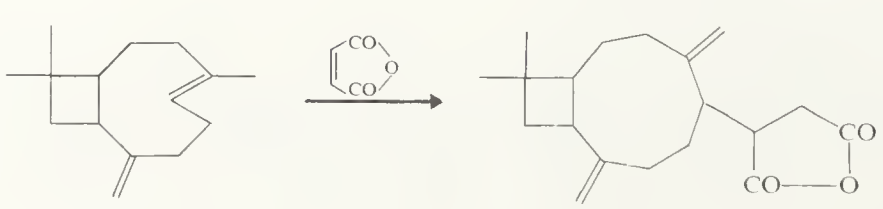
(**82**)

(183)

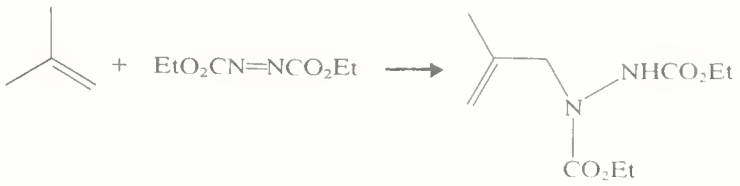
Closely related to cycloadditions is the so-called 'ene reaction'[86] shown schematically in equation (184). Here a C—H σ-bond plays the role corresponding to one of the diene double bonds in the Diels–Alder reaction. The prototype addition to caryophyllene is shown in equation (185). In this case there is a driving force due to migration of a double bond from a more to a less strained situation. Simple olefins form adducts with reactive eneophiles, *e.g.* azo compounds (equation 186); where choice exists there is preference for abstraction of primary hydrogen. A constitutionally related reaction is the conversion of olefins to allylic hydroperoxides by singlet oxygen,[87] *e.g.* equation (187), although the detailed mechanism is still controversial.



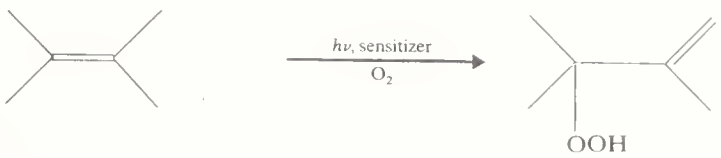
(184)



(185)



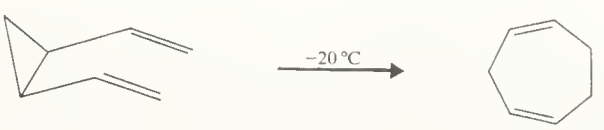
(186)



(187)

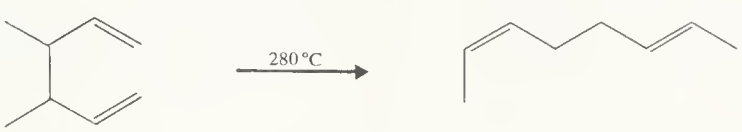
Amongst other relevant pericyclic reactions, probably the most important is the Cope rearrangement of 1,5-dienes,[88] also a six-electron suprafacial process, designated as a [3,3]-sigmatropic shift, and indicated schematically in equation (188). Equations (189)–(193) provide some examples which show how strain in the reactant influences ease of reaction and which illustrate stereochemical aspects.

(188)

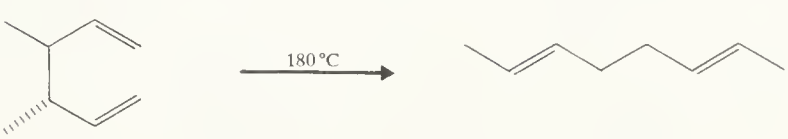


(189)

(190)



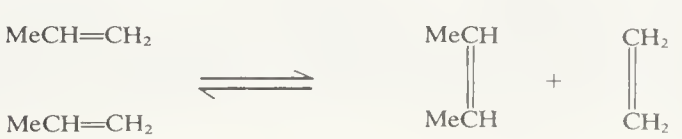
(191)



(192)

(193)

Olefin metathesis,[89] *e.g.* equation (194), which occurs under conditions of heterogeneous, *e.g.* $Mo(CO)_6$/alumina, or homogeneous catalysis, *e.g.* $WCl_6 \cdot EtAlCl_2$, is mentioned here because of its apparent similarity to a pericyclic reaction. Since organometallic intermediates are involved, this affinity is only superficial. The reaction has considerable potential and industrial importance.

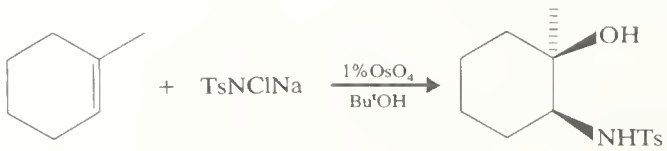


(194)

2.2.3.5 Oxidations

Long known and familiar oxidative additions to olefins, such as *syn* hydroxylation with potassium permanganate under alkaline conditions or with osmium tetroxide in organic solvents, need only brief mention.[90] Permanganate has the disadvantage of giving only moderate yields owing to further oxidative cleavage of the first formed 1,2-diol. Osmium tetroxide, though very efficient, has the disadvantage of expense. Attempts in the past to design a catalytic process based on osmium tetroxide have met with only partial success, but reproducible procedures involving (i) $Bu^tOOH/Et_4NOH/OsO_4$[91] and (ii) *N*-methylmorpholine *N*-oxide/OsO_4[92] have recently been developed and appear to be very promising.

Another development is the *syn* oxyamination of olefins by chloramine catalysed by osmium tetroxide. With constitutionally unsymmetrical olefins the hydroxyl group becomes attached to the more substituted carbon, *e.g.* equation (195).

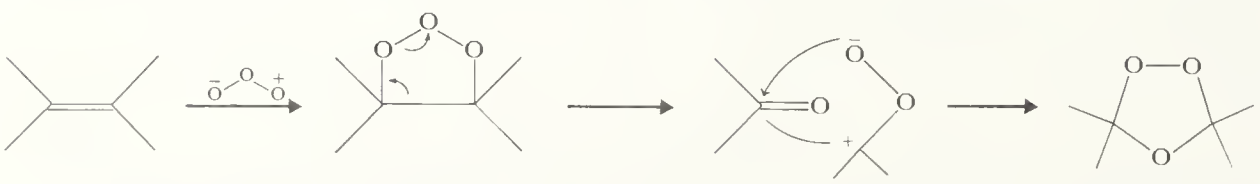


(195)

An alternative approach to olefin hydroxylation is based on initial addition using iodine–silver acetate (*cf.* equation 106) followed by solvolysis of the iodoacetate, either in dry acetic acid leading after hydrolysis of the intermediate diacetate to overall *anti* hydroxylation of the olefin, or in wet acetic acid leading to *cis* hydroxylation.[90]

Olefin hydroxylation followed by oxidative cleavage can often be usefully accomplished using the combination of periodate–permanganate which with 1,2-disubstituted olefins gives carboxylic acids, or periodate–osmium tetroxide where aldehydes are formed.[90]

One of the traditional methods for olefin cleavage is ozonolysis.[93] Despite much debate, Criegee's mechanism[94] still seems the most satisfactory. It invokes initial formation of a primary ozonide (**83**), by 1,3-dipolar addition of ozone to the olefin, followed by fragmentation–recombination to give an isolable secondary ozonide (**85**) (equation 196).



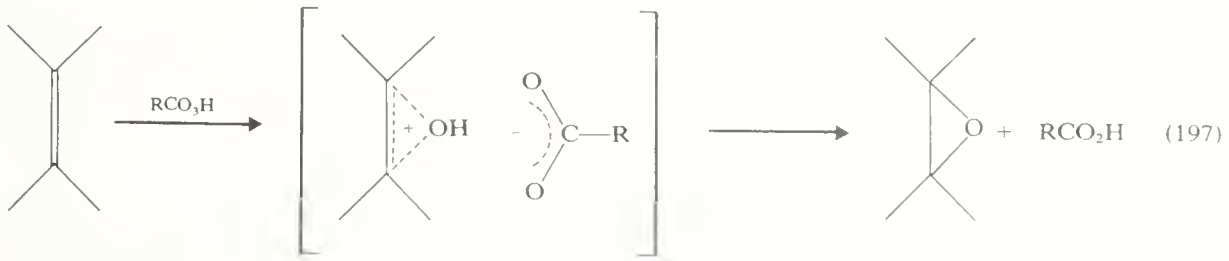
(196)

(**83**) (**84**) (**85**)

Ozonolysis in methanol gives α-methoxyhydroperoxides, thereby providing evidence for the intermediate zwitterion (**84**). For conversion of 1,2-disubstituted olefins to aldehydes, ozonolysis can be carried out in the presence of an oxygen acceptor such as dimethyl sulphide[95] or pyridine.[96]

Oxidation of olefin *via* initial oxymetallation has already been mentioned under electrophilic additions. Closely related is the industrially important Wacker process[97] for oxidation of ethylene to acetaldehyde by $O_2/CuCl_2$ catalysed by palladium chloride.

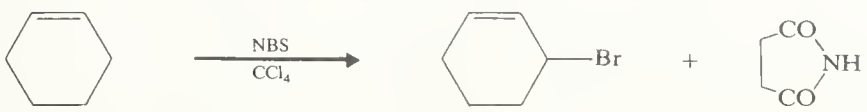
Another important oxidative addition is the epoxidation of olefins by peroxy acids.[98] On a large scale, commercially available peracetic acid is used, while for small-scale reactions the more stable solid *m*-chloroperbenzoic acid is convenient. A possible representation of the transition state for epoxidation is given in equation (197). It explains (i) the stereospecificity (configuration of olefin preserved in epoxide), (ii) the observation that addition of alkyl substituents at the double bond systematically increases the rate, and (iii) that with increasing acidity of the carboxylic acid formed in the reaction, the more rapid the epoxidation.



(197)

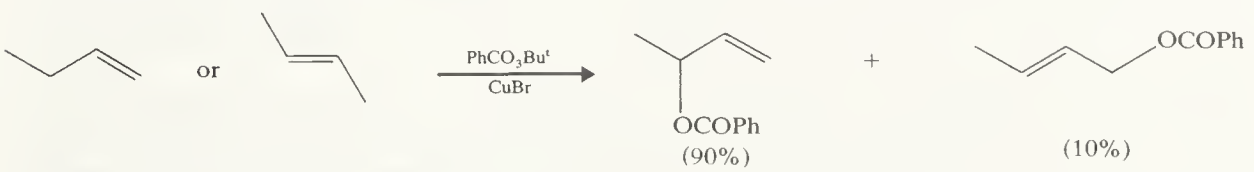
A recent development has been the discovery that vanadyl and molybdenum complexes can catalyse the epoxidation of olefins by t-butyl hydroperoxide.[99]

An important group of olefin oxidations are those leading to allylic substitution, one of the longest known being allylic bromination with *N*-bromosuccinimide (NBS),[100] *e.g.* equation (198). The reaction is believed to be a radical chain bromination by molecular bromine liberated gradually by reaction of NBS with the HBr formed. The process, which involves an allylic radical, is preparatively useful for constitutionally symmetrical olefins where only one type of allylic hydrogen is present. Allylic chlorination may be similarly achieved using t-butyl hypochlorite.[101]

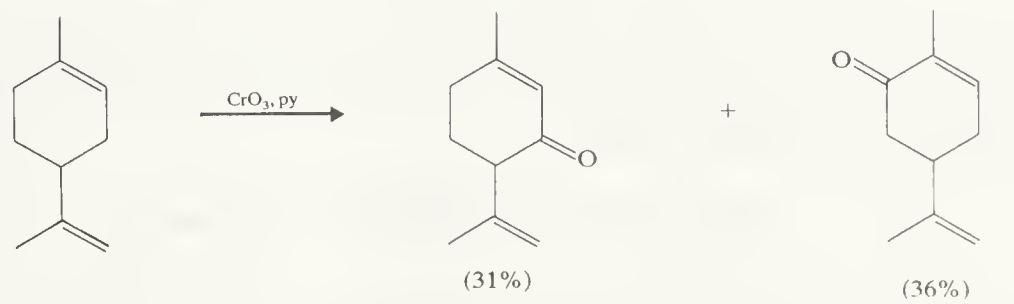


(198)

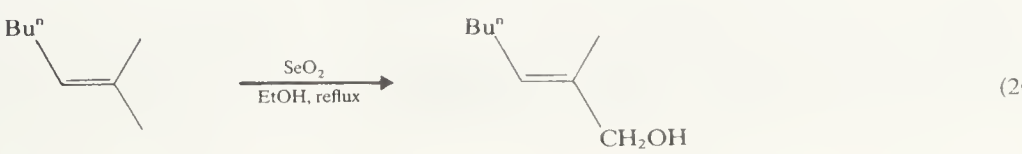
Other allylic oxidation reactions include the following: (i) the formation of allylic esters on treatment of olefins with peresters in the presence of copper salts,[102] *e.g.* equation (199); (ii) the direct oxidation of olefins to α,β-unsaturated ketones,[103] for which chromium trioxide–pyridine is recommended, *e.g.* equation (200); (iii) selenium dioxide oxidation,[104] which can give allylic alcohols or aldehydes/ketones depending on substrate and conditions, and for which allylic seleninic acid intermediates have in some cases been demonstrated, *e.g.* equation (201); (iv) an indirect hydroxylation method involving intermediate allylic metalation,[105] *e.g.* equation (202); and finally, (v) an allylic amination procedure considered to involve imidoselenium compounds as the active reagents,[106] *e.g.* equation (203). It should also be remembered that allylic hydroperoxides formed from olefins by autoxidation or reaction with singlet oxygen (equation 187) can be readily reduced to allylic alcohols.



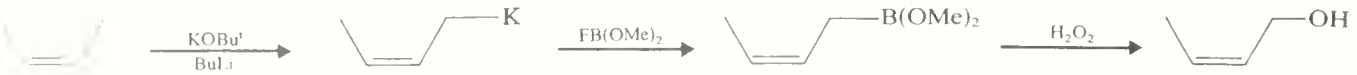
(199)



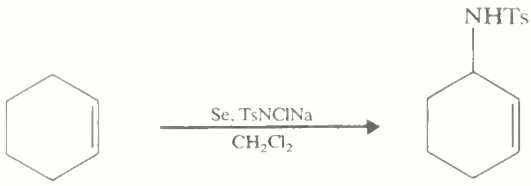
(200)



(201)



(202)



(203)

2.2.3.6 Reductions

The catalytic hydrogenation of olefins to alkanes has already been covered in Section 2.1.7.1 and extensive reviews are available.[107] One feature which should be mentioned here, however, is heats of hydrogenation of olefins,[108] which provide evidence about the relative strain energies of alkene and alkane. The heat of hydrogenation (ΔH_{hydrog}) of cyclohexene (in acetic acid at 25 °C) is -113 kJ mol^{-1}, which provides a normal value for hydrogenation of unstrained alkene to alkane. In contrast, *cis*-cyclodecene has ΔH_{hydrog} of -86 kJ mol^{-1}, medium-ring strain in the cycloalkane resulting in a less exothermic reaction, while *cis*-di-t-butylethylene has ΔH_{hydrog} of -148 kJ mol^{-1}, reflecting high strain energy of the olefin which is 'relieved' on hydrogenation. The heats of hydrogenation of pairs of *cis* and *trans* isomers give the energy difference, *i.e.* the heat of isomerization, *e.g.* *cis*-cyclo-octene has ΔH_{hydrog} of -96 kJ mol^{-1} and *trans*-cyclo-octene of -134 kJ mol^{-1}.

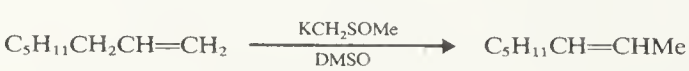
Except for di-imide reduction (already dealt with in Section 2.1.7.1) and hydroboration–protonation, conversion of alkenes to alkanes by other means is not a common reaction. The electron affinity of simple olefins is too low to allow reduction by dissolving metals, although conjugation with aryl groups increases the electron affinity and reduction by Li/liq. NH_3 is then possible.

2.2.3.7 Rearrangements

A number of olefin rearrangements involving change of skeleton have been mentioned already. It remains to consider isomerizations in which the skeleton stays intact.

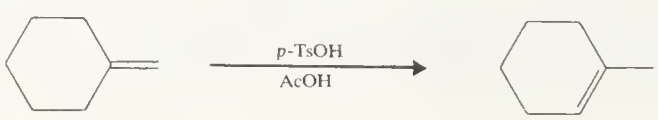
Photochemical *cis–trans* interconversions will be discussed later; the conversion of either of a diastereoisomeric pair of olefins to a thermodynamic equilibrium mixture of the two can often be carried out by treatment with iodine in daylight. Isomerization presumably involves addition–elimination of iodine atoms.

Rearrangement with double bond shift can be catalysed in a number of ways.[109] In the presence of very strong bases, 'prototropic' rearrangement can occur *via* an allyl anion which is then reprotonated at an alternative site, *e.g.* equation (204). Since a *cisoid* geometry for the allyl anion is preferred, there is a kinetic preference for formation of the *cis*-isomer in the early stages of an alk-1-ene to alk-2-ene isomerization. Such base-catalysed isomerizations are particularly useful for the conversion of non-conjugated to conjugated dienes where the greater thermodynamic stability of the latter provides a driving force, *e.g.* equation (205).



(204)

(205)

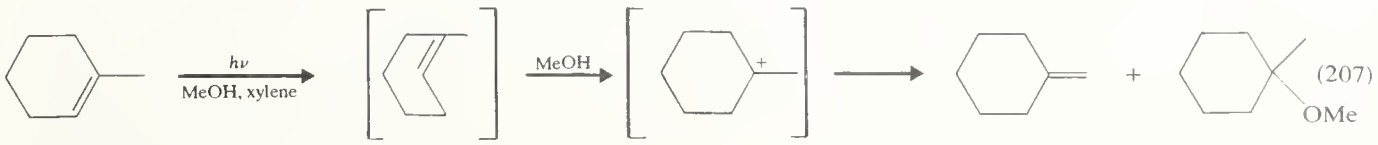


(206)

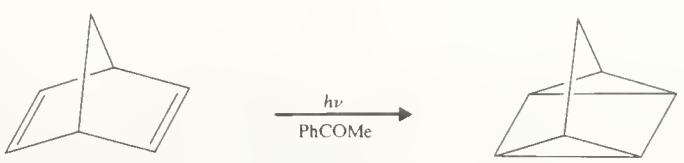
Olefin isomerizations under proton or Lewis acid catalysis also occur,[109] though since carbenium ions are involved, skeletal rearrangements are more likely. On occasion this provides a convenient way of converting a less to a more stable olefin, *e.g.* equation (206). In recent years, transition metal catalysed double bond shifts, particularly using rhodium trichloride,[110] have found favour and will probably be increasingly used.

2.2.3.8 Photochemical reactions[111]

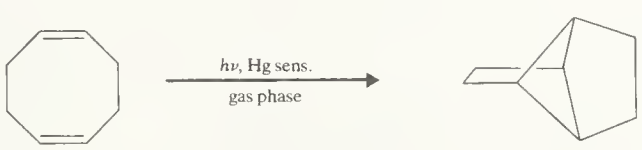
The characteristic photoreaction of simple olefins is *cis–trans* isomerization. A photostationary state is produced, the position depending on the absorption characteristics of the components and the wavelength of the irradiation, *e.g.* direct irradiation of stilbenes at 313 nm for which $\varepsilon_{trans}/\varepsilon_{cis} = 7.2$ leads to a mixture of 91.5% *cis* and 8.5% *trans* isomers. Some cycloalkenes, for which a stable *trans*-alkene cannot exist, give products derived apparently from protonation of such a species produced as a transient, *e.g.* equation (207).



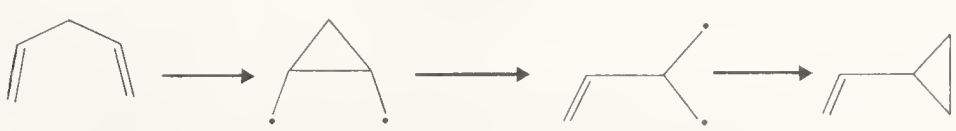
(207)



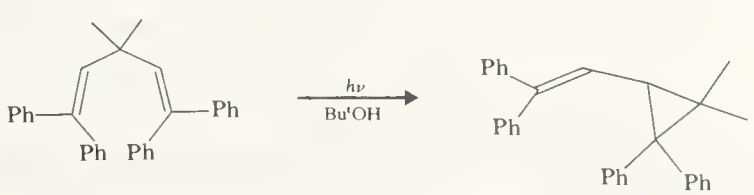
(208)



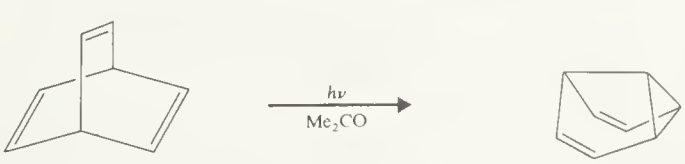
(209)



(210)



(211)



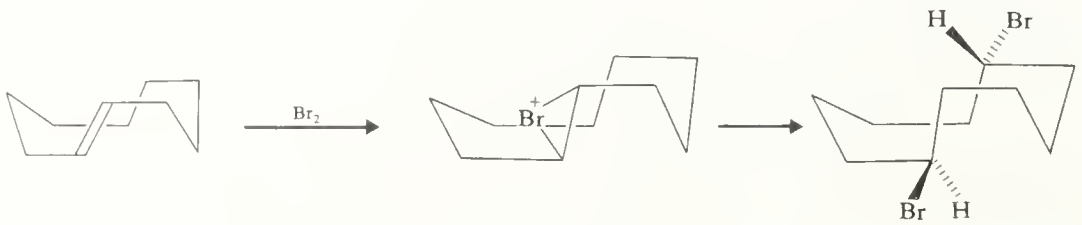
(212)

Photocycloadditions of the 2+2=4 type involving olefins have already been mentioned; intramolecular analogues are illustrated by equations (208) and (209). Another type of photoisomerization, which is characteristic of 1,4-dienes, is the di-π-methane rearrangement schematically designated in equation (210). Actual examples are provided by equations (211) and (212).

2.2.3.9 Special features

In concluding this section it is noteworthy that there are certain features of the reactions of olefinic hydrocarbons which cut through the mechanistic headings under which we have discussed them. For example, the high reactivity of strained olefins has been mentioned in a number of places, and the reactivity patterns of certain olefin types such as norbornenes, *trans*-cyclo-octene, *etc.* are often sufficiently characteristic to be of use in the diagnosis of mechanism. This aspect of olefin chemistry has been thoroughly reviewed recently.[112]

Another feature is the incursion of transannular reactions with medium-ring olefins, which has already been noticed for dienes where π-participation can lead to the formation of a transannular bond, *cf.* equation (144). A second manifestation is the occasional appearance of transannular hydride migration, *e.g.* the bromination of *trans*-cyclodecene (equation 213).



(213)

References

1. R. Rossi and P. Diversi, *Synthesis*, 1973, 25.
2. *Cf.* J. F. Liebman and A. Greenberg, *Chem. Rev.*, 1976, **76,** 311.
3. G. Köbrich, *Angew. Chem. Internat. Edn.*, 1973, **12,** 464; G. L. Buchanan, *Chem. Soc. Rev.*, 1974, **3,** 41; R. Keese, *Angew. Chem. Internat. Edn.*, 1975, **14,** 528.
4. A. Krebs, in 'Chemistry of Acetylenes', ed. H. G. Viehe, Dekker, New York, 1969, p. 987.
5. *Cf.* 'Methoden der Organischen Chemie (Houben-Weyl)', Thieme Verlag, Stuttgart, 1972, vol. V/1b; J. Reucroft and P. G. Sammes, *Quart. Rev.*, 1971, **25,** 135; D. J. Faulkner, *Synthesis*, 1971, 175.
6. W. H. Saunders, in 'Chemistry of Alkenes', ed. S. Patai, Interscience, 1964, p. 149.
7. M. Schlosser, in Ref. 5, p. 134.
8. H. Oediger, F. Moller, and K. Eiter, *Synthesis*, 1972, 591.
9. A. C. Cope and E. R. Trumbull, *Org. Reactions*, 1960, **11,** 317.
10. J. Sicher, *Angew. Chem. Internat. Edn.*, 1972, **11,** 200.
11. C. H. DePuy and R. W. King, *Chem. Rev.*, 1960, **60,** 431.
12. H. R. Nace, *Org. Reactions*, 1962, **12,** 57.
13. *Cf.* K. B. Sharpless, R. F. Lauer, and A. Y. Teranishi, *J. Amer. Chem. Soc.*, 1973, **95,** 6137.
14. J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 1959, 112, 2539.
15. S. Hara, H. Taguchi, H. Yamamoto, and H. Nozaki, *Tetrahedron Letters*, 1975, 1545.
16. R. A. Snow, C. R. Degenhardt, and L. A. Paquette, *Tetrahedron Letters*, 1976, 4447.
17. D. J. Peterson, *J. Org. Chem.*, 1968, **33,** 780; P. F. Hudrlik and D. Peterson, *J. Amer. Chem. Soc.*, 1975, **97,** 1464.
18. P. F. Hudrlik, D. J. Peterson, and R. J. Rona, *J. Org. Chem.*, 1975, **40,** 2263.
19. A. J. Bridges and G. H. Whitham, *J.C.S. Chem. Comm.*, 1974, 142.
20. J. Rémion and A. Krief, *Tetrahedron Letters*, 1976, 3743.
21. G. L. Larson, E. Hernandez, C. Alonso, and I. Nieves, *Tetrahedron Letters*, 1975, 4005.
22. J. A. Marshall, *Synthesis*, 1971, 229.
23. R. M. Carlson and S. Y. Lee, *Tetrahedron Letters*, 1969, 4001.
24. W. Adam, J. Baeza, and J. C. Liu, *J. Amer. Chem. Soc.*, 1972, **94,** 2000.
25. G. Crank and F. W. Eastwood, *Austral. J. Chem.*, 1964, **17,** 1392; F. W. Eastwood, K. J. Harrington, J. S. Josan, and J. L. Pura, *Tetrahedron Letters*, 1970, 5223.
26. E. J. Corey and R. A. E. Winter, *J. Amer. Chem. Soc.*, 1963, **85,** 2677; E. J. Corey, F. A. Carey, and R. A. E. Winter, *ibid.*, 1965, **87,** 934.
27. J. N. Hines, M. J. Peagram, E. J. Thomas, and G. H. Whitham, *J.C.S. Perkin I*, 1973, 2332; M. Jones, P. Temple, E. J. Thomas, and G. H. Whitham, *ibid.*, 1974, 433.
28. M.-G. Kim and J. D. White, *J. Amer. Chem. Soc.*, 1977, **99,** 1172.
29. E. F. Magoon and L. H. Slaugh, *Tetrahedron*, 1967, **23,** 4509.
30. H. Gutmann and H. Lindlar, in 'Chemistry of Acetylenes', ed. H. G. Viehe, Dekker, New York, 1969, p. 355; E. N. Marvell and T. Li, *Synthesis*, 1973, 457.
31. I. Jardine and F. J. McQuillin, *Tetrahedron Letters*, 1966, 4871.
32. A. J. Birch and H. Smith, *Quart. Rev.*, 1958, **12,** 17.

33. R. A. Benkeser, R. K. Agnihotri, M. L. Burrous, E. M. Kaiser, J. M. Mallan, and P. W. Ryan, *J. Org. Chem.*, 1964, **29,** 1313.
34. R. H. Shapiro, *Org. Reactions*, 1976, **23,** 405.
35. S. Trippett, *Quart. Rev.*, 1963, **17,** 406; A. Maercker, *Org. Reactions*, 1965, **14,** 270.
36. M. Schlosser, *Topics Stereochem.*, 1970, **5,** 1; see also R. J. Anderson and C. A. Henrick, *J. Amer. Chem. Soc.*, 1975, **97,** 4327.
37. M. Schlosser and K. F. Christmann, *Synthesis*, 1969, 38.
38. L. Horner, H. Hoffmann, and H. G. Wippel, *Chem. Ber.*, 1958, **91,** 61; L. Horner, H. Hoffmann, W. Klink, H. Ertel and V. G. Toscano, *Chem. Ber.*, 1962, **95,** 581.
39. L. Horner, H. Hoffmann, H. G. Wippel and G. Klahre, *Chem. Ber.*, 1959, **92,** 2499; J. Boutagy and R. Thomas, *Chem. Rev.*, 1974, **74,** 87.
40. *Cf.* C. Earnshaw, C. J. Wallis and S. Warren, *J.C.S. Chem. Comm.*, 1977, 314.
41. E. J. Corey and G. T. Kwiatkowski, *J. Amer. Chem. Soc.*, 1968, **90,** 6816.
42. E. J. Corey and T. Durst, *J. Amer. Chem. Soc.*, 1968, **90,** 5548, 5553.
43. F. Bertini, P. Grasselli, G. Zubiani and G. Cainelli, *Tetrahedron*, 1970, **26,** 1281.
44. R. L. Sowerby and R. M. Coates, *J. Amer. Chem. Soc.*, 1972, **94,** 4758.
45. M. Julia and J. M. Paris, *Tetrahedron Letters*, 1973, 4833.
46. J. E. McMurry, *Accounts Chem. Res.*, 1974, **7,** 281.
47. D. H. R. Barton, F. S. Guziec, and I. Shahak, *J.C.S. Perkin I*, 1974, 1794; D. H. R. Barton and B. J. Willis, *ibid.*, 1972, 305.
48. L. A. Paquette, *Accounts Chem. Res.*, 1968, **1,** 209.
49. J. M. Photis and L. A. Paquette, *J. Amer. Chem. Soc.*, 1974, **96,** 4715.
50. G. Wilke, *Angew. Chem. Internat. Edn.*, 1963, **2,** 105; P. Heimbach, *ibid.*, 1973, **12,** 975.
51. M. F. Semmelhack, *Org. Reactions*, 1972, **19,** 115.
52. E. E. van Tamelen and M. A. Schwartz, *J. Amer. Chem. Soc.*, 1965, **87,** 3277.
53. G. H. Posner, *Org. Reactions*, 1975, **22,** 253.
54. H. C. Brown, 'Organic Synthesis via Boranes', Wiley, New York, 1975.
55. E. Negishi and S. Baba, *J.C.S. Chem. Comm.*, 1976, 596.
56. K. Utimoto, M. Kitai, and H. Nozaki, *Tetrahedron Letters*, 1975, 2825.
57. P. B. D. de la Mare and R. Bolton, 'Electrophilic Additions to Unsaturated Systems', Elsevier, London, 1966; R. C. Fahey, *Topics Stereochem.*, 1968, **3,** 237.
58. Ref. 57 and A. J. Kresge, Y. Chiang, P. H. Fitzgerald, R. S. McDonald, and G. H. Schmid, *J. Amer. Chem. Soc.*, 1971, **93,** 4907.
59. W. H. Mueller, *Angew. Chem. Internat. Edn.*; 1969, **8,** 482.
60. Ref. 57 and R. C. Fahey, C. A. McPherson, and R. A. Smith, *J. Amer. Chem. Soc.*, 1974, **96,** 4534 and references therein.
61. P. B. D. de la Mare, 'Electrophilic Halogenation', Cambridge University Press, 1966.
62. Ref. 61 and C. V. Wilson, *Org. Reactions*, 1957, **9,** 332; A. Hassner, *Accounts Chem. Res.*, 1971, **4,** 9.
63. G. Zweifel and H. C. Brown, *Org. Reactions*, 1963, **13,** 1.
64. H. C. Brown, 'Organic Synthesis via Boranes', Wiley, New York, 1975.
65. W. Kitching, *Organometallic Chem. Rev.*, 1968, **3,** 61.
66. H. Arzoumanian and J. Metzger, *Synthesis*, 1971, 527.
67. R. M. Moriarty, in 'Selective Organic Transformations', ed. B. S. Thyagarajan, Wiley-Interscience, New York, 1972, p. 183.
68. V. I. Isagulyants, T. G. Khaimova, V. R. Melikyan, and S. V. Pokrovskaya, *Russ. Chem. Rev.*, 1968, **37,** 17.
69. J. K. Groves, *Chem. Soc. Rev.*, 1972, **1,** 73.
70. H. Koch and W. Haaf, *Annalen*, 1958, **618,** 251; 1960, **638,** 111.
71. L. I. Krimen and D. J. Cota, *Org. Reactions*, 1969, **17,** 213.
72. D. N. Kursanov, Z. N. Parnes, and N. M. Loim, *Synthesis*, 1974, 633.
73. M. Szwarc, 'Carbanions, Living Polymers and Electron Transfer Processes', Interscience, New York, 1968; J. K. Stille, *Chem. Rev.*, 1958, **58,** 541.
74. E. S. Huyser, 'Free Radical Chain Reactions', Interscience, New York, 1970.
75. P. I. Abell, in 'Free Radicals', ed. J. K. Kochi, Wiley-Interscience, New York, 1973, vol. II, p. 63.
76. J. M. Tedder and J. C. Walton, *Accounts Chem. Res.*, 1976, **9,** 183.
77. M. Julia, *Accounts Chem. Res.*, 1971, **4,** 386.
78. R. B. Woodward and R. Hoffmann, 'The Conservation of Orbital Symmetry', Verlag Chemie, Weinheim, 1970.
79. W. Kirmse, 'Carbene Chemistry', Academic, New York, 1964; R. A. Moss and M. Jones, 'Carbenes', Wiley, New York, 1975.
80. H. E. Simmons, T. L. Cairns, S. A. Vladuchick, and C. M. Hoiness, *Org. Reactions*, 1973, **20,** 1.
81. J. D. Roberts and C. M. Sharts, *Org. Reactions*, 1962, **12,** 1; P. D. Bartlett, *Quart. Rev.*, 1970, **24,** 473; L. L. Muller and J. Hamer, '1,2-Cycloaddition Reactions', Interscience, New York, 1967.
82. W. L. Dilling, *Chem. Rev.*, 1969, **69,** 845; *P. G. Sammes, Quart. Rev.*, 1970, **24,** 37.
83. D. R. Arnold, *Adv. Photochem.*, 1968, **6,** 301.
84. R. Huisgen, *Angew. Chem. Internat. Edn.*, 1963, **2,** 565, 633; 1968, **7,** 321; T. Kauffmann, *ibid.*, 1974, **13,** 627.

85. U. M. Kempe, T. K. Das Gupta, K. Blatt, P. Gygax, D. Felix, and A. Eschenmoser, *Helv. Chim. Acta*, 1972, **55,** 2187.
86. H. M. R. Hoffmann, *Angew. Chem. Internat. Edn.*, 1969, **8,** 556.
87. R. W. Denny and A. Nickon, *Org. Reactions*, 1973, **20,** 133.
88. S. J. Rhoads and N. R. Raulins, *Org. Reactions*, 1975, **22,** 1.
89. R. J. Haines and G. J. Leigh, *Chem. Soc. Rev.*, 1975, **4,** 155; N. Calderon, *Accounts Chem. Res.*, 1972, **5,** 127.
90. F. D. Gunstone, in 'Advances in Organic Chemistry Methods and Results', ed. R. A. Raphael, E. C. Taylor and H. Wynberg, Interscience, New York, 1960, vol. 1, p. 103.
91. K. B. Sharpless and K. Akashi, *J. Amer. Chem. Soc.*, 1976, **98,** 1986.
92. V. Van Rheenen, R. C. Kelly, and D. Y. Cha, *Tetrahedron Letters*, 1976, 1973.
93. P. S. Bailey, *Chem. Rev.*, 1958, **58,** 925.
94. R. Criegee, *Angew. Chem. Internat. Edn.*, 1975, **14,** 745.
95. J. J. Pappas, W. P. Keaveney, E. Gancher, and M. Berger, *Tetrahedron Letters*, 1966, 4273.
96. J. M. Conia and P. Leriverend, *Compt. rend.*, 1960, **250,** 1078.
97. J. Smidt, W. Hafner, R. Jira, J. Sedlmeier, R. Sieber, R. Rüttinger, and H. Kojer, *Angew. Chem.*, 1959, **71,** 176; R. Hüttel, *Synthesis*, 1970, 225.
98. D. Swern, 'Organic Peroxides', Wiley-Interscience, New York, 1971, vol. II, p. 355; D. Swern, *Org. Reactions*, 1953, **7,** 378.
99. M. N. Sheng and J. G. Zajacek, *J. Org. Chem.*, 1970, **35,** 1839; H. Mimoun, I. S. de Roch, and L. Sajus, *Tetrahedron*, 1970, **26,** 37.
100. L. Horner and E. H. Winkelmann, *Newer Methods Prep. Org. Chem.*, 1964, **3,** 151.
101. C. Walling and W. Thaler, *J. Amer. Chem. Soc.*, 1961, **83,** 3877.
102. D. J. Rawlinson and G. Sosnovsky, *Synthesis*, 1972, 1.
103. W. G. Dauben, M. Lorber, and D. S. Fullerton, *J. Org. Chem.*, 1969, **34,** 3587.
104. N. Rabjohn, *Org. Reactions*, 1976, **24,** 261.
105. G. Rauchschwalbe and M. Schlosser, *Helv. Chim. Acta*, 1975, **58,** 1094.
106. K. B. Sharpless, T. Hori, L. K. Truesdale, and C. O. Dietrich, *J. Amer. Chem. Soc.*, 1976, **98,** 269.
107. P. N. Rylander, 'Catalytic Hydrogenation Over Platinum Metals', Academic. New York, 1967; R. L. Augustine, 'Reduction', Arnold, London, 1968; A. J. Birch and D. H. Williamson, *Org. Reactions*, 1976, **24,** 1.
108. R. B. Turner and W. R. Meador, *J. Amer. Chem. Soc.*, 1957, **79,** 4133.
109. A. J. Hubert and H. Reimlinger, *Synthesis*, 1969, 97; 1970, 405.
110. J. Andrieux, D. H. R. Barton, and H. Patin, *J.C.S. Perkin I*, 1977, 359.
111. J. D. Coyle, *Chem. Soc. Rev.*, 1974, **3,** 329.
112. F. Freeman, *Chem. Rev.*, 1975, **75,** 439.

2.3

Dienes, Polyenes, and Acetylenic Hydrocarbons

G. PATTENDEN
University of Nottingham

2.3.1 CONJUGATED DIENES AND POLYENES 172
2.3.1.1 Introduction 172
2.3.1.2 Preparation of conjugated dienes 172
2.3.2 REACTIONS OF CONJUGATED DIENES 177
2.3.2.1 Chemical properties 177
2.3.2.2 Reductions 178
2.3.2.3 Hydroborations 178
2.3.2.4 Diels–Alder reactions 178
2.3.2.5 Iron carbonyl complexes 182
2.3.2.6 Photochemical and thermal reactions 182
2.3.2.7 Other reactions 184
2.3.3 CONJUGATED POLYENES 185
2.3.4 NATURALLY OCCURRING DIENES AND POLYENES 186
2.3.5 ALLENES AND CUMULENES 187
2.3.5.1 Introduction 187
2.3.5.2 Preparation of allenes 187
2.3.6 REACTIONS OF ALLENES 191
2.3.6.1 General reactions 191
2.3.6.2 Hydrogenations 191
2.3.6.3 Metal–allene reactions 192
2.3.7 CUMULENES 192
2.3.8 NATURALLY OCCURRING ALLENES AND CUMULENES 193
2.3.9 ACETYLENES AND POLYACETYLENES 193
2.3.9.1 Introduction 193
2.3.9.2 Preparation of acetylenes 194
2.3.10 REACTIONS OF ACETYLENES 197
2.3.10.1 Chemical properties 197
2.3.10.2 Isomerizations 197
2.3.10.3 Propargylic rearrangements 197
2.3.10.4 Additions 198
2.3.10.5 Hydroborations and hydroaluminations 199
2.3.10.6 Substitutions 200
2.3.10.7 Reductions 200
2.3.10.8 Oxidations 201
2.3.10.9 Cycloadditions 201
2.3.10.10 Metal-catalysed reactions 202
2.3.11 POLYACETYLENES 204

2.3.12 NATURALLY OCCURRING ACETYLENES AND POLYACETYLENES 204
2.3.13 CONJUGATED ENYNES 205
2.3.13.1 Preparation of conjugated enynes 205
2.3.14 REACTIONS OF CONJUGATED ENYNES 207
2.3.15 NATURALLY OCCURRING CONJUGATED ENYNES 208

2.3.1 CONJUGATED DIENES AND POLYENES

2.3.1.1 Introduction

1,3-Dienes are the most important practical diene monomers and are used extensively in the synthetic rubber industry.[1] The dienes buta-1,3-diene, chloroprene [CH_2=C(Cl)CH=CH_2], and isoprene [CH_2=C(CH_3)CH=CH_2], which have been most widely studied, polymerize under several conditions both with themselves and with a variety of other monomers, leading to several commercially important elastomers.

Buta-1,3-diene is manufactured by removal of hydrogen from the C_4 fraction (butane and butenes) obtained by cracking of crude oil, or by dehydrogenation of butane from natural gas. Polybutadiene finds use as a blend with natural rubber in heavy-duty tyres fitted to large vehicles. However, over half of the butadiene manufactured emerges in the form of styrene-butadiene rubber, which is much used, for example, as a shoe-soling compound and for motor car tyres. Nitrile rubbers, which are co-polymers of acrylonitrile and butadiene, are used in oil seals, and esters of 1,2,5.6-tetrahydrophthalic anhydride, the Diels–Alder adduct from buta-1,3-diene and maleic anhydride, are speciality plasticizers.

Chloroprene is the monomer for neoprene, a speciality oil-resistant rubber. The monomer is manufactured by addition of hydrogen chloride to vinylacetylene, itself obtained by dimerization of acetylene. Polymerization of isoprene, which is obtained in an analogous process to that described above for buta-1,3-diene from the C_5 fraction of cracked oil, leads to polyisoprene, a rubber which closely resembles natural rubber.

A detailed discussion of the earlier chemistry of conjugated dienes and polyenes is contained in 'Rodd's Chemistry of Carbon Compounds'.[2] More recent accounts have also been published,[3,4] and the literature from 1971–1977 has been covered in detail in the U.K. Chemical Society Specialist Periodical Reports, 'Aliphatic Chemistry'[5] and 'General and Synthetic Methods'.[6]

2.3.1.2 Preparation of conjugated dienes

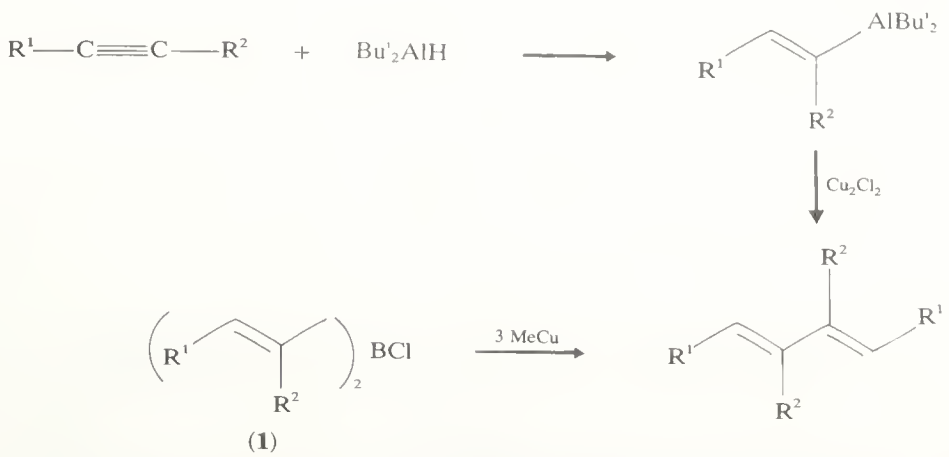
(i) By partial reduction of 1,3-diynes and conjugated enynes

A number of methods are available for the synthesis of conjugated diynes and of (*Z*)- or (*E*)-enynes (see Sections 2.3.9–2.3.15). Partial reduction of these substrates has provided an attractive route to conjugated dienes of predictable geometry. Both catalytic hydrogenation of 1,3-diynes over Lindlar's catalyst[7] and dihydroboration of 1,3–diynes with dicyclohexylborane followed by protonolysis[8] afford the corresponding (*Z,Z*)-dienes. (*Z,Z*)-1,3-Dienes are also produced from monohydroboration–protonolysis of conjugated (*Z*)-enynes using disiamylborane[8] or by partial catalytic hydrogenation. In a similar manner, the catalytic hydrogenation of conjugated (*E*)-enynes leads to (*E,Z*)-dienes.[9,10]

(ii) From alkynes via *hydroalumination and hydroboration*

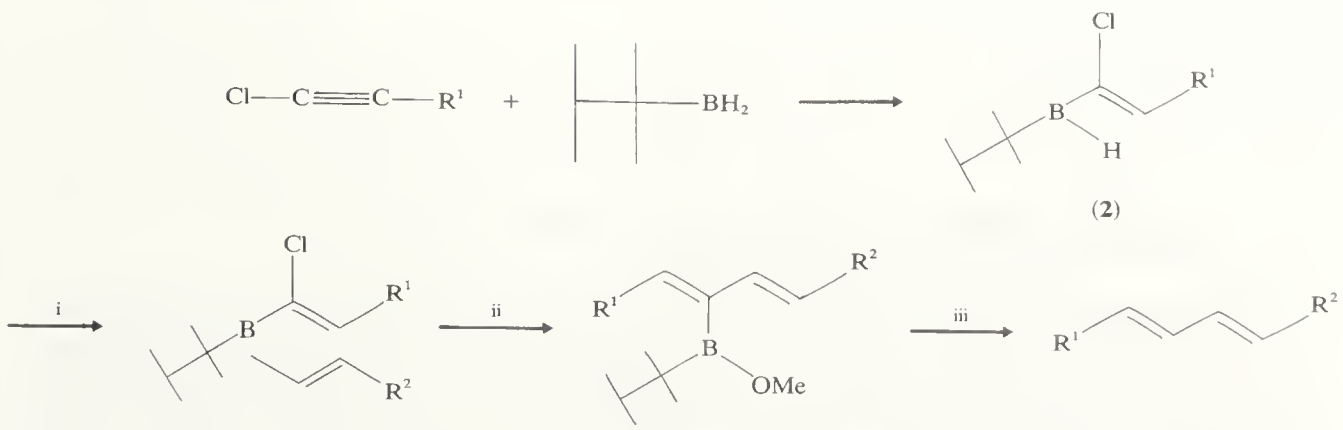
High yields of (*E,E*)-dienes are obtained from alkynes by addition of cuprous chloride to vinylalanes produced by reaction of the alkyne with di-isobutylaluminium hydride

(Scheme 1).[11,12] Reaction between dialkenylchloroboranes (**1**) and methylcopper at 0 °C also leads to the same (*E,E*)-dienes.[13] Symmetrically substituted (*Z,E*)-dienes are produced from disubstituted acetylenes by hydroboration–iodination,[14] whereas unsymmetrically substituted (*E,E*)-dienes can be obtained by stepwise addition of two acetylenic units to thexylborane, *via* the novel chloro-organoborane (**2**) according to Scheme 2.[15]



(**1**)

SCHEME 1



(**2**)

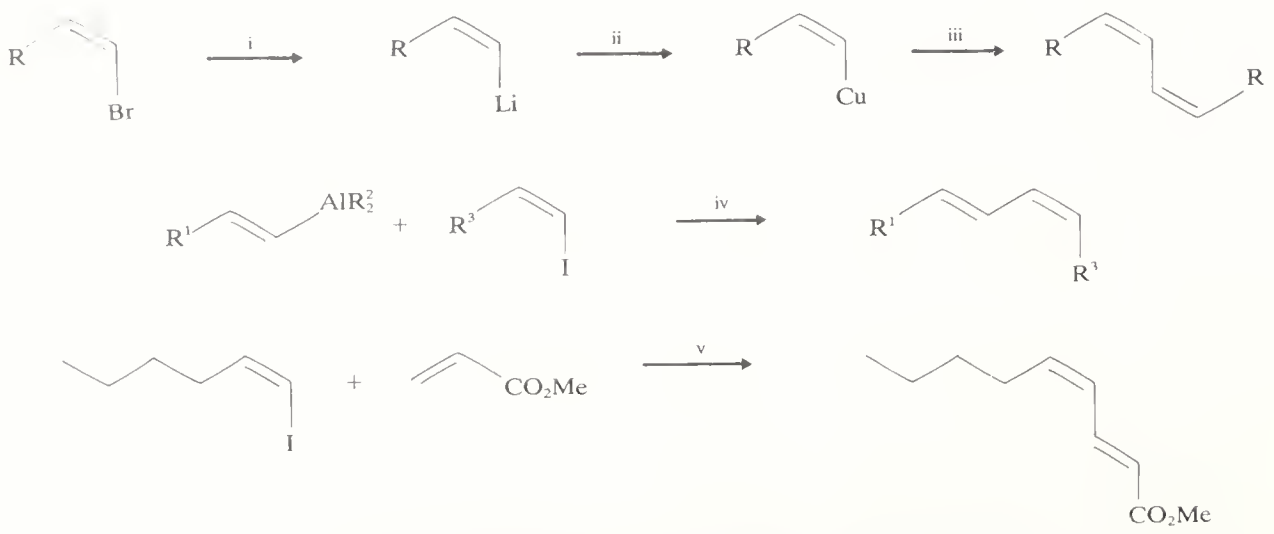
i, $R^2C{\equiv}CH$; ii, NaOMe; iii, H^+.

SCHEME 2

Larock[16] has shown that vinylmercuric compounds, prepared through mercuration of acetylenes, undergo reaction with $PdCl_2$ and $LiCl_2$ in HMPT at 0 °C to produce symmetrical (*E,E*)-dienes in near quantitative yields. This method is complementary to those based on vinylalanes and vinylboranes, and also to those based on Co, Cu, Li, Mg, Ni, and Ag reagents (see below). However, it has the advantage that it tolerates functionality.

(*iii*) *From vinyl halides*

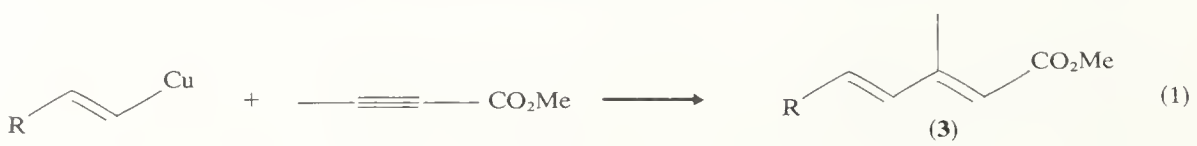
A number of methods are now available for the controlled synthesis of (*Z*)- and (*E*)-vinyl halides.[17] Under various catalytic conditions the vinyl halides undergo self-coupling, leading to 1,3-dienes with preservation of the (*Z*) or (*E*) configuration in the vinyl halide. Reaction of vinyl halides with bis(cyclo-octa-1,5-diene)nickel(0) produces dienes directly,[18] whereas coupling of the corresponding vinyl copper reagents can be accomplished either thermally[19,20] or oxidatively.[21,22] The coupling reactions between vinyl halides and vinylalanes or olefinic compounds in the presence of palladium catalysts show appreciable stereoselectivity and can be used to synthesize isomeric dienes (Scheme 3).[23,24]



i, Bu^{t}Li; ii, CuI; iii, Δ or O_2; iv, PdL_n or NiL_n; v, $Pd(PPh_3)(OAc)_2$.

SCHEME 3

Conjugate addition of vinyl copper reagents to acetylenic esters provides[25,26] a particularly facile route to (*Z*)-diene esters (**3**) (equation 1).

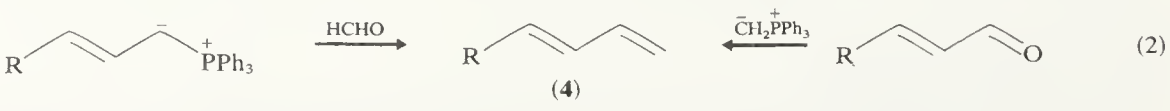


(1)

(3)

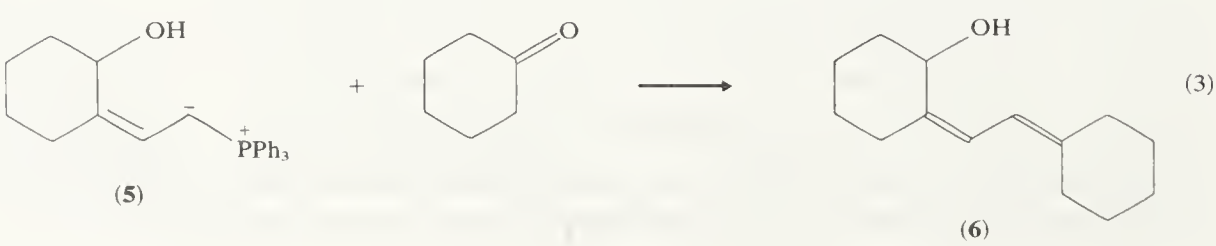
(*iv*) *From allylic halides and α,β-unsaturated carbonyl compounds using the Wittig reaction and its variants*

Without doubt the Wittig olefin synthesis and its variants constitute the most general and flexible approach towards the synthesis of diastereoisomers of all types of substituted 1,3-dienes.[27] For example, ylides from allylic phosphonium salts react with formaldehyde to produce dienes of type (**4**), which are also obtained by reaction between α,β-unsaturated aldehydes and methylene ylide (equation 2). Homologous aldehydes (and ketones) also react with allylic primary ylides, but a mixture of diastereoisomers about the newly formed double bond usually results. On the other hand, studies have shown that both (*Z*)-allylic *P*-ylides[28–30] and (*Z*)-α,β–unsaturated aldehydes[31]can be used in Wittig reactions to give dienes in which the original (*Z*) configuration is retained, *e.g.* (**5**) → (**6**) and (**7**) → (**8**) in equations (3) and (4). Configurationally homogeneous allylic diphenylphosphine oxides also react with carbonyl compounds in Horner reactions, leading[30,32] to dienes with preservation of the configuration in the phosphine oxide, *e.g.* (**9**) → (**10**) in equation (5).



(2)

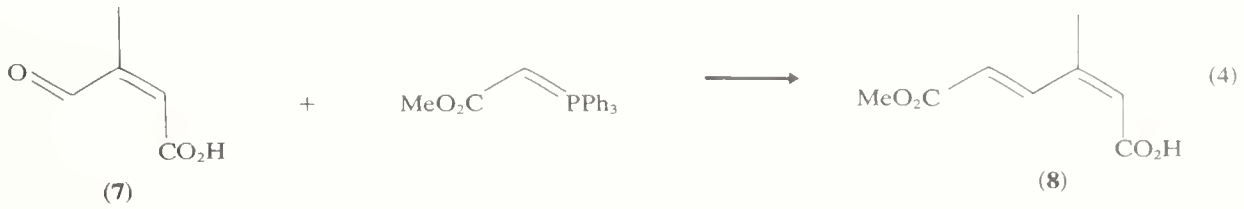
(4)



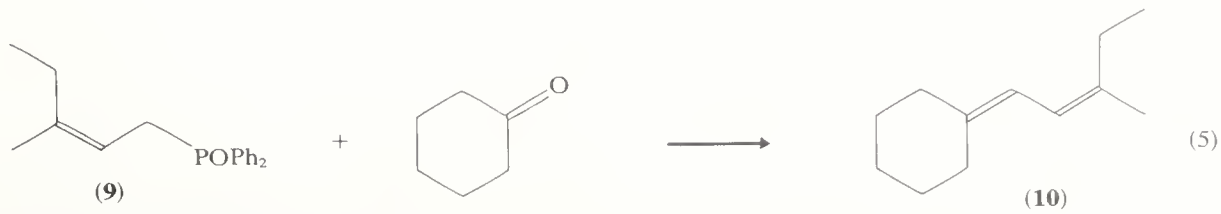
(3)

(5)

(6)

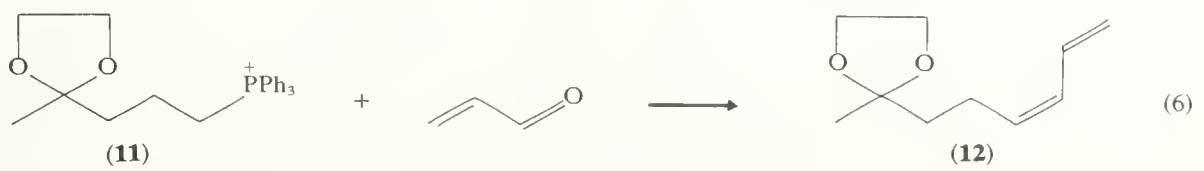


(7) (8) (4)

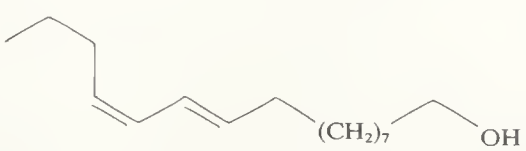


(9) (10) (5)

Although some steric control can be exercised over the Wittig synthesis, using 'salt-free' conditions, as in the synthesis of diene (**12**) from salt (**11**) and acrolein (equation 6),[33] a feature of the Horner approach to diene synthesis is that it produces crystalline intermediates which can be separated by chromatography and crystallization; elimination with sodium hydride then gives dienes stereospecifically about the newly introduced double bond. However, the Wittig reaction has been applied in the synthesis of all four isomers of bombykol (**13**), the sex attractant of the silkworm *Bombyx mori* L.[34]



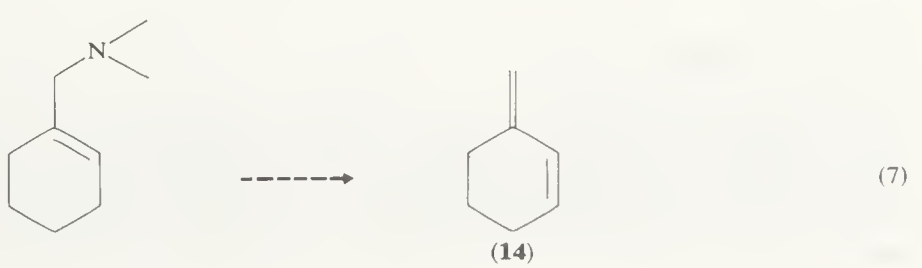
(11) (12) (6)



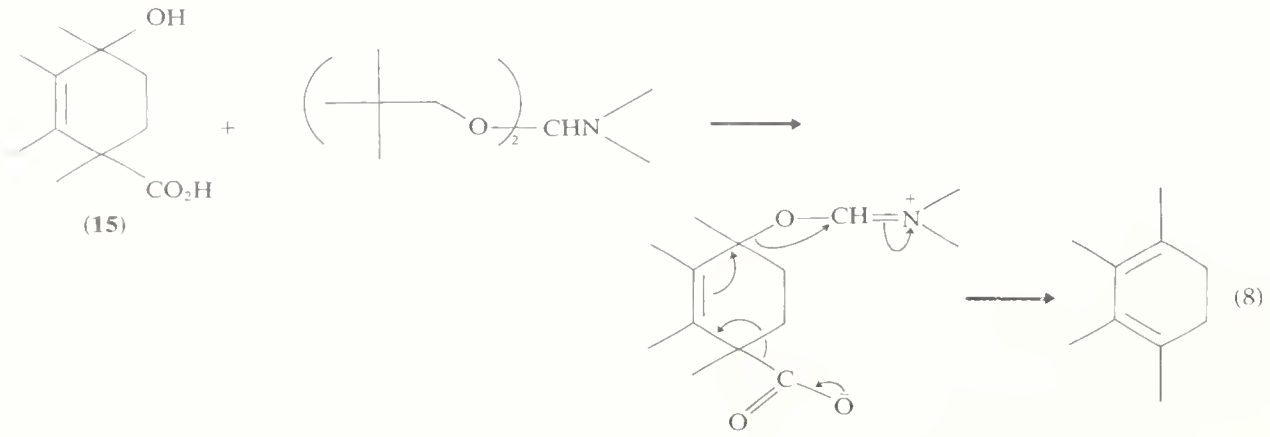
(13)

(*v*) *By eliminations from saturated diols and unsaturated alcohols and derivatives*

Dienes are produced by a wide range of methods based on eliminations from saturated 1,3- and 1,4-diols as well as from α,β-unsaturated alcohols and their derivatives (*e.g.* halides and esters). A discussion of these methods, many of which have industrial importance, is beyond the scope of this article, but excellent summaries have been presented previously.[2,4,35] A recent and simple route to conjugated dienes from dehydration of allylic alcohols under mild conditions uses methyltriphenoxyphosphonium iodide in HMPT.[36]

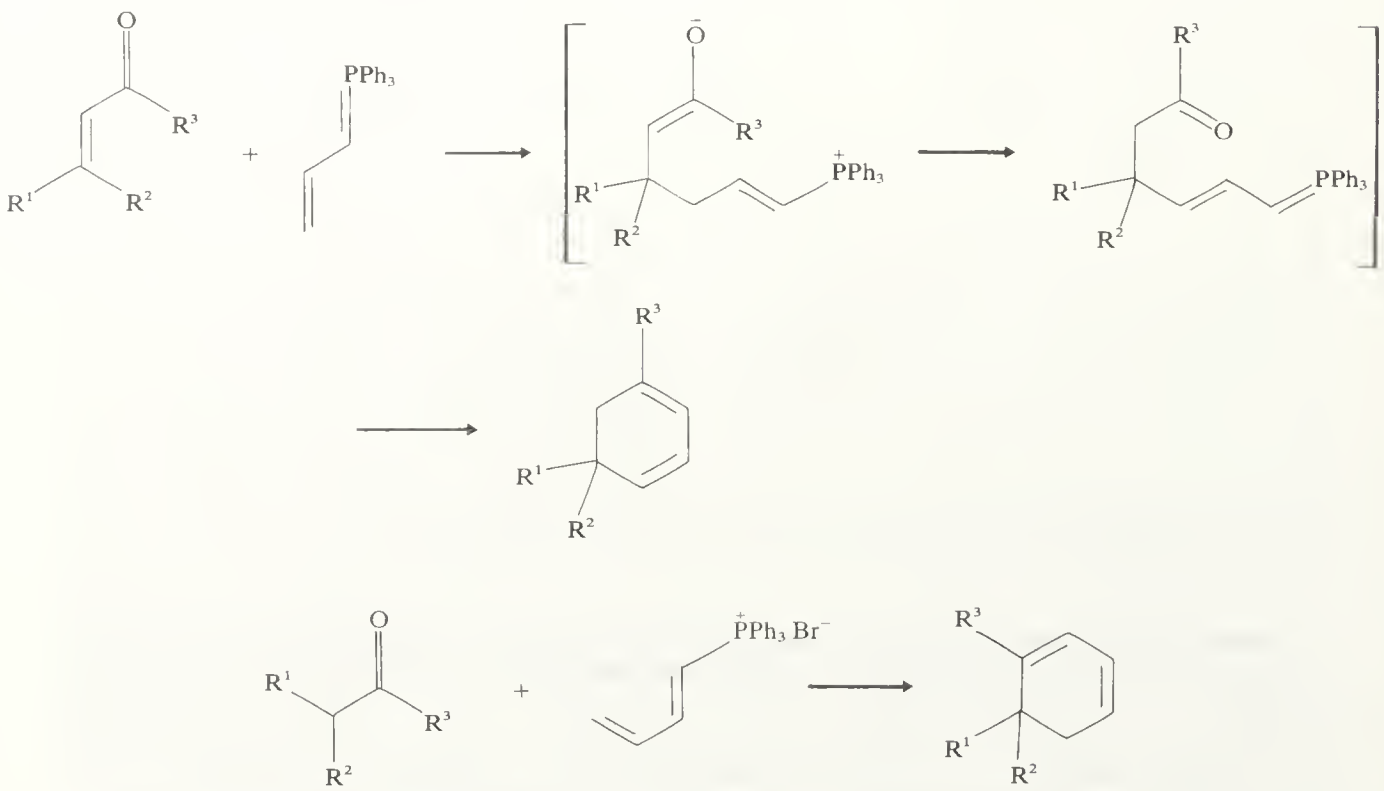


(14) (7)



(8)

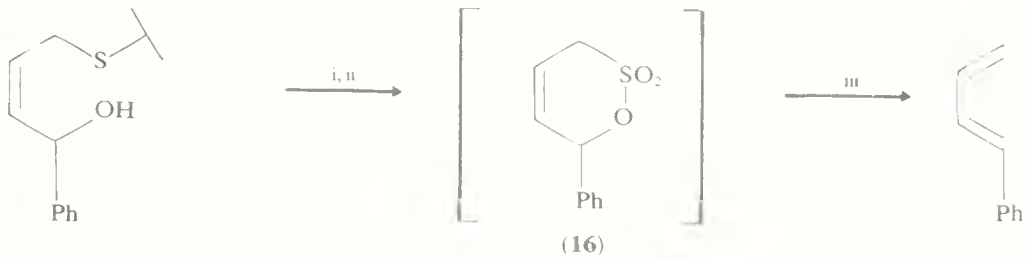
Short[37] has described a novel 1,4 Hofmann elimination to prepare s-*trans*-dienes (**14**) from amines (equation 7). β,γ-Unsaturated δ-hydroxycyclohexenecarboxylic acids (**15**) undergo[38] smooth decarboxylative elimination when treated with DMF–dineopentyl acetal (equation 8). The latter procedure provides an expeditious method for the regiospecific preparation of cyclohexa-1,3-diene derivatives under conditions which lead to no isomerization of the double bonds. Two useful alternative methods for the synthesis of cyclohexa-1,3-dienes are based on the reactions between enolate anions and vinylic phosphonium salts (Scheme 4).[39,40]



SCHEME 4

(*vi*) *From cycloreversions*

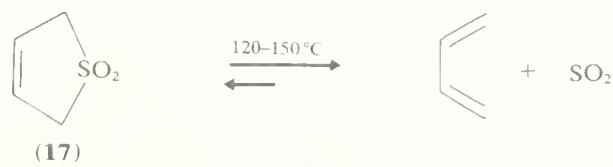
An exceptionally mild and stereospecific diene synthesis relies on the facile $_{\pi}4_s + _{\pi}2_s$ cycloreversion of a dihydro-oxathiin 2-oxide (**16**) (Scheme 5).[41] A feature of this reaction is that it proceeds with remarkable ease, at least 120 °C lower than the related and better known method in equation (9) based on thermolysis of cyclic sulphones (**17**).[42] The ease with which (*E*)-dienes undergo reversible cycloadditions with SO_2, and, indeed, other



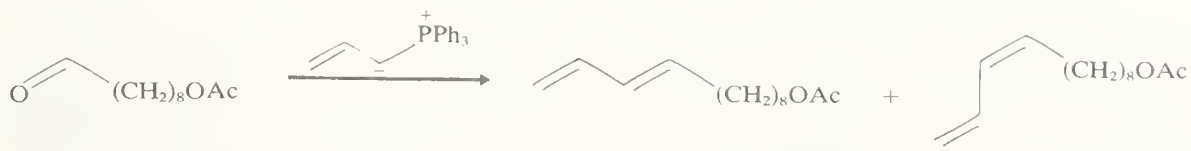
i, *m*-$ClC_6H_4CO_3H$; ii, NCS; iii, <0 °C.

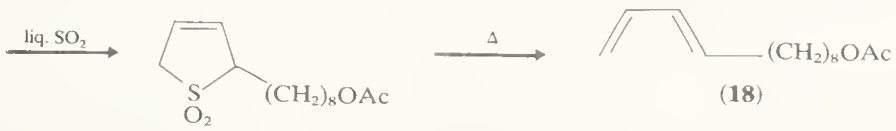
SCHEME 5

dienophiles, can be employed to separate (*Z*)-dienes from synthetic mixtures of (*Z*)- and (*E*)-dienes. This approach has recently been applied in the purification of the sex pheromone (**18**) of the female red bollworm moth, *Diparopsis castanea* Hmps (equation 10).[43]

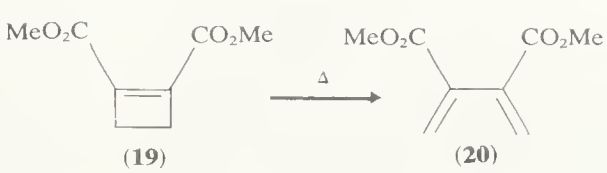


(9)





(10)



(11)

Functionalized butadienes[44,45] are also obtained by thermal ring opening of the corresponding cyclobutenes, e.g. (**19**)→(**20**) in equation (11).

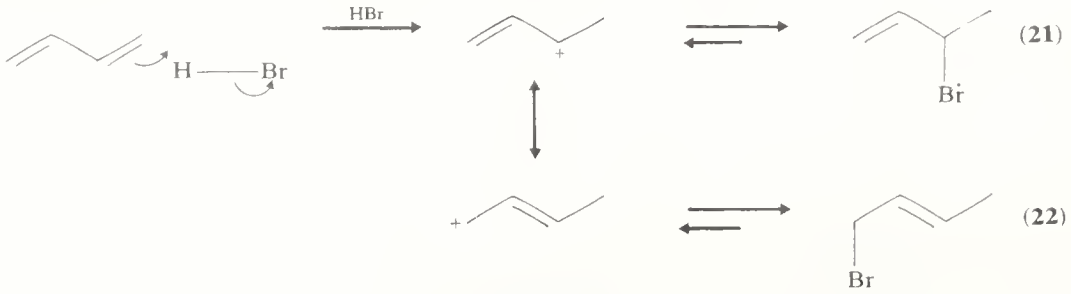
2.3.2 REACTIONS OF CONJUGATED DIENES

2.3.2.1 Chemical properties

Conjugated dienes display considerably enhanced chemical reactivity over that found amongst monoenes and dienes which are not conjugated. This feature is associated with the special molecular structure of the diene unit involving interaction of the two double bonds by overlap of the appropriate *p*-orbitals on C-2 and C-3; indeed, the incidence of this overlap, discussed at length elsewhere,[46] goes some way towards explaining why conjugated dienes function as a single unit rather than as two independent double bonds.

More often than not, electrophilic additions to conjugated dienes lead to mixtures of 1,2- and 1,4-addition products, whose formation is rationalized on the basis of charge

delocalization in the intermediate carbenium ion (carbocation) (Scheme 6). Thus, hydrobromination of butadiene leads[47] to a mixture of bromides, (**21**) and (**22**). Bromide (**21**) is produced more rapidly than (**22**) at low temperatures, and is the kinetically controlled product, whereas (**22**) is more stable than (**21**) and accumulates preferentially, under thermodynamic control, at 40 °C in the equilibrium mixture.



SCHEME 6

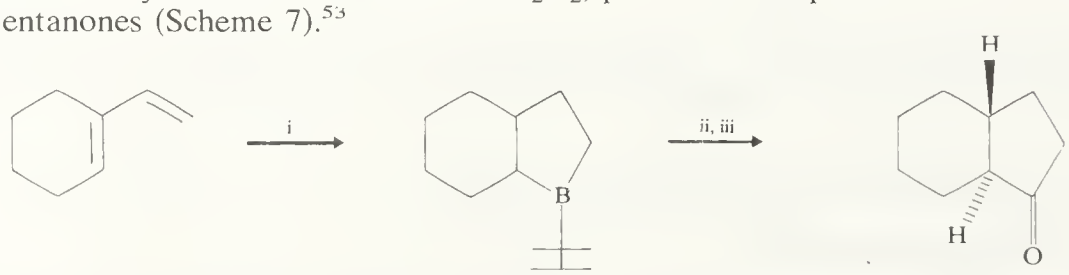
2.3.2.2 Reductions

Catalytic hydrogenation of conjugated dienes usually results in the formation of olefins resulting from simultaneous 1,2- and 1,4-addition of hydrogen; furthermore, the olefins produced tend to undergo further hydrogenation, leading to the corresponding alkane.[48] More recently, the selective hydrogenation of 1,3-dienes to (*Z*)-2-enes using aromatic tricarbonylchromium complexes has been demonstrated[49] and Kawakami *et al.*[50] have described a novel catalyst system, $CoBr(PPh_3)$–BF_3, which permits the selective hydrogenation of conjugated dienes to monoenes *via* 1,2-addition at the more substituted double bond, *e.g.* isoprene → 3-methylbut-2-ene. The reduction of dienes by sodium in liquid ammonia produces products resulting from 1,4-addition.[51]

2.3.2.3 Hydroborations

Monohydroboration of certain conjugated dienes can be accomplished with disiamylborane; oxidation of the intermediate adduct then leads to unsaturated carbinols.[52] Dihydroboration–oxidation of 1,3-dienes produces a mixture of 1,4- and 1,3-diols whose relative proportions depend markedly on the hydroborating agent and the structure of the diene; the 1,4-product usually predominates and in some instances is the exclusive product.[52]

Reaction between dihydroborated dienes and carbon monoxide at atmospheric pressure, followed by oxidation with alkaline H_2O_2, provides an expeditious route to certain cyclopentanones (Scheme 7).[53]

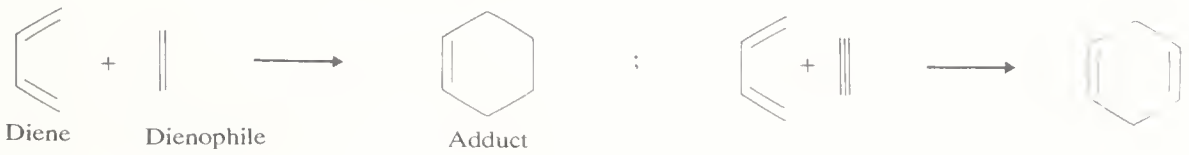


i, ⊢⊣BH_2; ii, CO, H_2O; iii, H_2O_2, NaOH.

SCHEME 7

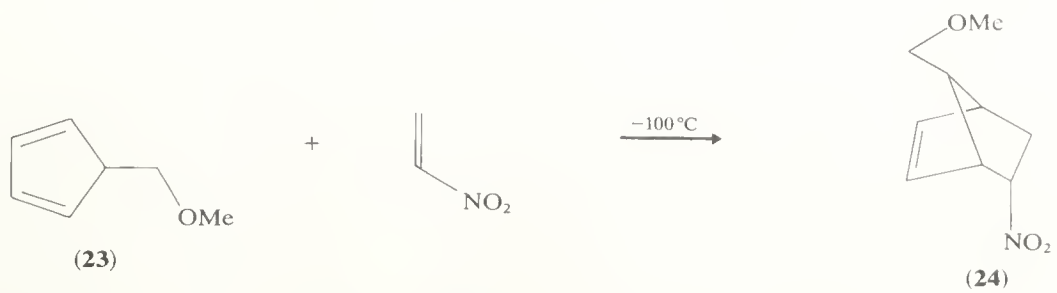
2.3.2.4 Diels–Alder reactions

In the celebrated Diels–Alder reaction, 1,3-dienes react with olefinic or acetylenic 'dienophiles' to form adducts with a six-membered hydroaromatic ring (Scheme 8).[54-57] The reaction, which is reversible, is generally effected by simply mixing the components at



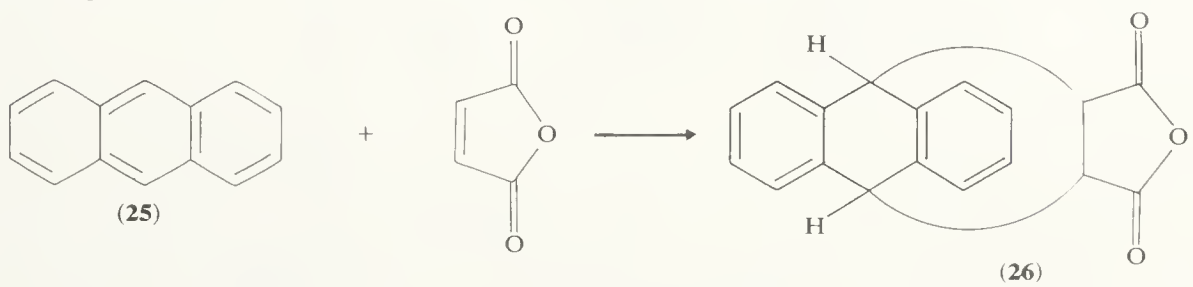
SCHEME 8

room temperature or by gentle warming in a suitable solvent. Nitroethylene even undergoes[58] a Diels–Alder addition with (**23**) at −100 °C, leading to the important prostaglandin intermediate (**24**) (equation 12). With relatively unreactive substrates, vigorous conditions are sometimes necessary. The application of very high pressures has provided the necessary driving force in some instances.[59,60]

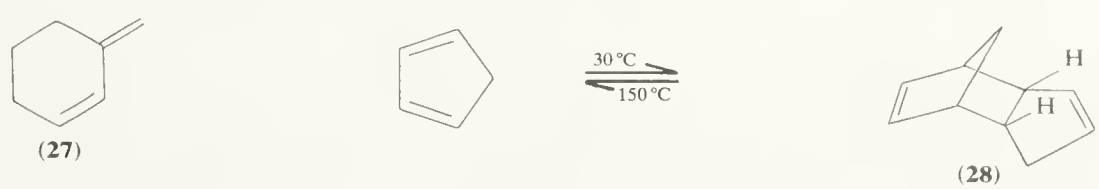


(**23**) (**24**) (12)

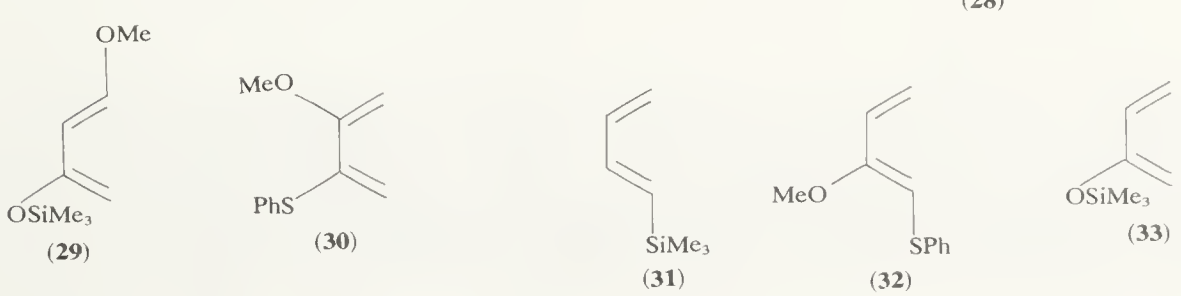
The Diels–Alder reaction is one of the most versatile reactions in modern organic synthesis; furthermore, it is remarkably regioselective and stereoselective, a feature which has contributed greatly to its use in the synthesis of natural products. The diene reactant may be acyclic or cyclic, or it may comprise part of an aromatic system, *e.g.* (**25**) → (**26**) in equation (13), but in any situation it must be capable of adopting a *cisoid* conformation. Thus the diene (**27**), where the double bonds are constrained in a *transoid* conformation, does not take part in the Diels–Alder reaction. A number of dienes undergo reaction with themselves, *e.g.* cyclopentadiene → (**28**) in equation (14). The scope for the reaction has been greatly expanded in recent years with the utilization of novel dienes, *e.g.* (**29**)–(**33**), which introduce 'usable' functionality in the adducts produced from reaction with dienophiles.[61–64]



(**25**) (**26**) (13)

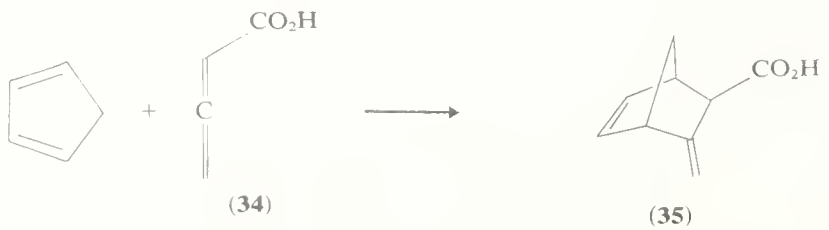


(**27**) (**28**) (14)

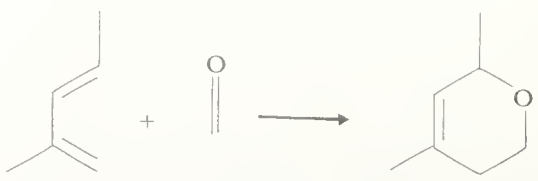


(**29**) (**30**) (**31**) (**32**) (**33**)

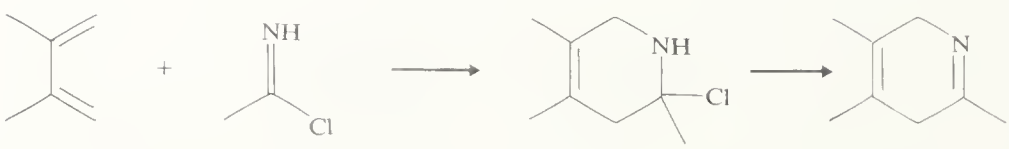
The reaction is facilitated by using a dienophile which is activated by electron-attracting groups (*e.g.* CO_2R, CN, CO, NO_2) attached to the double or triple bond. Allenes take part in the Diels–Alder reaction with dienes, *e.g.* (**34**) → (**35**) in equation (15), but ketens do not react and instead lead to products resulting from 1,2-addition to the double bond. Carbonyl compounds also react, leading to 5,6-dihydropyrans (**36**) (equation 16). Dihydropyridines (**37**) can be obtained from iminochlorides (equation 17). The light-induced 1,4-addition of oxygen to dienes leads to endoperoxides, *e.g.* (**38**), and this useful reaction, which may have significance in biosynthesis, has been exploited in recent total syntheses of the plant hormone abscissic acid (**39**)[65] and of solanofuran (**40**) found in Burley tobacco condensate (equations 18 and 19).[66]



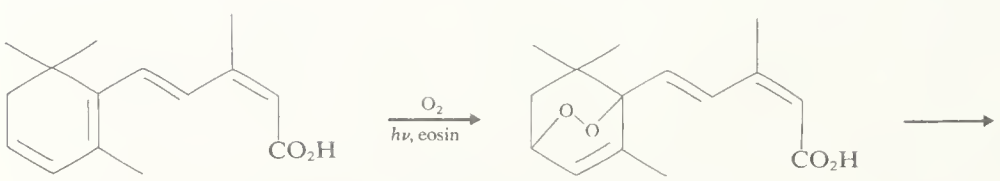
(34) (35) (15)



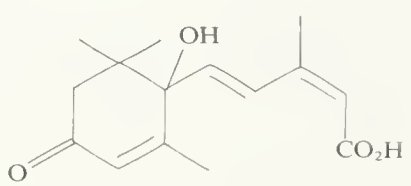
(36) (16)



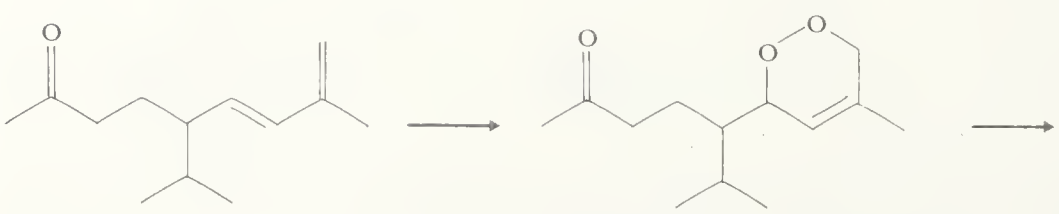
(37) (17)

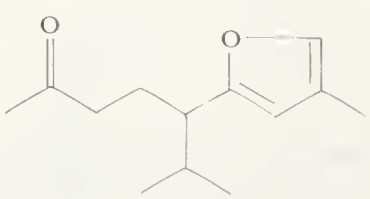


(38)



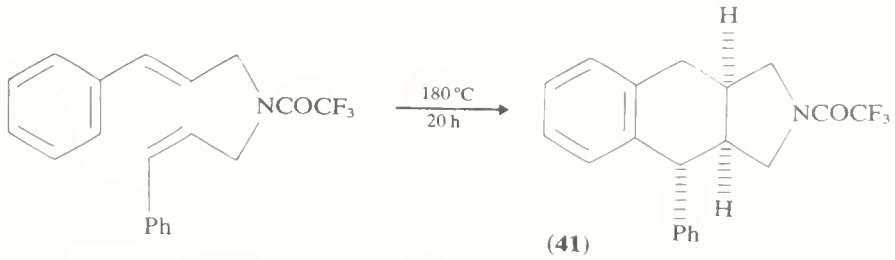
(39) (18)



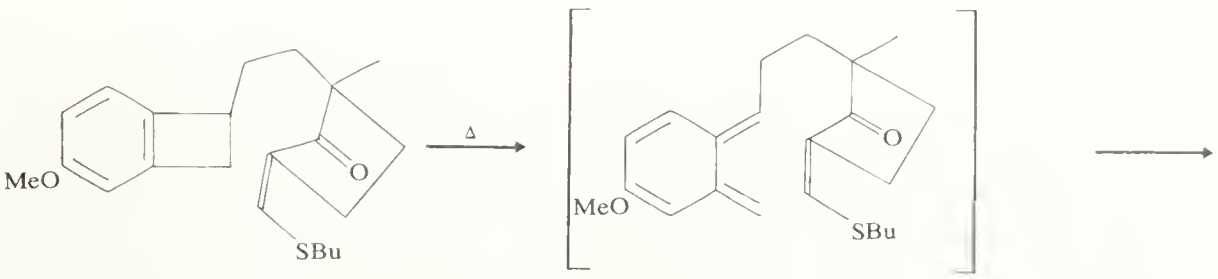


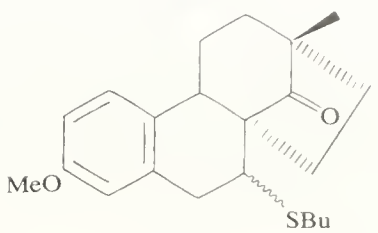
(40) (19)

The intramolecular variant of the Diels–Alder reaction[67] has featured prominently in a number of elegant approaches towards the total synthesis of natural products, *e.g.* the alkaloid tricyclic system (**41**),[68] tetracyclic diterpenoids (**42**),[69] the cedrene skeleton (**43**),[70] and the dilactone (**44**), an intermediate in a projected synthesis of the cytochalasans[71] (equations 20–23).

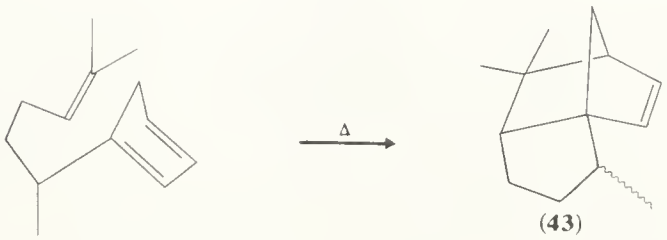


(41) (20)

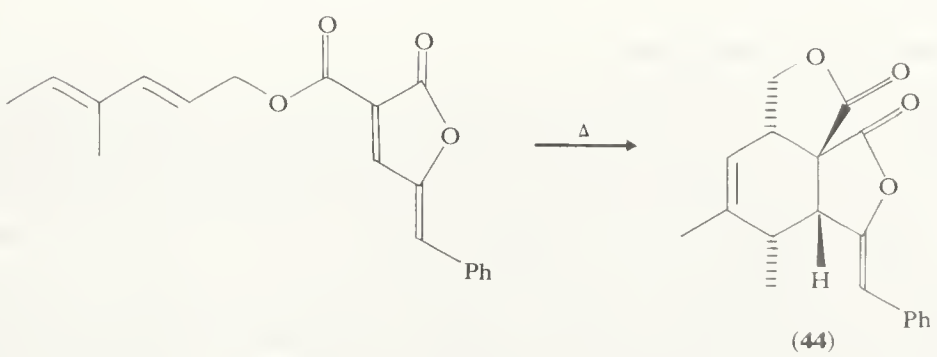




(42) (21)



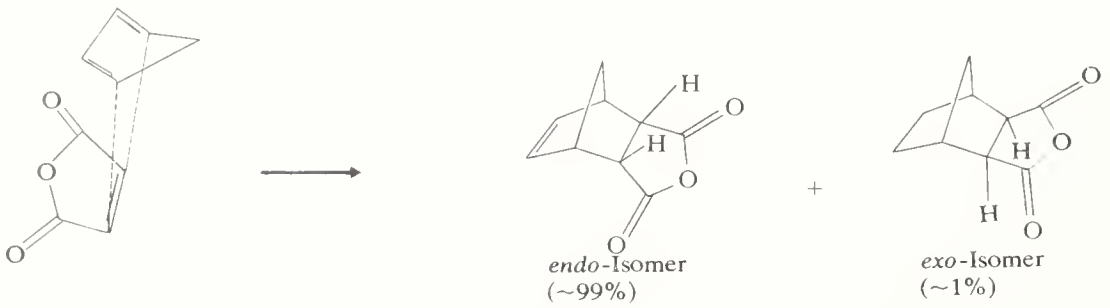
(43) (22)



(44) (23)

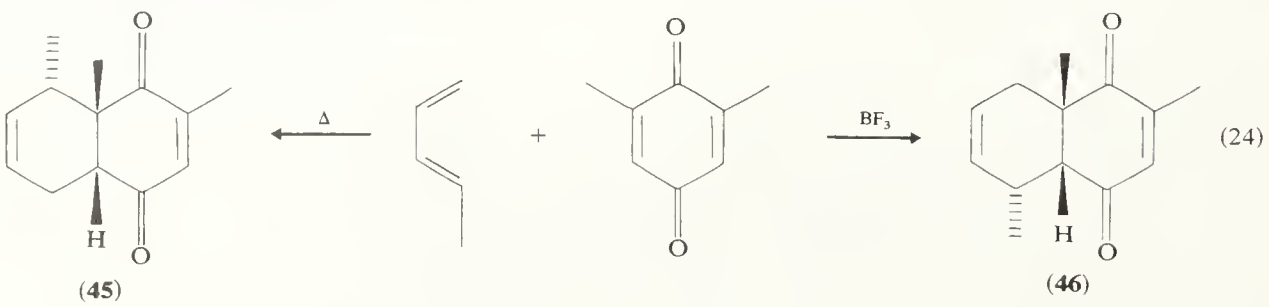
As a general rule-of-thumb, the relative stereochemistry of the substituents in both the diene and the dienophile are retained in the Diels–Alder adduct. This feature has provided compelling evidence for a largely concerted mechanism in which both new bonds between the diene and dienophile are formed at the same time.[72,73] A second general feature of the reaction is that the diene and dienophile so arrange themselves in parallel planes to provide a transition state permitting maximum accumulation of double bonds

(Scheme 9). This rule, known as the '*endo*-addition' rule, is strictly followed in Diels–Alder reactions between cyclic dienes and cyclic dienophiles and provides a useful guide in most other additions.



SCHEME 9

The rates of a number of Diels–Alder reactions are accelerated remarkably by Lewis acids such as $AlCl_3$, BF_3, and $SnCl_4$; furthermore, in many instances increased regioselectivity and stereoselectivity occur at the same time. For example, the Lewis acid catalysed reaction between 1,4-diphenylbutadiene and β-nitrostyrene leads to the corresponding *endo*-nitro adduct exclusively, whereas in the normal thermal process a 1:1 mixture of *endo*-nitro and *endo*-phenyl adducts is produced.[74] The thermal Diels–Alder reaction between penta-1,3-diene and 1,5-dimethylbenzoquinone leads to (**45**), but in the presence of BF_3–etherate at 0 °C the reaction gives exclusively (**46**) (equation 24).[75] The catalytic activity of Lewis acids in Diels–Alder processes[76] has been rationalized on the basis of complex formation between the Lewis acid and the polar portion of the dienophile, leading to further reduction of electron density at the double bond and increasing 'dienophilicity'. A number of attempts have been made to rationalize the reversals by the frontier-orbital treatment.[76–78]



(24)

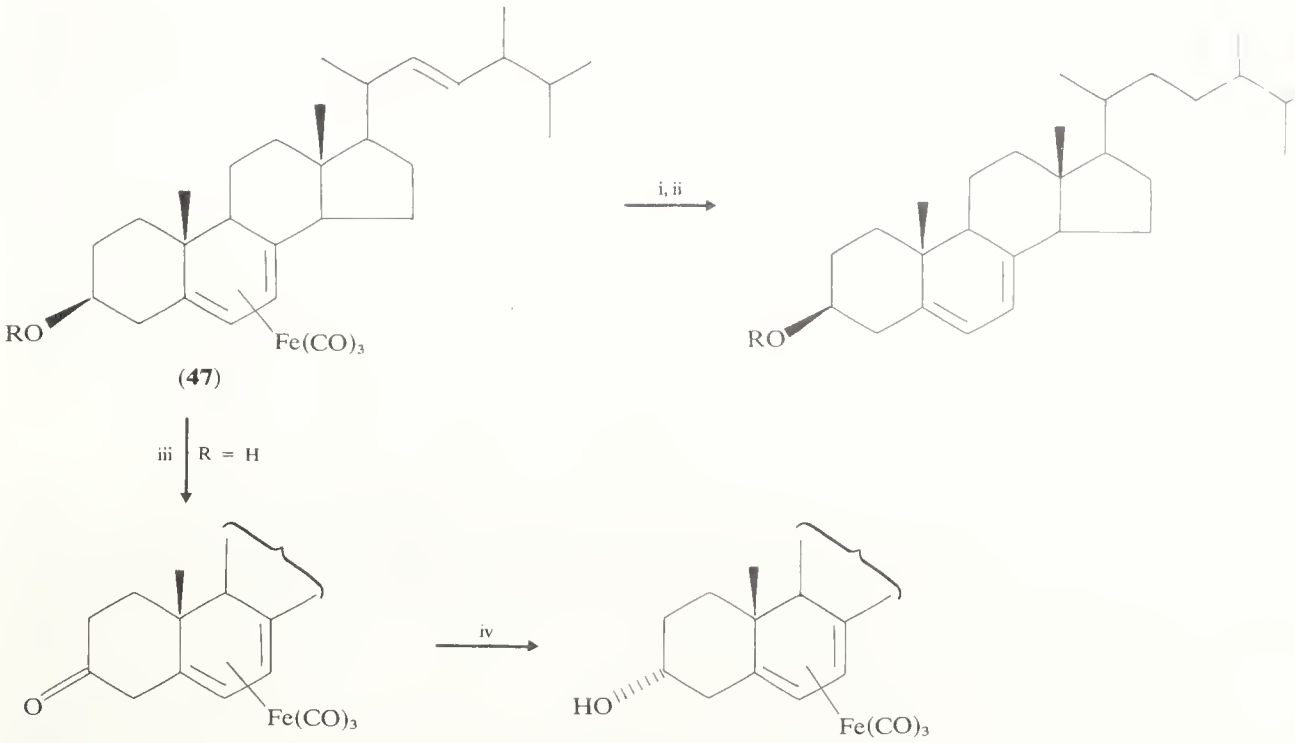
2.3.2.5 Iron carbonyl complexes

Conjugated dienes react smoothly with iron carbonyls to produce stable complexes, which can be employed as protecting groups for the dienes. Thus, protection of the ring B 1,3-diene function in ergosterol as the iron carbonyl complex (**47**) has permitted selective reactions to be carried out on other parts of the molecule (Scheme 10),[79] and Corey and Moinet[80] have described the use of stable diene complexes of the type (**48**) in a total synthesis of prostaglandin C_2 (**49**) (equation 25).

π-Allyliron tetracarbonyl cations are easily prepared from diene–iron carbonyl complexes by protonation (HBF_4) in the presence of carbon monoxide. These cations are attacked by a variety of nucleophiles, leading to products of 1,4-addition with preservation of the *cis* configuration in the original complex (Scheme 11).[81,82]

2.3.2.6 Photochemical and thermal reactions

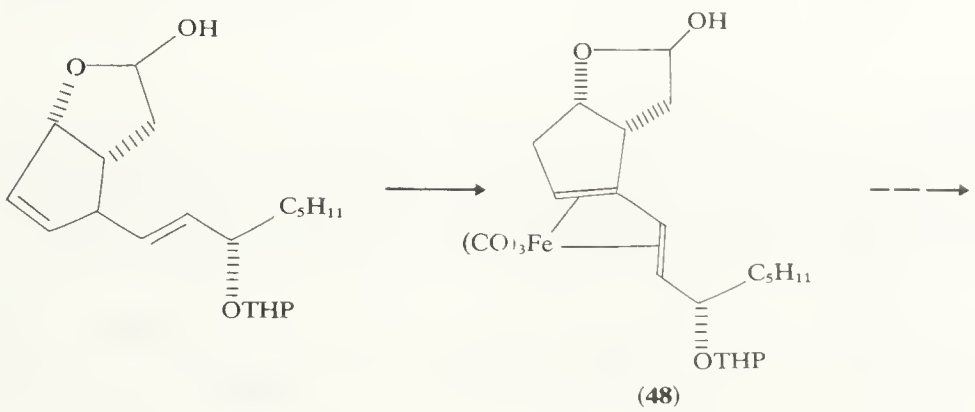
Photolysis of a number of 1,3-dienes leads to Diels–Alder adducts which probably arise through diallylic biradical intermediates. These adducts are produced in addition to



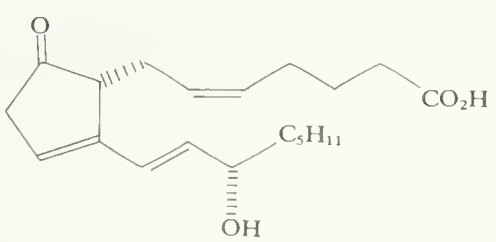
(47)

i, H_2; ii, $FeCl_3$; iii, [O]; iv, $LiAlH_4$.

SCHEME 10

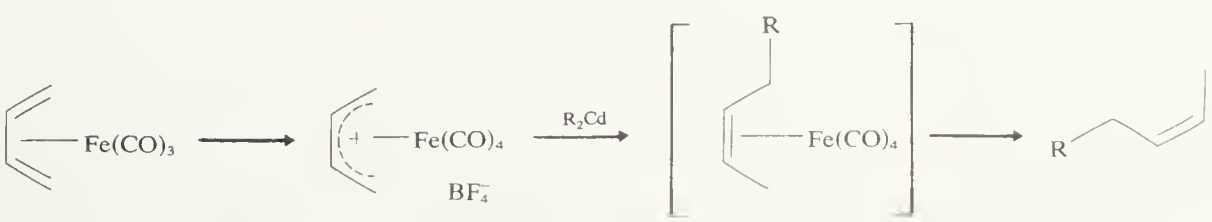


(48)



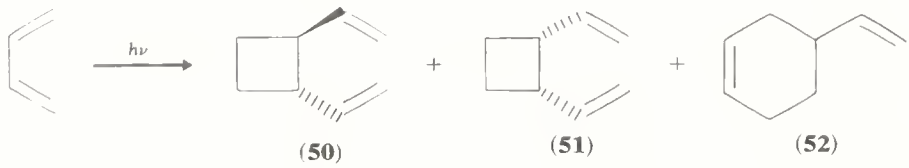
(25)

(49)

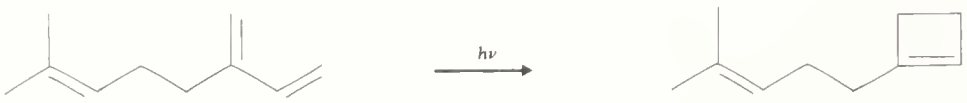


SCHEME 11

[2 + 2] cycloaddition products; thus, photolysis of butadiene produces[83] a mixture of (**50**), (**51**), and (**52**) (equation 26). Several 1,3-dienes undergo[84] photo-induced electrocyclic reactions leading to cyclobutenes, *e.g.* mycene → (**53**) in equation (27).

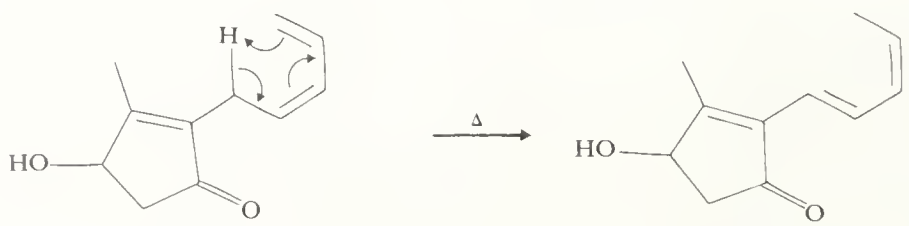


(**50**) (**51**) (**52**) (26)



(**53**) (27)

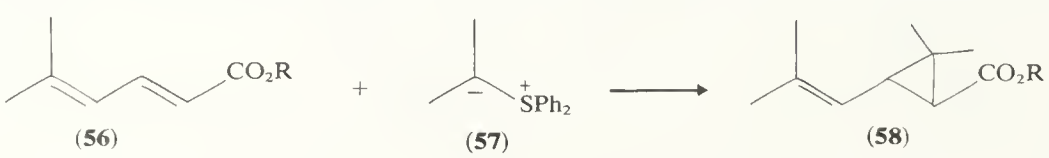
Thermal rearrangement of penta-1,3-dienes in which the vinyl and the alkyl group are *cis* to each other, as in the pyrethrolone molecule (**54**), results[85] in [1,5]-H transfer with concomitant migration of the double bonds, producing the diene (**55**) (equation 28).



(**54**) (**55**) (28)

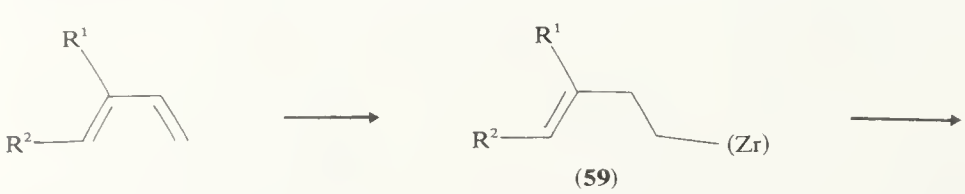
2.3.2.7 Other reactions

Organic peracids convert 1,3-dienes into unsaturated epoxides by 1,2-addition, and addition of carbenes and carbenoids leads to vinylcyclopropanes, *e.g.* the synthesis[86] of chrysanthemic acid ester (**58**) from the diene (**56**) and the *S*-ylide (**57**) in equation (29).

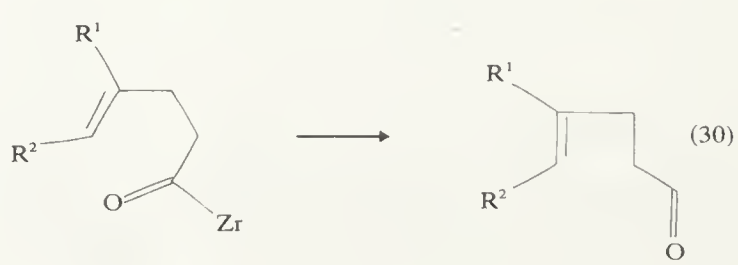


(**56**) (**57**) (**58**) (29)

Hydrozirconation of the sterically less hindered double bond of 1,3-dienes can be accomplished with $[Zr(\eta^5\text{-}C_5H_5)_2HCl]$, producing γ,δ-unsaturated complexes of the type (**59**), which are easily elaborated to γ,δ-unsaturated aldehydes (equation 30).[87]

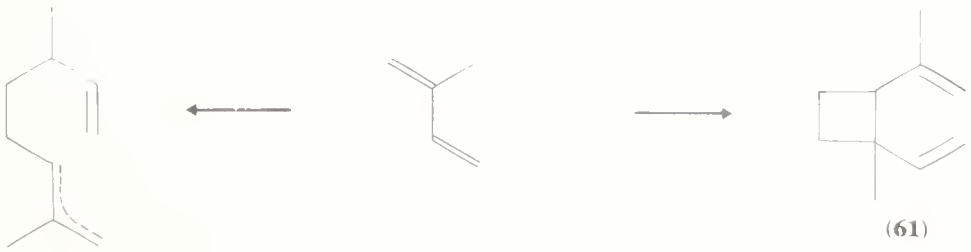


(**59**)



(30)

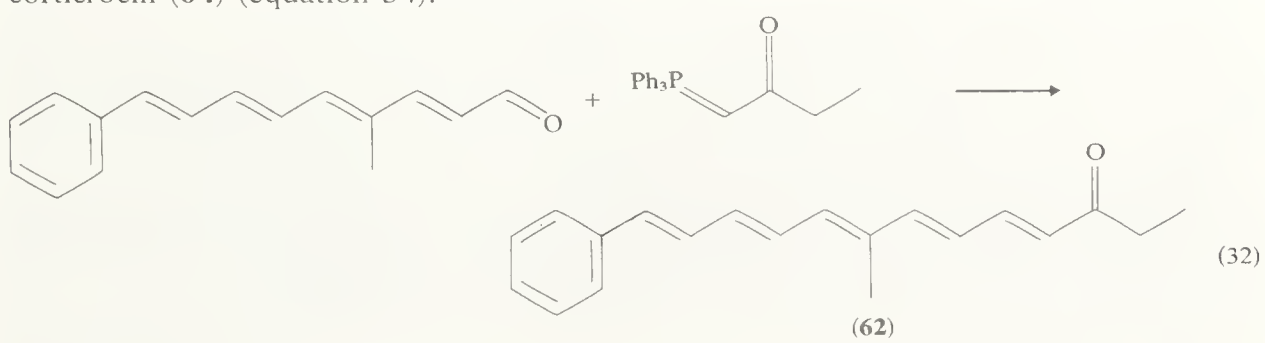
A η^3-allylpalladium acetate catalyst in the presence of triphenylphosphine catalyses the dimerization of isoprene to the desired head-to-tail terpene structure (**60**) in high yield,[88] whereas dimerization to (**61**) can be effected selectively by nickel cyclo-octadiene (equation 31).[89]



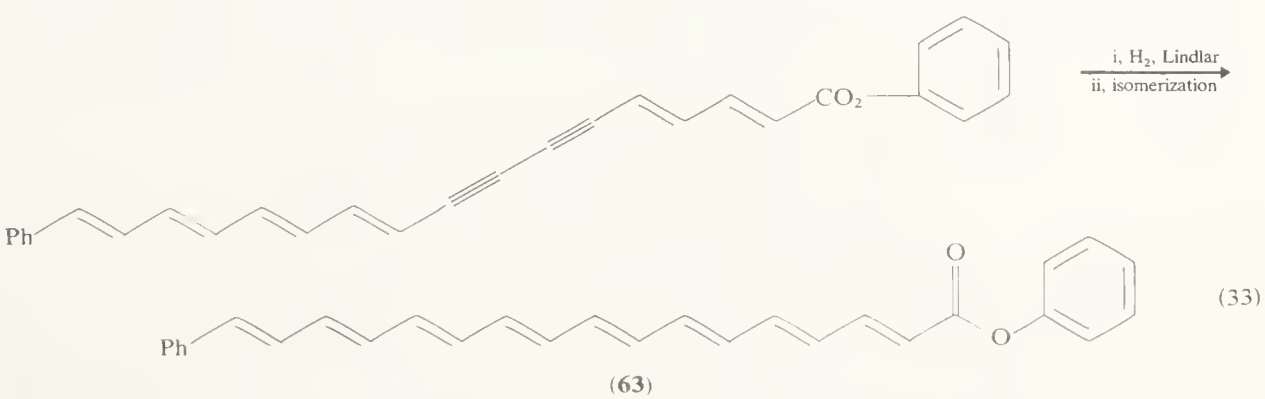
(**60**) (**61**) (31)

2.3.3 CONJUGATED POLYENES

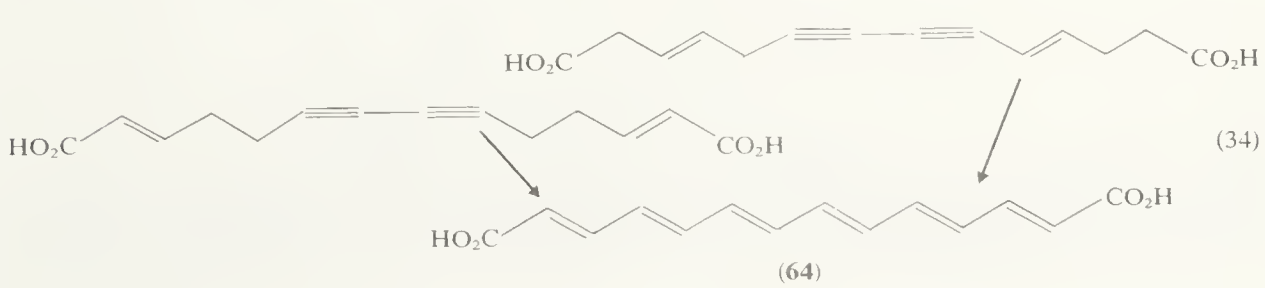
Conjugate polyenes become increasingly unstable as the number of double bonds increases. Outside the carotenoid group, polyenes containing up to and including 12 conjugated disubstituted double bonds have been synthesized. The most practical methods for the synthesis of these polyenes involve: (i) the Wittig reaction with polyunsaturated mono- or di-aldehydes, or polyunsaturated mono- or di-phosphonium salts, *e.g.* synthesis[90] of the fungal polyene pigment asperenone (**62**) (equation 32); (ii) selective reductions of conjugated polyenyne precursors, themselves prepared by acetylene coupling reactions, *e.g.* synthesis[91] of the bacterium pigment flexirubin (**63**) (equation 33); and (iii) base-catalysed prototropic rearrangement of alkenynes, *e.g.* synthesis[92] of the polyene corticrocin (**64**) (equation 34).



(**62**) (32)

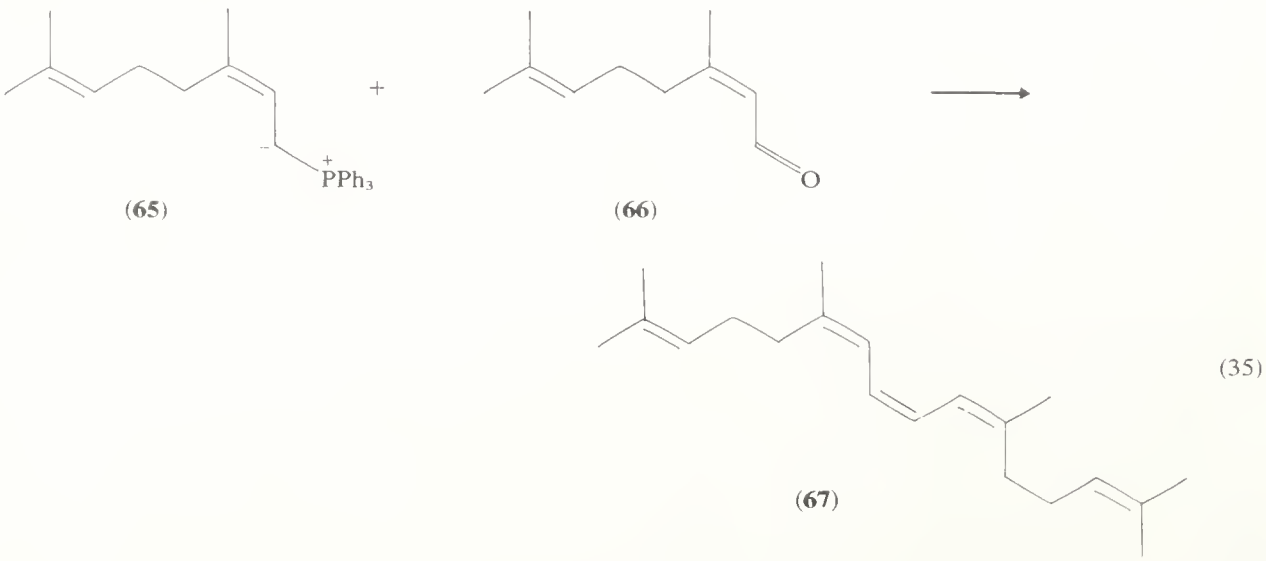


(**63**) (33)



(**64**) (34)

The instability and ease of stereomutation amongst higher conjugated polyenes has limited the development of stereospecific syntheses of this class of compound. The potential for (*Z*)-α,β-unsaturated phosphoranylides and (*Z*)-α,β-unsaturated aldehydes in the preparation of all-(*Z*)-conjugated polyenes is well illustrated by a synthesis of the all-(*Z*)-triene (**67**) from (**65**) and (**66**) (equation 35).[29]

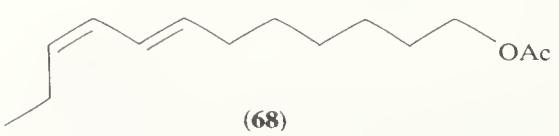


(**65**) (**66**) (**67**) (35)

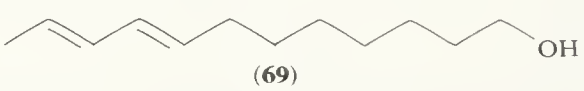
2.3.4 NATURALLY OCCURRING DIENES AND POLYENES

Simple aliphatic conjugated dienes are commonly found in Nature as important constituents of insect sex pheromones. For example, the sex pheromone of the European grapevine moth *Lobesia botrana* (Schiff) is (**68**),[93] whereas the alcohol (**69**) and acetate (**70**) are sex pheromones of the codling moth[94] and red bollworm moth[95], respectively. The diene (**71**) is a pheromone of the bark beetle *Ips paraconfusus* Lanier.[95]

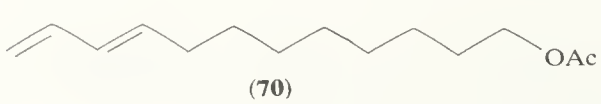
Unsaturated isobutylamides like anacyclin (**72**, *ex. Anacylin pyrethrum*)[96] are insecticidal and several polyene amides are found in species of the genus *Piper*, *e.g.* (**73**) from *P. guineense*.[97] The diene pyrethrolone (**54**) is an important alcohol component of the insecticidal pyrethrin esters found in *Chrysanthemum cinerariaefolium*.[98]



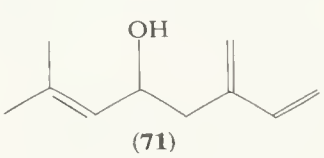
(**68**)



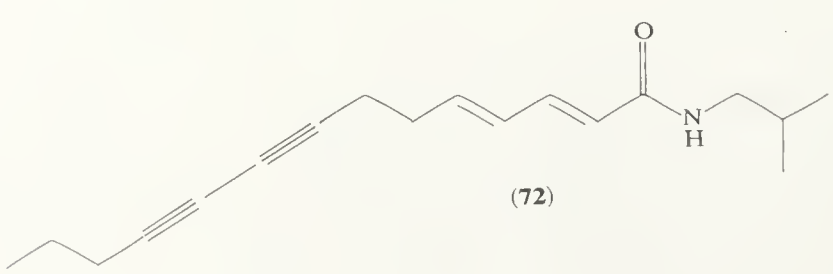
(**69**)



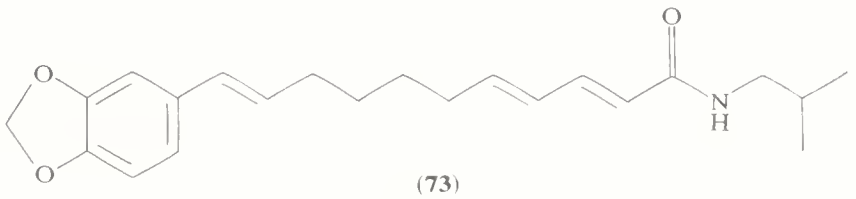
(**70**)



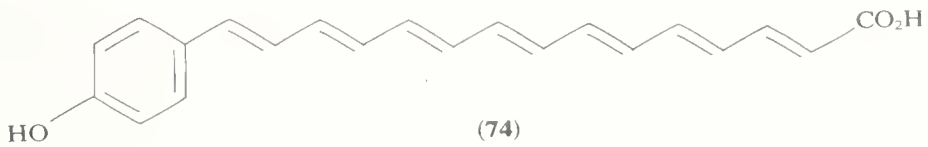
(**71**)



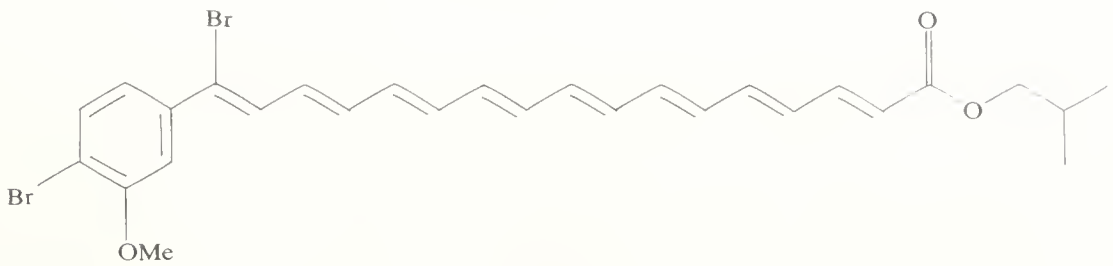
(**72**)



(73)



(74)



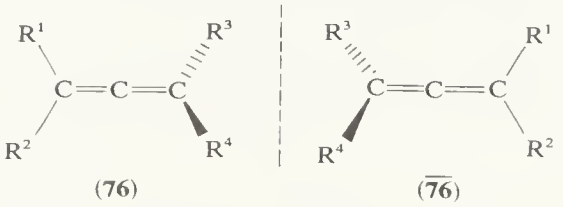
(75)

Excluding the carotenoids, higher conjugated polyenes have been found only rarely in Nature. Cortisalin (**74**) is a red pigment isolated from *Corticium salicinum*[99] and asperenone (**62**) is found in *Aspergillus niger*.[90] Flexirubin (**63**) is the main pigment isolated from the bacterium *Gleitenden bacterien*[91] and xanthomonadin (**75**) is found in the bacterium *Xanthomonas juglandis*.[100]

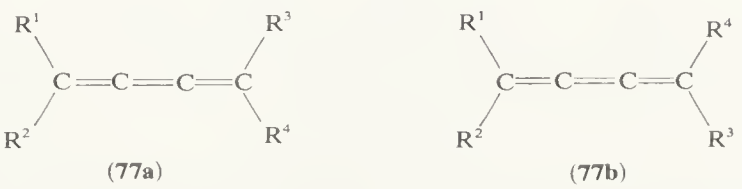
2.3.5 ALLENES AND CUMULENES

2.3.5.1 Introduction

A number of allenes (1,2-dienes, cumulated dienes) and cumulenes (cumulated polyenes) are found in Nature, and several display interesting biological properties (see under Section 2.3.8). Allenes, and cumulenes with an *even* number of double bonds, containing the substitution pattern shown in (**76**) and (**$\overline{76}$**) exhibit optical activity (*i.e.* they are capable of enantiomerism, see Section 1.4.3.1), whereas cumulenes with an *odd* number of double bonds, *e.g.* (**77**), display *cis–trans* isomerism (*i.e.* **77a** and **77b** are diastereoisomers).



(76) (**$\overline{76}$**)



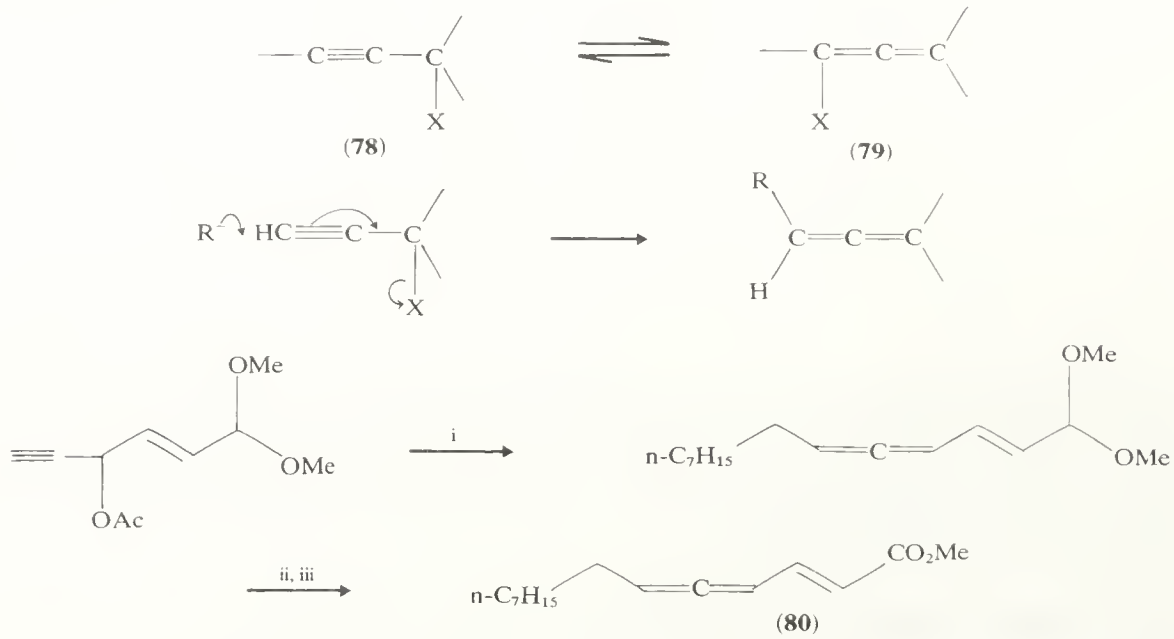
(77a) (77b)

Several excellent reviews of the chemistry of allenes have been published[101–106] and annual comprehensive accounts of the literature since 1971 are given in the Specialist Periodical Reports.[5,6]

2.3.5.2 Preparation of allenes

(i) By displacements from propargylic systems

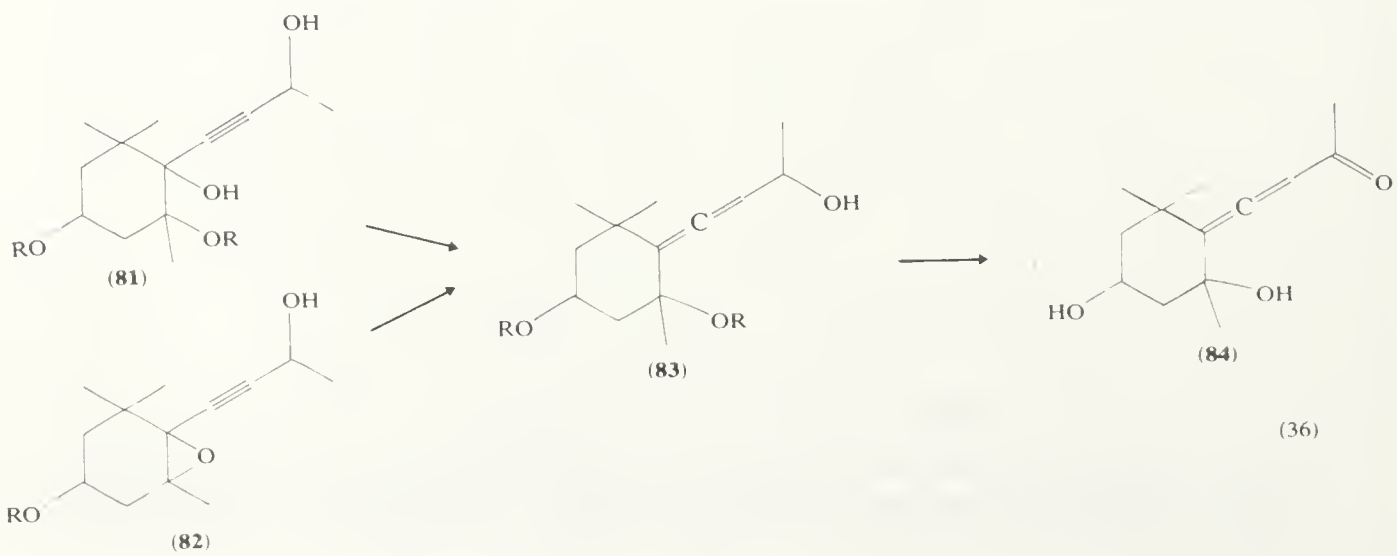
The propensity with which propargylic systems, *viz.* (**78**), undergo rearrangement to allenes (**78**) → (**79**) has been exploited in several useful synthetic approaches to substituted allenes based on the additions of Grignard reagents to propargyl halides in the presence of $FeCl_3$,[107] or of copper reagents to propargyl acetates.[108] The latter approach, for example, has been employed as a key stage in a synthesis of the natural allene (**80**), a sex pheromone of the Dried Bean beetle *Acanthoscelides obtectus* (Scheme 12).[109]



i, $(C_8H_{17})_2CuLi$; ii, H^+; iii, NaCN, H^+, MnO_2, MeOH.

SCHEME 12

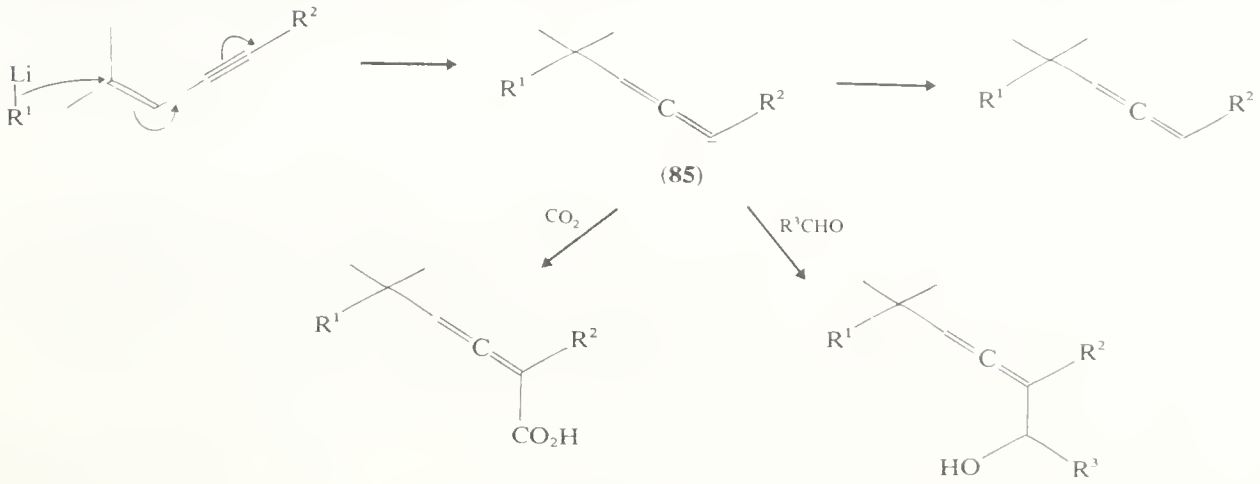
In a similar manner, the dehalogenation of propargyl halides to allenes can be effected with lithium aluminium hydride,[110] and under forcing reduction conditions the tertiary hydroxy group in propargyl alcohols will act as a leaving group, leading to allenes. Thus, both the butynediol (**81**) and the epoxide (**82**) can be converted into allene (**83**) with lithium aluminium hydride (equation 36). Oxidation of (**83**) with manganese dioxide then produces the allene ketone (**84**), a secretion isolated from the large flightless grasshopper *Romalea microptera*.[111]



(36)

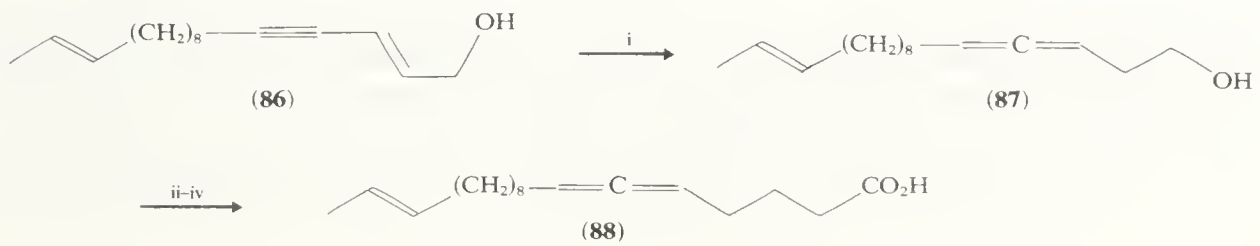
(ii) From conjugated enynes

Allenes are produced from 1,4-addition of alkyl-lithium reagents to conjugated enynes, followed by hydrolysis (Scheme 13). A feature of the method is that the intermediate adducts (**85**) can be employed to synthesize functionalized allenes (see Scheme 13).[112]



SCHEME 13

Reduction of the conjugated enyne system in (**86**) with lithium aluminium hydride has led to the allene (**87**), which was then elaborated to the natural allene (**88**) found in seed oils of higher plants (Scheme 14).[113]

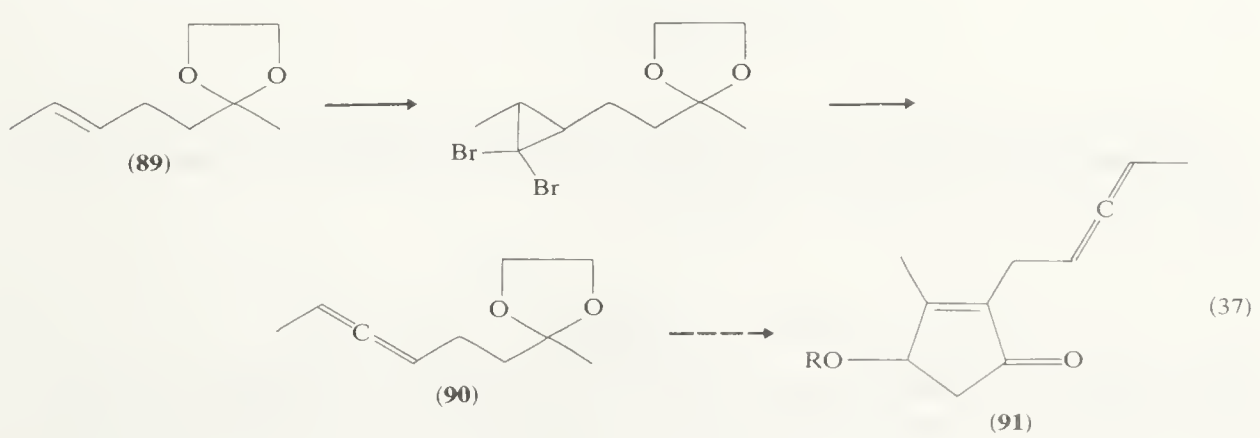


i, $LiAlH_4$; ii, $(PhO)_3PBr_3$; iii, NaOEt, $CH_2(CO_2Et)_2$; iv, $-OH$, $-CO_2$

SCHEME 14

(iii) By dehalogenation of gem*-dihalocyclopropanes*

Allenes are obtained from alkenes by sequential treatment with the carbene produced from bromoform and potassium t-butoxide, followed by treatment of the resulting dibromocyclopropane with magnesium,[114] or, better, with either MeLi[115] or BuLi.[116] Thus, treatment of the alkene (**89**) with $HCBr_3$–$KOBu^t$ and then Mg led to the allene (**90**) which was elaborated to the allene (**91**), regarded[33] for many years as the structure of the insecticidal pyrethrin esters (equation 37).

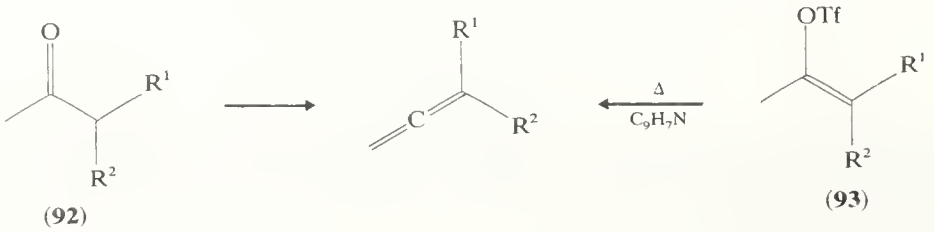


(37)

In some cases the alkene–allene transformation can be carried out in one stage, using bromoform and two equivalents of base. With certain substituted dibromocyclopropanes, bicyclobutanes accompany the formation of allenes,[117] and attention must be given to the reaction conditions if acetylenic by-products resulting from base-catalysed isomerization of the initially produced allenes are to be avoided.[118] Debrominations with Bu^nLi complexed with the chiral tertiary diamine (−)-sparteine lead to optically active allenes.[119]

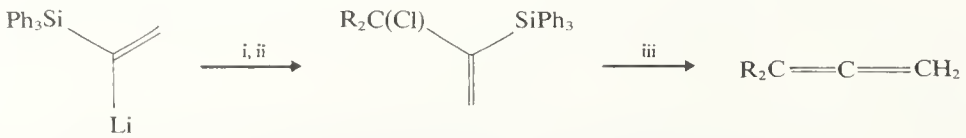
(*iv*) *From other eliminations*

Allenes are produced from a variety of dehydrohalogenations, dehalogenations, and dehydrations involving vinylic or allylic halides, homoallylic halides, and alcohols and diols, respectively.[105] Treatment of enol phosphates with aqueous sodium hydroxide at 0 °C leads to allenes,[120] and ketones of the type (**92**) can be converted into allenes by reaction with Br_2PPh_3–Et_3N[121] or *via* the corresponding vinyl triflates (**93**) (equation 38).[122]



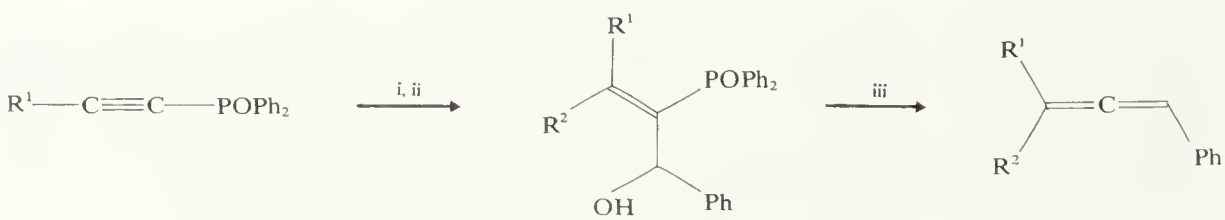
(38)

The Peterson reaction using α-lithiovinyltriphenylsilane provides an expeditious route to allenes from ketones (Scheme 15),[123] and the Horner synthesis can be used to prepare allenes from acetylenic phosphine oxides according to Scheme 16.[124]



i, R_2CO; ii, $SOCl_2$; iii, F^-, DMSO.

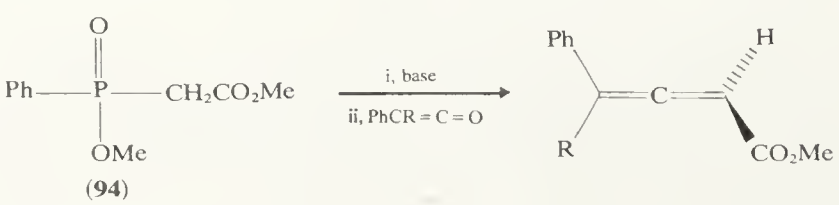
SCHEME 15



i, R^2MgX; ii, PhCHO; iii, NaH.

SCHEME 16

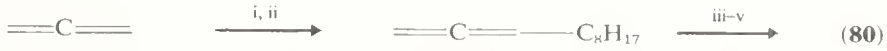
Allenes are produced in Wittig reactions between phosphoranylides and Schiff bases,[125] and optically active allenes can be obtained [126] from the optically active phosphine oxide (**94**) using ketens as substrates (equation 39).



(39)

(*v*) *Other methods*

A number of alternative, but generally less useful, methods are available for the preparation of allenes.[105] The potential for allenic lithiums and cuprates in synthesis is admirably illustrated[127] in a synthesis of the Dried Bean insect pheromone (**80**) shown in Scheme 17.



(**80**)

i, Bu^nLi; ii, n-$C_8H_{17}Br$; iii, $LiBu^t$; iv, CuI; v, $\equiv$—CO_2Me.

SCHEME 17

Both terminal and internal allenes can be obtained from acetylenic, sulphonium ylides by [2,3]-sigmatropic rearrangement,[128] and some allenes are produced by photolysis of 1,3-dienes.[129]

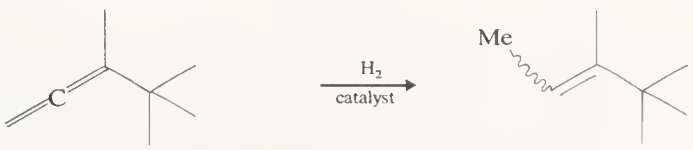
2.3.6 REACTIONS OF ALLENES

2.3.6.1 General reactions

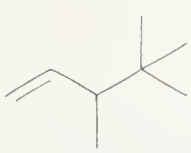
Allenes are sensitive to both bases and acids, leading to acetylenes, by prototropic rearrangement,[130] and to carbonyl compounds, respectively. Bromination of allene itself produces first 2,3-dibromopropene, and then 1,2,2,3-tetrabromopropane. Ozonolysis of allenes leads to carbonyl compounds and cyclopropanes or allene oxides, depending on the structure of the allene;[131] carbonyl compounds are also produced from photo-oxidation of allenes.[132] The oxidation of sterically encumbered allenes by peroxy acids gives rise to a range of interesting products.[133] Allenes are susceptible to polymerization at elevated temperatures, but at moderate temperatures they undergo dimerization to methylenecyclobutanes.[134] Allene–allene and allene–alkene cycloaddition reactions have been reviewed.[135]

2.3.6.2 Hydrogenations

Studies of the regio- and stereo-selectivity of heterogeneous catalytic semi-hydrogenation of allenes have indicated that the alkene products of the first stage of the hydrogenation are those expected from consideration of relative hindrances of the different orientations of the allene towards the catalyst surface, *i.e.* allene (**95**) is first reduced to (**96**) (equation 40), rather than to (**97**).[136] Furthermore, the results are consistent with a simple picture of overall *cis*-1,2-hydrogenation, and can be used to determine the absolute configuration of allenes.[137]



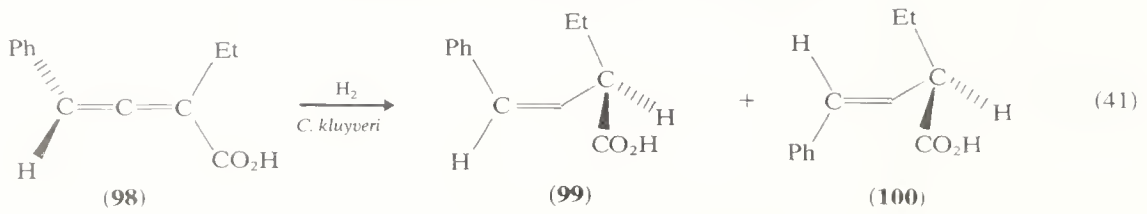
(**95**) (**96**) (40)



(**97**)

Hydrogenations of allenes using the micro-organism *Clostridium kluyveri* as catalyst are highly stereospecific, the racemic acid (**98**), for example, giving[138] equal amounts of (**99**)

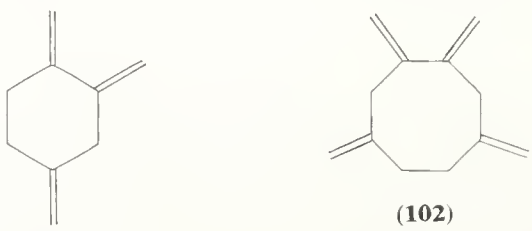
and (**100**) (equation 41). Wilkinson's catalyst has also been used for the stereoselective reduction of allenes, *e.g.* nona-1,2-diene → *cis*-non-2-ene (66%).[139]



(98) (99) (100) (41)

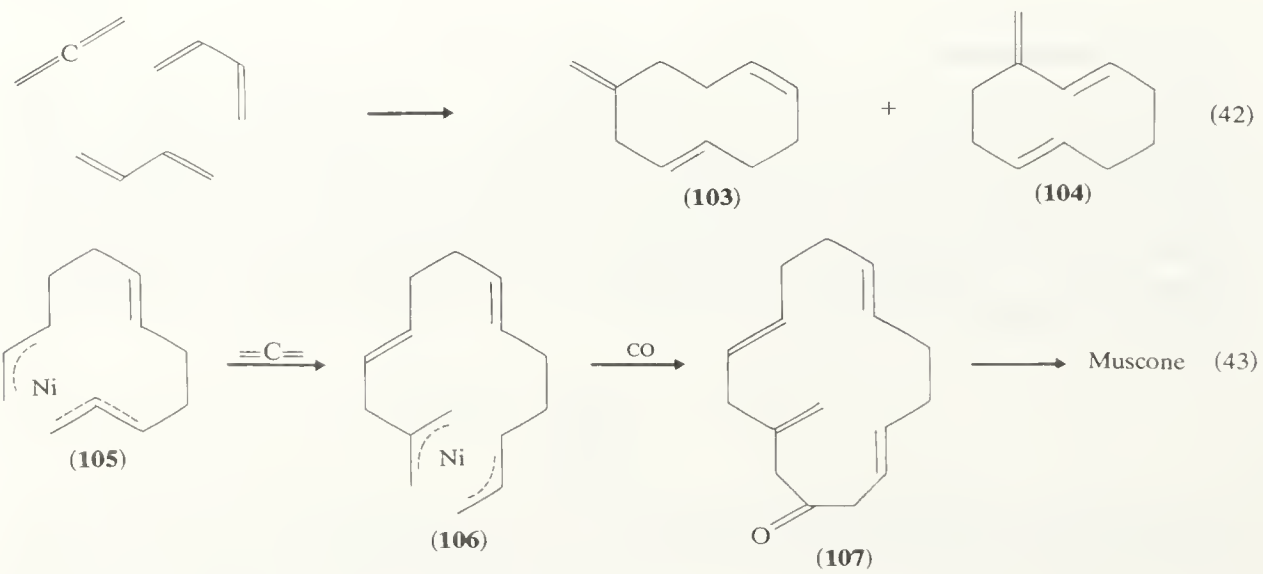
2.3.6.3 Metal–allene reactions

The oligomerization of allene with metal catalysts has been investigated extensively in recent years.[140] Cyclo-oligomerization of allene by $Ni(PPh_3)_2$ leads to a mixture of trimer (**101**), tetramer (**102**), pentamer, and hexamer, whereas use of a complex from $Ni(cod)_2$ and 1–4 moles of phosphine leads mainly to (**102**), and using $P(OPh)_3$ largely to (**101**).[141]



(101) (102)

Mixed catalytic oligomerization of butadiene and allene in the presence of tris-(2-biphenylyl)nickel(0) provides[142] (**103**) and (**104**) (equation 42). The dodecatrienylnickel complex (**105**) absorbs allene to yield the bis-π-allyl intermediate (**106**) which reacts with carbon monoxide to give (**107**); hydrogenation of (**107**) then produces[143] muscone (equation 43).



(103) (104) (42)

(105) (106) (107) (43)

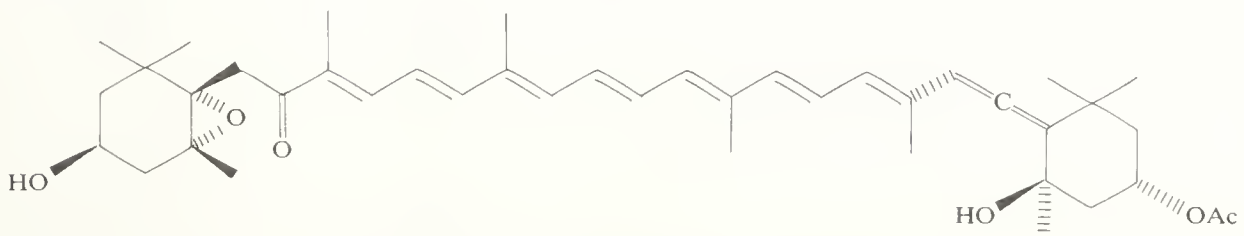
2.3.7 CUMULENES

The simplest cumulene, butatriene, was first described in 1921. Substituted butatrienes have been prepared by eliminations from 1,4-dihalo (or 1,4-dihydroxy) alk-2-ynes[144] or dihalocyclopropanes,[145] and by dimerization of vinyl–copper[146] or vinyl–boron intermediates[147] prepared from acetylenic precursors. The accumulation of more than five

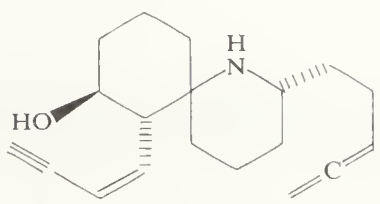
double bonds has proved to be a formidable problem.[148] Most synthetic approaches towards cumulenes have proceeded *via* eliminations from poly-yne α,ω-diols.

2.3.8 NATURALLY OCCURRING ALLENES AND CUMULENES

The most widely distributed allenic compound in Nature is the algal pigment fucoxanthin (**108**), found in common marine seaweeds and in diatoms; other allenic carotenoid pigments are less widely distributed.[149] The allene (**109**) has been isolated from extracts of skins of the arrow poison frog *Dendrobates histrionicus*;[150] (**80**) is the sex pheromone of the Dried Bean bettle; the allenes (**110a**) and (**110b**) are produced by micro-organisms;[151] and (**88**) has been isolated from seed oils of higher plants. A number of butatrienes (*e.g.* **111**) co-occur with polyacetylenes in *Compositae*[152] and some allenes are found in animal alkaloids.[153]

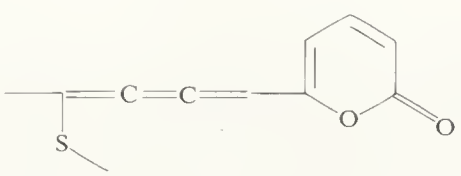


(**108**)



(**109**)

(**110 a**) R = OH
(**110 b**) R = $(CH_2)_3OH$



(**111**)

2.3.9 ACETYLENES AND POLYACETYLENES

2.3.9.1 Introduction

For many years acetylene has provided a chemical feedstock for the industrial production of vinyl chloride (for PVC plastics), vinyl acetate (for PVA emulsion paints and adhesives), acetaldehyde (for conversion into acetic acid, used in cellulose acetate fibres, and into plasticizer alcohols), and acrylonitrile (for acrylic fibres and adiponitrile, used in nylon production). Before the advent of petroleum as a cheap raw material, acetylene was manufactured from calcium carbide produced from coal and lime; today, it is obtained largely from cracking of crude oil.[1] However, the production of acetylene is expensive and in recent years much effort has been expended towards developing alternative routes to the industrial products above which have hitherto been based on acetylene. Indeed, all these products are now made competitively starting from ethylene, and this feature has accounted for the decline in the importance of acetylene as an industrial feedstock in the past two decades.[1]

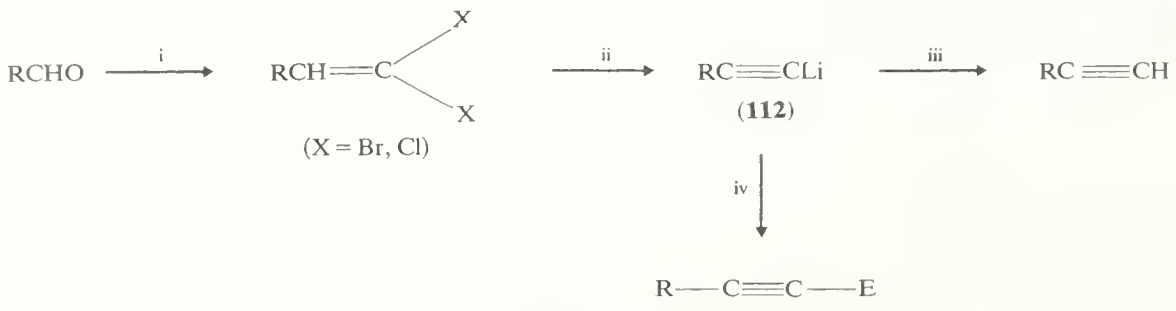
A number of books and reviews provide comprehensive accounts of all aspects of the

chemistry of acetylenic compounds;[2,154–157] the literature since 1971 is summarized on an annual basis in the Specialist Periodical Reports.[5,6]

2.3.9.2 Preparation of acetylenes

(i) By dehydrohalogenation of haloalkenes

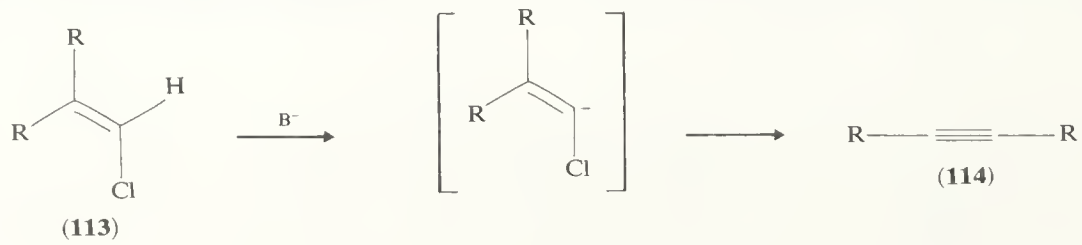
Treatment of 1,1-dihalo alkenes with Bu^nLi, followed by quenching with acid, provides an expeditious synthesis of terminal acetylenes (Scheme 18). Furthermore, the lithium acetylide intermediate (**112**) can be treated *in situ* with carbon halides, and a variety of other electrophiles, leading to disubstituted acetylenes. The 1,1-dihaloalkenes are synthesized by Wittig-type reactions involving the lower homologous aldehyde (Scheme 18).[158,159]



i, CBr_4, PPh_3 or $(EtO)_2POCCl_2$; ii, Bu^nLi; iii, H^+; iv, E^+.

SCHEME 18

Similarly, monohaloalkenes undergo dehydrohalogenation to acetylenes, those bearing the hydrogen and halogen atoms on the same carbon by way of the Fritsch–Buttenberg–Wiechell rearrangement,[160,161] *viz.* (**113**) →(**114**) (equation 44).



(44)

(ii) By dehydrohalogenation of haloalkanes

Vicinal dibromides, easily available by bromination of disubstituted alkenes, are smoothly dehydrobrominated to acetylenes using strong bases like alkoxide, sodamide, Bu^nLi, or DMSO anion.[161,162] Acetylenes are produced directly from ketones by heating the ketone with PCl_5 in pyridine in anhydrous benzene;[163] the reaction proceeds *via* the intermediate *gem*-dichloride (**115**) (equation 45).

$$R^1COCH_2R^2 \longrightarrow R^1CCl_2CH_2R^2 \longrightarrow R^1C{\equiv}CR^2 \qquad (45)$$

(**115**)

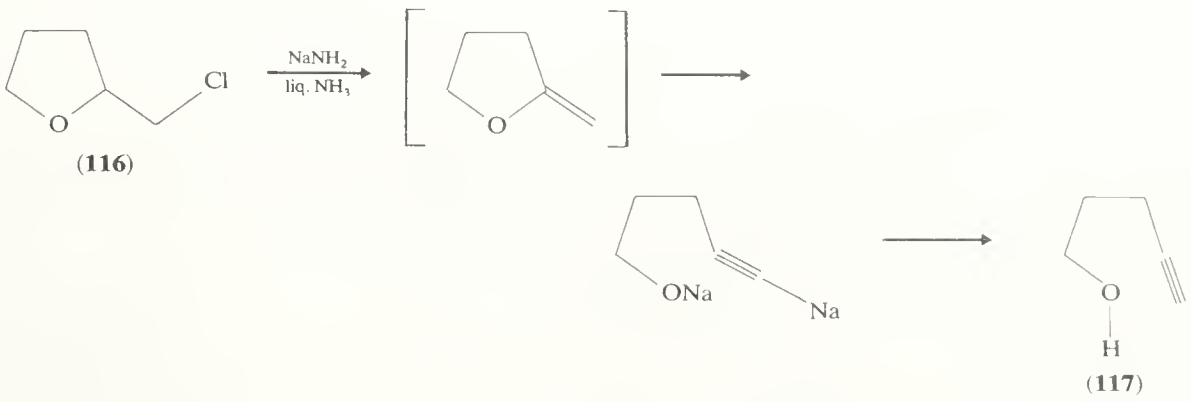
(iii) From α-diketones and β-keto-esters

The oxidation of bishydrazone derivatives of α-diketones, using mercury(II) oxide or molecular oxygen in the presence of cuprous chloride in pyridine as catalyst leads to acetylenes.[164] Diaryl- or arylalkyl-substituted α-diketones are converted directly into acetylenes by heating them with triethyl phosphite at 215 °C.[165]

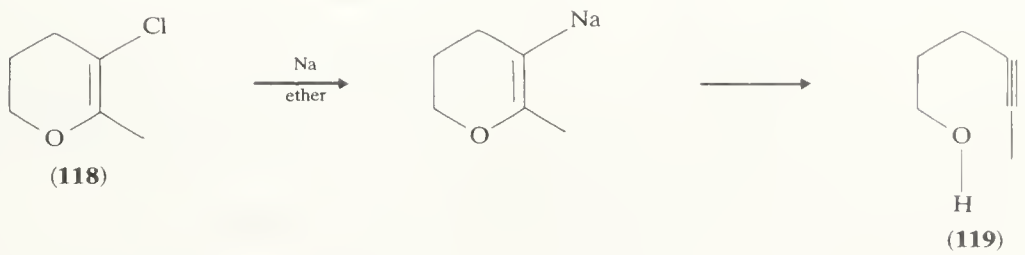
β-Keto-esters are converted into alk-2-ynoic esters by oxidation of the corresponding pyrazolines with thallium(III) nitrate or by treatment of the corresponding 3,4-disubstituted 4-halo-2-pyrazolin-5-ones with aqueous sodium hydroxide and potassium ferricyanide.[166]

(iv) By other eliminations

1,2-Dihaloalkenes can be dehalogenated to acetylenes using Zn or Li/Hg, while base treatment of cyclic vinyl ethers has provided[167] a versatile synthesis of certain hydroxyacetylenes, *e.g.* (**116**) → (**117**) and (**118**) → (**119**) in equations (46) and (47), respectively.

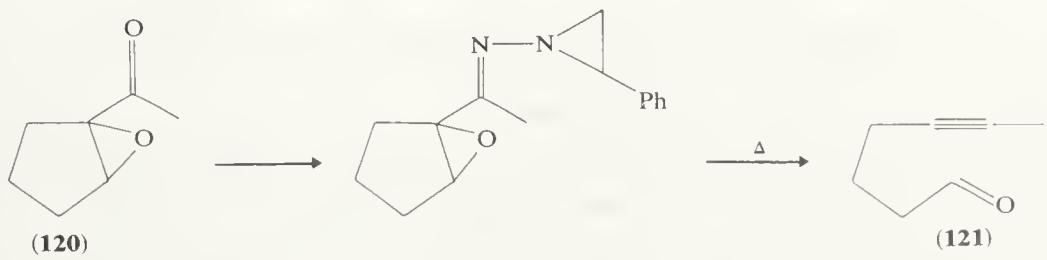


(**116**) (**117**) (46)



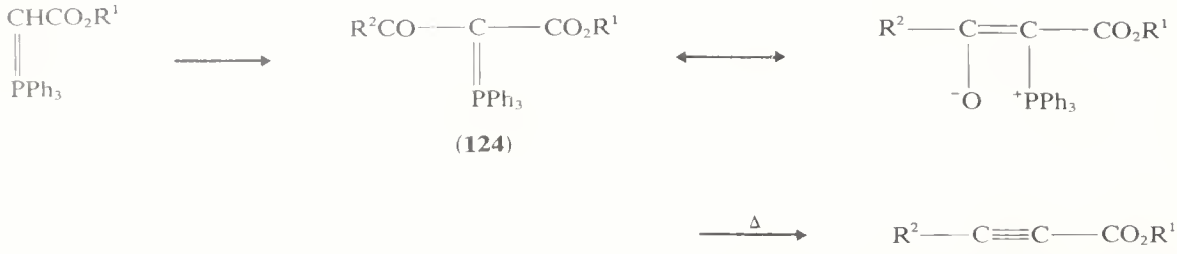
(**118**) (**119**) (47)

Acetylenic carbonyl compounds are produced[168] by fragmentation of hydrazones derived from α,β-epoxy ketones and certain 1-aminoaziridines, *e.g.* (**120**) → (**121**) in equation (48), and salts of α,β-unsaturated β-halo acids are smoothly converted[169] into acetylenes when heated in water, *e.g.* (**122**) → (**123**) in equation (49). Pyrolysis of alkoxycarbonylmethylenephosphoranes (**124**) provides[170] a useful synthesis of acetylenecarboxylic esters (equation 50).



(**120**) (**121**) (48)

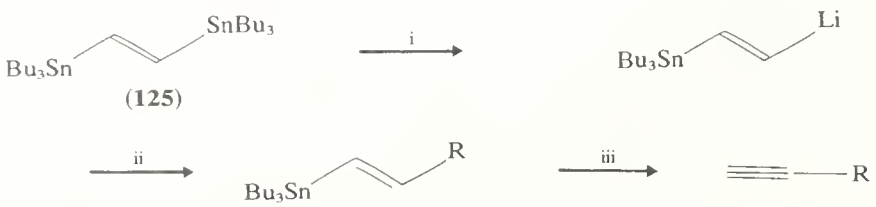
(**122**) (**123**) (49)



(124)

(50)

Terminal acetylenes are produced by sequential metallation and alkylation of 1,2-bis(tri-n-butylstannane)ethylene (**125**), following by unmasking of the acetylene by treatment with lead tetra-acetate (Scheme 19).[171]



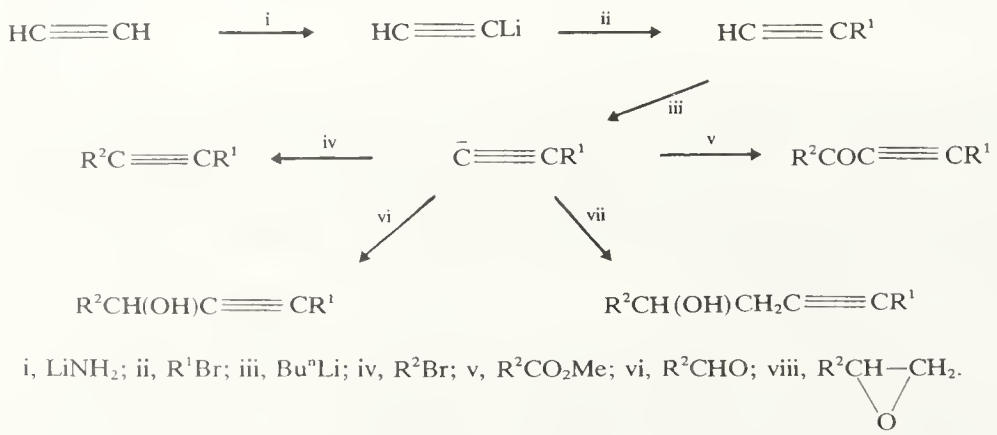
(125)

i, BuLi; ii, RX; iii, $Pb(OAc)_4$.

SCHEME 19

(*v*) *By substitutions using acetylides*

Monosodium or lithium acetylides are produced when acetylene gas is passed into a suspension of the corresponding alkali metal amide (prepared *in situ*) in liquid ammonia.[172–174] These derivatives then react with alkyl halides or sulphates, producing monosubstituted acetylenes (Scheme 20). The monosubstituted acetylenes can be metallated further and the resulting acetylides react with a variety of electrophilic reagents, producing a range of functionalized acetylenes (see Scheme 20).[172]



i, $LiNH_2$; ii, R^1Br; iii, Bu^nLi; iv, R^2Br; v, R^2CO_2Me; vi, R^2CHO; viii, $R^2CH{-}CH_2$ (O).

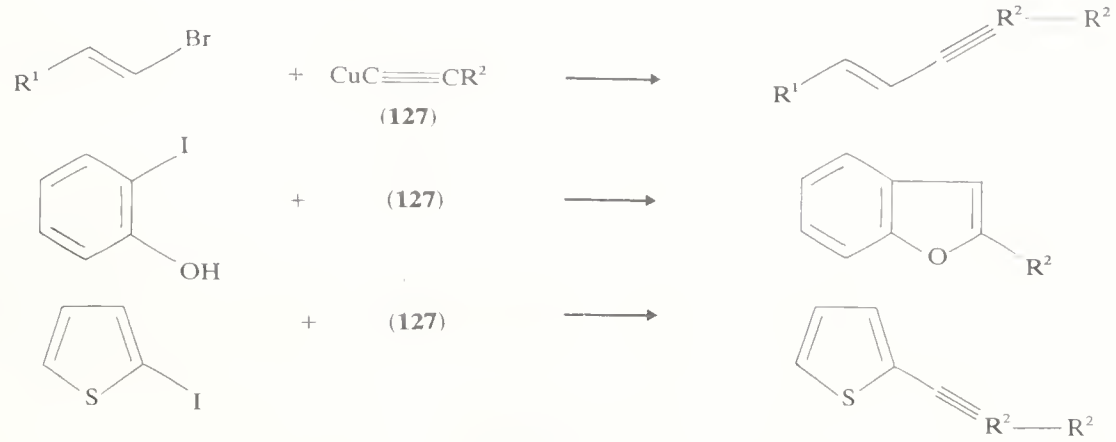
SCHEME 20

Lithium acetylides react with trialkylboranes, leading to trialkylalkynylborate anions (**126**); in the presence of iodine[175] or methanesulphinyl chloride[176] these transfer an alkyl group from boron, yielding alkyl acetylenes (equation 51). In a similar manner, the borate anion prepared from commercially available ($LiC{\equiv}CH)(NH_2CH_2CH_2NH_2$) gives rise to terminal acetylenes.[177]

(51)

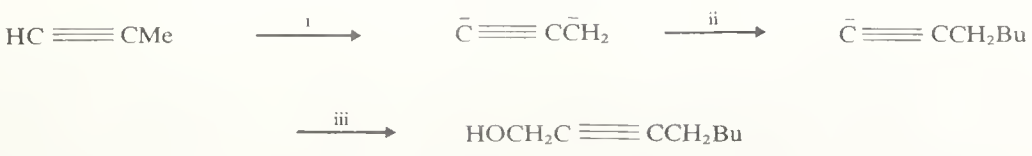
(**126**)

Acetylenic cuprous derivatives condense with vinyl, aryl (Castro–Stevens reaction), and acetylenic halides, leading to a range of functionalized acetylenes (Scheme 21),[178,179] and



SCHEME 21

in a 'one-pot' process, linear chain extensions at both termini of propyne can be carried out according to Scheme 22.[180]



i, BuLi; ii, BuBr; iii, CH_2O.

SCHEME 22

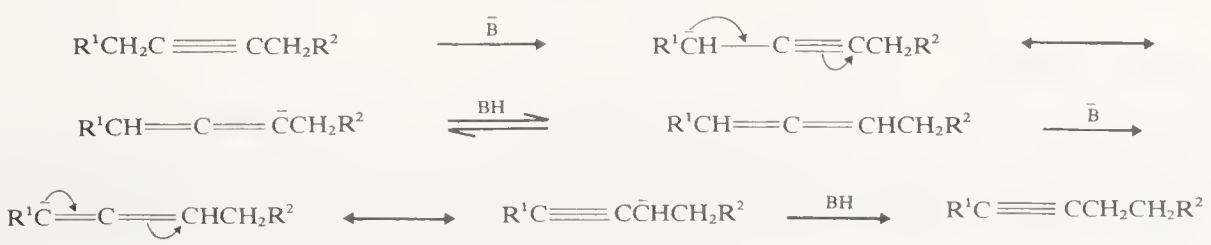
2.3.10 REACTIONS OF ACETYLENES

2.3.10.1 Chemical properties

Acetylene and alk-1-ynes show relatively strong acidity compared with alkenes and alkanes, and they readily produce salts with a variety of metals. Surprisingly, electrophilic additions to the acetylenic bond occur less readily than to olefinic bonds, whereas nucleophilic additions are relatively easy. Acetylenic compounds undergo a variety of interesting cycloaddition reactions, which are induced either thermally or photochemically.

2.3.10.2 Isomerizations

Unbranched acetylenes are isomerized smoothly in base *via* allene intermediates (Scheme 23).[181] The equilibrium is displaced by removal of the alk-1-yne as its Na or K salt derivative, and use of the base $KNH(CH_2)_3NH_2$, which has been termed the 'acetylene zipper', leads to virtually instantaneous migration of a triple bond from an internal to a terminal position.[182]

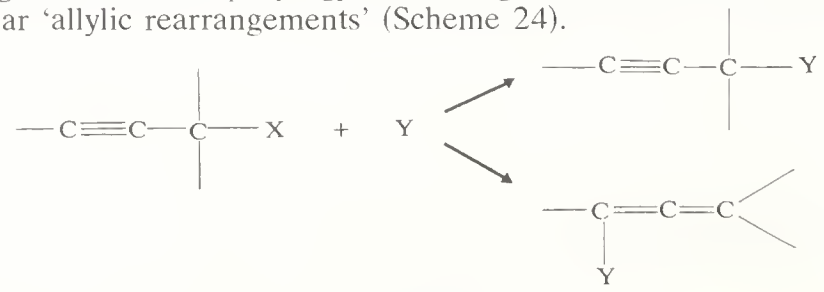


SCHEME 23

The base-catalysed isomerization–prototropic rearrangement of certain enynes leads to polyenes, and this approach has been employed in two syntheses of the naturally occurring polyene dicarboxylic acid corticrocin (**64**),[92] and of several other polyenes.[183]

2.3.10.3 Propargylic rearrangements

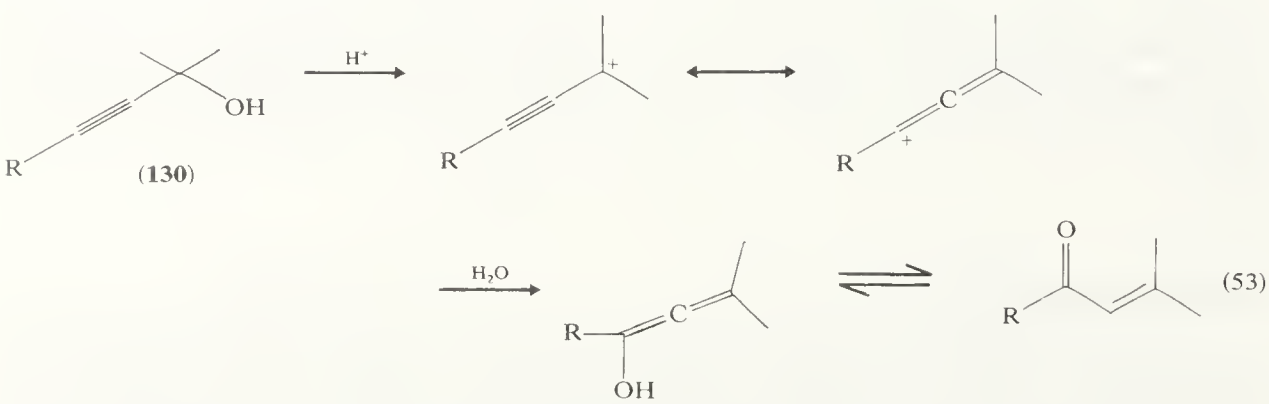
The base-catalysed acetylene–allene isomerization above is just one example of a general rearrangement termed 'propargylic rearrangements';[130,184] these are analogous to the more familiar 'allylic rearrangements' (Scheme 24).



SCHEME 24

Propargylic 'anionotropic' rearrangements take place under a variety of conditions and with various catalysts. Thus the propargyl chloride (**128**) is rearranged[185] to the allene (**129**) in the presence of cuprous chloride and ammonium chloride (equation 52), and propargyl alcohols (*e.g.* **130**) undergo 'Rupe'-type rearrangement in the presence of strong acids, leading[186] to α,β-unsaturated carbonyl compounds (equation 53).

(**128**) (**129**) (52)



(**130**) (53)

Propargyl halides and haloallenes react with metals, leading to organometallic compounds which, on further reaction, usually produce a mixture of acetylenic and allenic products.[186b]

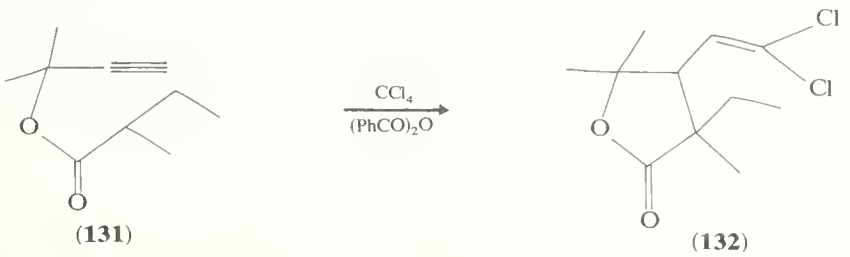
2.3.10.4 Additions

The addition of water to acetylene in the presence of a mercuric salt catalyst leads to acetaldehyde, an important industrial intermediate; hydration of mono- and di-substituted acetylenes produces ketones. Carboxylic acids also add to acetylenes, under mercuric ion catalysis, and the resulting enol acetates are easily hydrolysed to the corresponding ketones.[187]

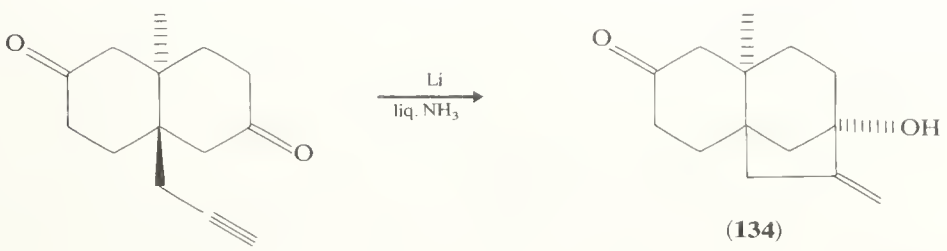
The alkali-catalysed addition of methanol to acetylenes leads to vinyl ethers. In a similar manner, thiols can be added to acetylenes, thiophens being produced from conjugated diacetylenes.[188]

Bromination of the triple bond gives first dihalides, and then the tetrahalides. Chlorine in solution in tetrachloroethane, and in the presence of $FeCl_3$, reacts with acetylene to produce a range of useful chlorinated hydrocarbons (*e.g.* $Cl_2C{=}CCl_2$) used as commercial solvents. Until recently the hydrochlorination of acetylene in the presence of mercuric chloride constituted an important industrial route to vinyl chloride.

Radical additions to triple bonds occur less readily than to alkenes,[189] but a number of intramolecular radical additions involving triple bonds are known and lead[190,191] to a range of interesting cyclic products, *e.g.* (**131**) → (**132**) and (**133**) → (**134**) in equations (54) and (55), respectively.



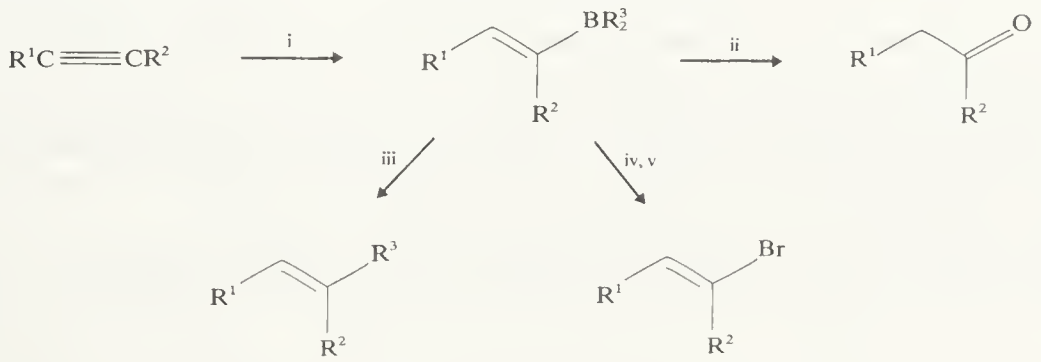
(**131**) (**132**) (54)



(**133**) (**134**) (55)

2.3.10.5 Hydroborations and hydroaluminations

Hydroboration of alk-1-ynes with $(Me_2Pr^iC)_2BH$, followed by oxidation with hydrogen peroxide, produces aldehydes. In a similar manner, the hydroboration–oxidation of disubstituted acetylenes leads to ketones, the direction of the initial boron–hydrogen addition being dependent on the size of the substituents.[192] Treatment of vinylboranes with NaOH and I_2 leads to alkenes,[193] whereas reaction with Br_2 and NaOMe constitutes a useful synthetic route to *cis*-vinyl halides (Scheme 25).[194]



i, R^3_2BH; ii, H_2O_2; iii, NaOH, I_2; iv, Br_2; v, NaOMe.

SCHEME 25

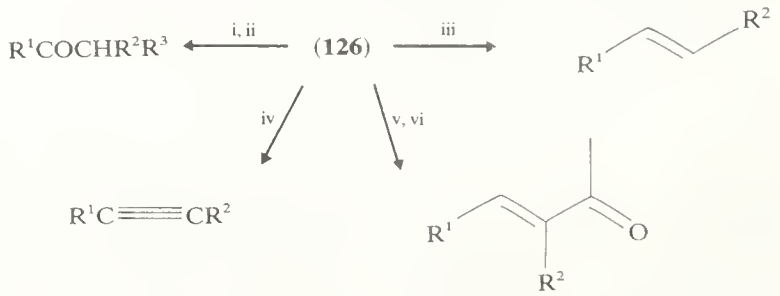
The hydroalumination of constitutionally unsymmetrical acetylenes can be directed to yield *cis* or *trans* addition products; the *cis* addition is promoted by the presence of an equivalent of tertiary amine.[195] Treatment of the resulting vinylalanes with acid leads to

olefins, whereas halogenation gives vinyl halides with preservation of the stereochemical integrity about the olefinic bonds; reaction with methyl-lithium, followed by carboxylation, produces α,β-unsaturated carboxylic acids.[196]

2.3.10.6 Substitutions

Alkali-metal acetylides are easily prepared from alk-1-ynes by treatment with the alkali metal amide in liquid ammonia; they are also prepared using lithium alkyls, and in some cases using dimsyl sodium ($MeSOCH_2Na$). The corresponding alkynylmagnesium halides are prepared by reaction with alkyl Grignard reagents. The metal acetylides are extremely valuable in synthesis and undergo a wide range of reactions with electrophilic reagents, leading to functionalized acetylenes (Scheme 20).[172]

The addition of lithium acetylides to trialkylboranes produces alkynyltrialkylborates, *e.g.* (**126**), which are useful precursors of a range of functional groups (Scheme 26).[197,198]



i, R^3X; ii, H_2O_2; iii, H^+; iv, I_2; v, MeCOCl; vi, CrO_3.

SCHEME 26

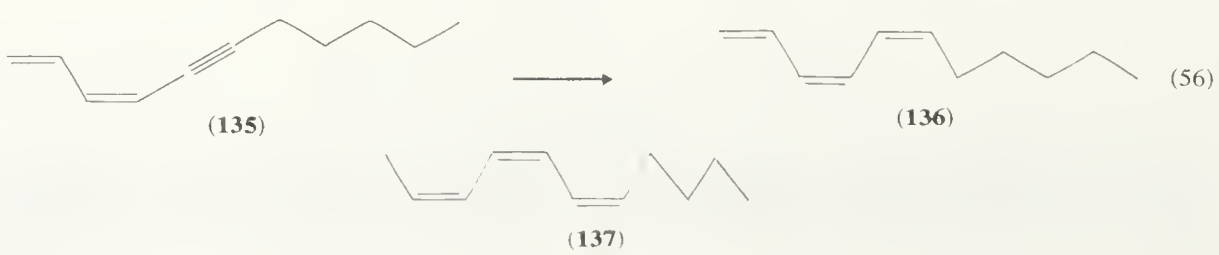
2.3.10.7 Reductions

Acetylenes are hydrogenated to *cis*-alkenes using a palladium/calcium carbonate catalyst treated with lead acetate (Lindlar catalyst); optimal selectivity is achieved by addition of quinoline or a sulphide.[199,200] Homogeneous hydrogenations in the presence of cationic rhodium complexes of the type $[Rh(norbornadiene)(PPhMe_2)_3]^+ ClO_4^-$ offer some advantages over the Lindlar-type heterogeneous systems,[201] and another useful alternative uses a particular nickel (P-2) catalyst prepared by simple reduction of Ni(II) acetate with $NaBH_4$ in ethanol in the presence of ethylenediamine.[202]

Providing attention is given to detail, the reduction of acetylenes, by $LiAlH_4$ in the presence of $TiCl_4$, can be controlled to produce largely *cis*-alkenes.[203] The preferential reduction of an internal triple bond in the presence of a terminal can be achieved when the latter is protected by trimethylsilylation.[204]

Disubstituted acetylenes are reduced to the corresponding *trans*-alkenes by dissolving metals (conveniently Na in liquid NH_3) and by reaction of the diorganoborane derivatives with alkaline $AgNO_3$.[205] The reduction of alk-1-yn-3-ols by $LiAlH_4$ proceeds *via* site-specific hydride transfer to C-2, leading to *trans*-alkene alcohols.[206]

Excess of zinc powder activated by potassium cyanide in n-propanol reduces (**135**) to (**136**) (equation 56), where all other procedures instead produce (**137**).[207]



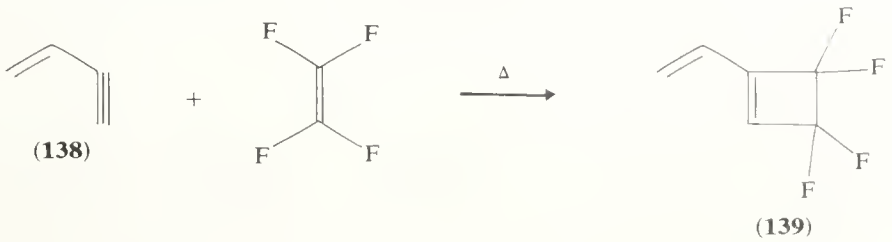
(56)

2.3.10.8 Oxidations

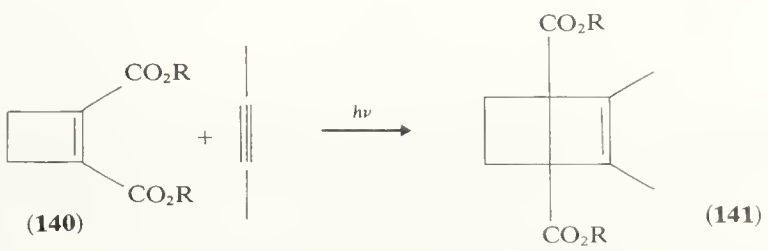
Acetylenes are less readily oxidized than alkenes. Internal acetylenes are oxidized to the corresponding α-diketones by RuO_4,[208] ozone, permanganate, and, in some cases, by *N*-bromosuccinimide in DMSO.[209] The allylic oxidation of acetylenes is rare, but conjugated ketones can be obtained from internal acetylenes by treatment with excess of Collins reagent;[210] terminal acetylenes are unreactive under these conditions. Alk-1-ynes are oxidatively coupled to diacetylenes (see Section 2.3.11).

2.3.10.9 Cycloadditions

Acetylenes undergo many types of cycloadditions and provide valuable starting materials for the synthesis of a range of carbo- and hetero-cyclic compounds.[211] Cycloadditions of alkenes to acetylenes can be brought about either thermally,[212] *e.g.* (**138**) → (**139**) in equation (57), photochemically,[213] *e.g.* (**140**) → (**141**) in equation (58), or in the presence of Lewis acids,[214] *e.g.* (**142**) → (**143**) in equation (59).



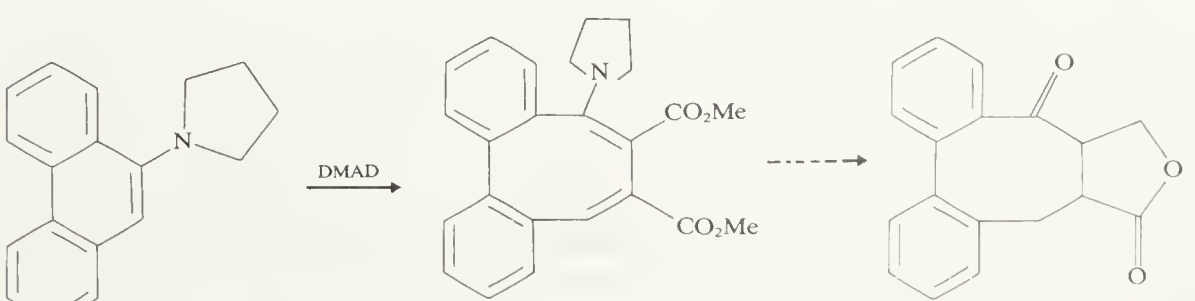
(**138**) (**139**) (57)



(**140**) (**141**) (58)

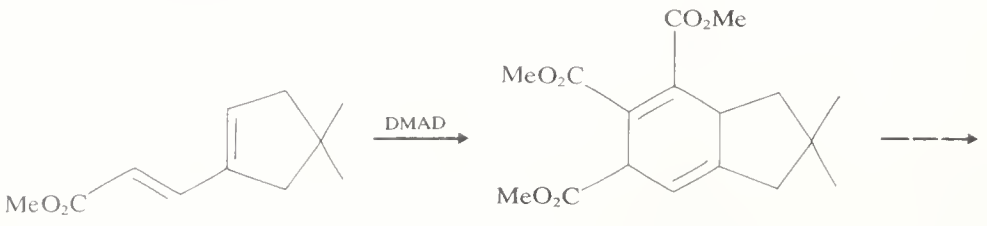
(**142**) (**143**) (59)

The reactions between enamines and acetylenecarboxylates produce cyclobutene intermediates which on heating lead to cyclic compounds resulting from a two-carbon ring expansion. This useful synthetic transformation has been employed[215] in a route to the analogue (**145**) of naturally occurring steganone starting from enamine (**144**) (equation 60).

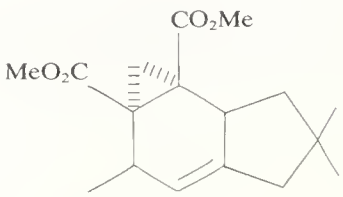


(**144**) (**145**) (60)

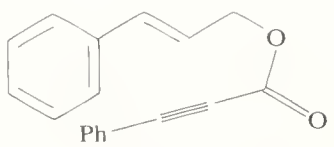
Acetylenes take part in the Diels–Alder reaction with a variety of dienes, leading to 1,4-dihydroaromatic derivatives, *e.g.* the synthesis of adduct (**146**) (equation 61), employed in a synthesis of the marasmic acid skeleton.[216] The intramolecular variant of the Diels–Alder reaction employing acetylenic dienophiles is also widely applied in synthesis, *e.g.* the preparation[217] of the phenolic cyclolignan lactone (**148**) from cinnamyl phenylpropiolate (**147**) (equation 62).



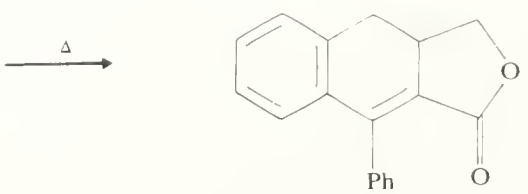
(**146**)



(61)



(**147**)



(**148**)

(62)

A number of five-ring heterocycles can be formed by cycloadditions of 1,3-dipolar species to acetylenes,[211] *e.g.* pyrazoles from diazomethane, triazoles from azides, and isoxazoles from nitrile oxides, *e.g.* (**149**) → (**150**)[211,218,219] in equation (63).

(**149**) (**150**)

(63)

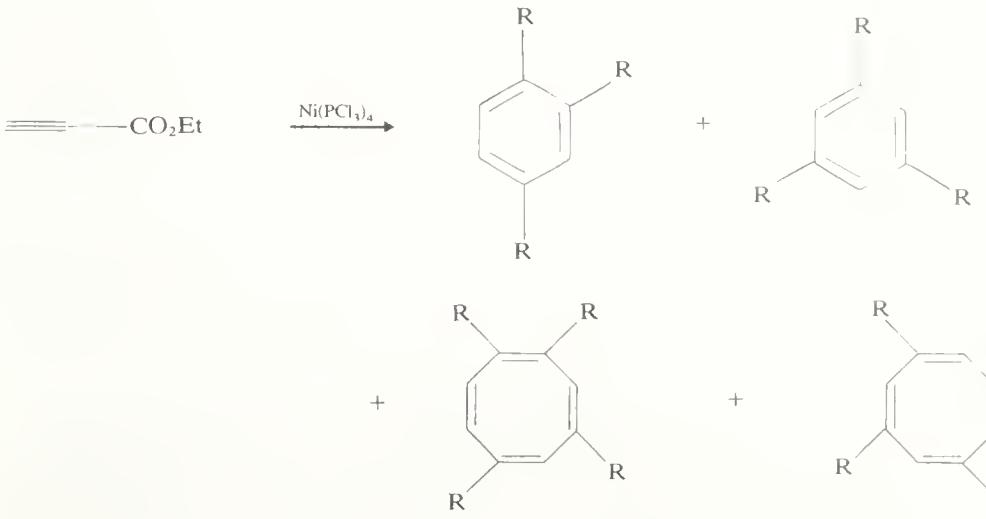
The addition of carbenes to acetylenes in many cases leads to cyclopropenes, *e.g.* the synthesis of the naturally occurring cyclopropene sterculic acid,[220] but can also give rise to bicyclobutanes and to products from C—H insertion reactions in the case of terminal acetylenes.

2.3.10.10 Metal-catalysed reactions

The metal-catalysed oligomerization reactions of acetylenes lead to a variety of structurally novel and chemically interesting compounds.[221] Oligomerization of acetylene itself in the presence of $Ni(CN)_2$ leads to 70% cyclo-octatetraene in addition to polyenes and cyclic trimers.[222] Monosubstituted acetylenes give rise to a complex mixture of isomeric cyclo-octatetraenes and aromatic compounds (Scheme 27),[223] whereas diacetylenes can be cyclotrimerized to (**151**) in high yield using $Ni(CO)_2(PPh_3)_2$[224] (equation 64).

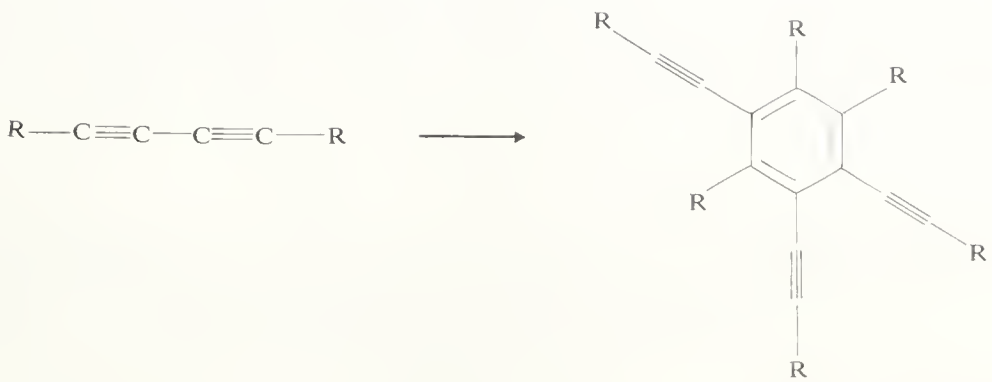
Terminal diacetylenes react[225] with a cobalt catalyst to give trimers of the type (**152**) (equation 65) and they co-dimerize with disubstituted acetylenes in a useful general synthesis of indans and tetralin.[226]

Deca-2,8-diyne and cyclohexene when heated in the presence of the catalyst



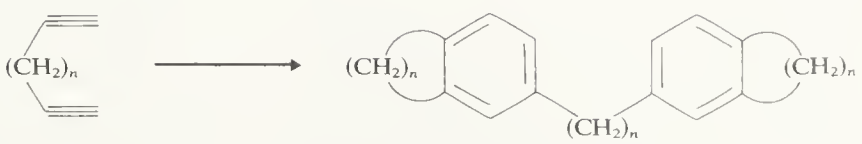
(R = CO_2Et)

SCHEME 27



(64)

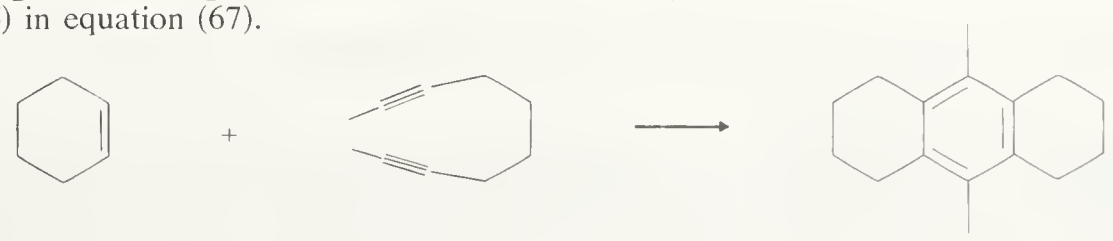
(**151**)



(65)

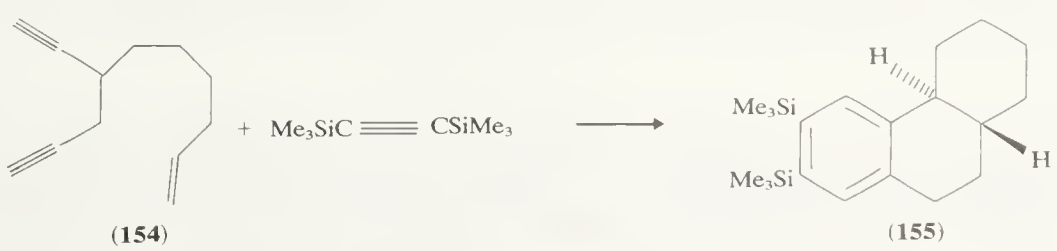
(**152**)

$[(C_2H_4)_2RhCl]_2$ produce[227] octahydroanthracene (**153**) (equation 66), and the *in situ* generation and intramolecular trapping of *o*-xylxylenes by cobalt-catalysed acetylene co-oligomerization gives[228] a convenient two-stage synthesis of carbocycles, *e.g.* (**154**) → (**155**) in equation (67).



(66)

(**153**)



(67)

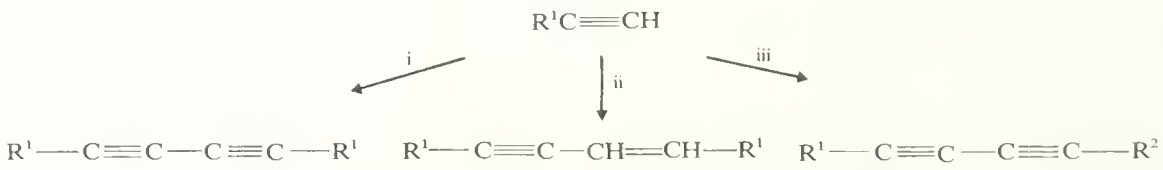
(**154**) (**155**)

The acetylenic bond can be 'protected' by preparing the corresponding dicobalt hexacarbonyl complex. These complexes are stable under a variety of conditions and the acetylene group is conveniently regenerated by mild oxidation with cerium(IV) salts.[229]

2.3.11 POLYACETYLENES

A number of conjugated polyacetylenes have been isolated from members of the *Compositae* during the past two decades (see Section 2.3.12).[152] Almost without exception their syntheses have been accomplished *via* the oxidative coupling of terminal acetylenes as a key stage.

The oxidative coupling of alk-1-ynes to symmetrical conjugated diynes can be achieved in a number of ways.[178,230] In the Glaser coupling, a cuprous derivative is first prepared *in situ* from the acetylene and a cuprous salt, which is then oxidized using either oxygen, potassium ferricyanide, or hydrogen peroxide. The coupling reaction is accelerated enormously by the addition of *N,N,N′,N′*-tetramethylethylene diamine[231] and yields are improved considerably by using dimethoxyethane as solvent.[232] The same coupling is more readily accomplished when the acetylene is simply warmed in anhydrous pyridine solution to 60–70 °C with excess of cupric acetate (Eglinton modification). In acidic media the acetylenes couple to give conjugated enynes (Straus coupling) (Scheme 28).



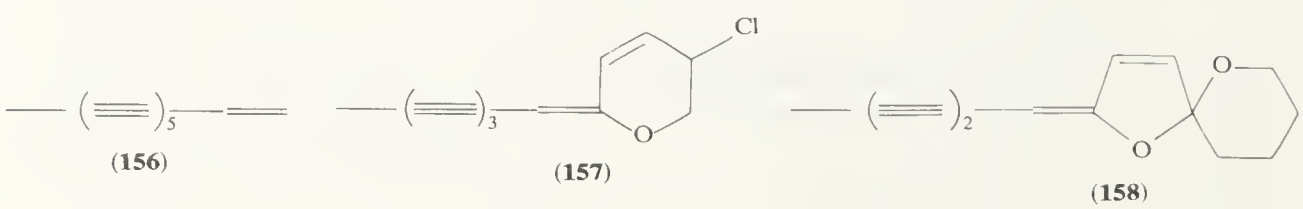
i, Cu^+, oxidation; ii, Cu^+, H^+; iii, $BrC{\equiv}CR^2$, Cu^+, amine.

SCHEME 28

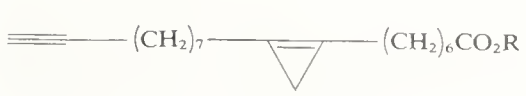
The Glaser coupling reaction is not usually satisfactory for the synthesis of constitutionally unsymmetrical diynes because of the simultaneous formation of constitutionally symmetrical diynes. Constitutionally unsymmetrical diynes are most conveniently prepared by the Cadiot–Chodkiewicz coupling whereby a haloacetylene is reacted with a terminal acetylene in the presence of a cuprous salt and a suitable amine (Scheme 28). The trimethylsilyl protecting group is especially suitable in the synthesis of terminal diynes by this reaction.[233] Both constitutionally symmetrical and unsymmetrical diynes are prepared by the reaction of lithium dialkyldialkynylboranes, $Li^+[R^1_2B(C{\equiv}CR^2)_2]^-$, with iodine.[234]

2.3.12 NATURALLY OCCURRING ACETYLENES AND POLYACETYLENES

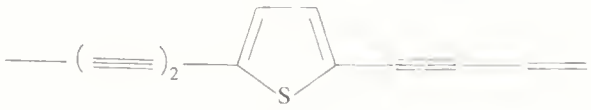
Acetylenes and polyacetylenes are widely distributed in higher plants and in microorganisms.[152,235] The degree of unsaturation ranges from simple monoacetylenes to pentaynes; very often vinyl end-groups are present, while in a few cases the free acetylenic group forms the end of the molecule. The variation in the ring systems is extensive and some representative examples are shown in formulae (**156**)–(**161**).



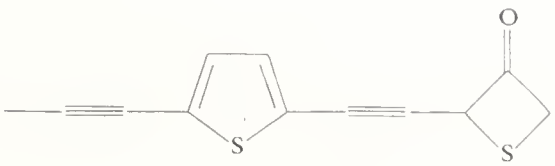
(**156**) (**157**) (**158**)



(159)

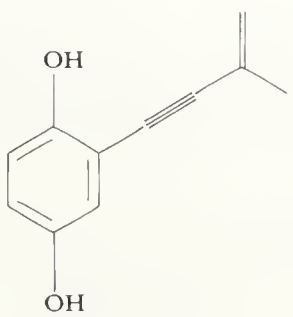


(160)

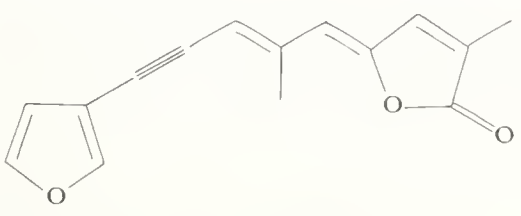


(161)

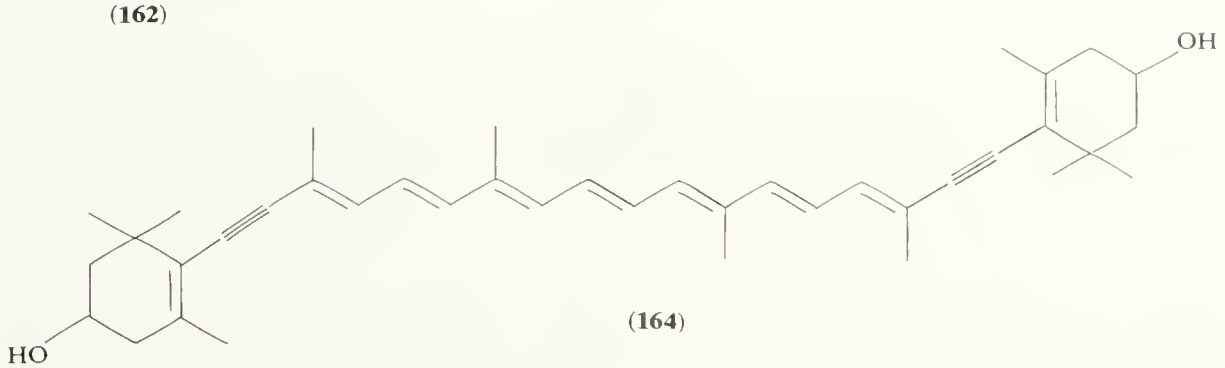
Freelingyne (**163**) was the first acetylenic terpene to be found in Nature.[236] Other representative acetylenic terpenes include the hydroquinone derivative (**162**) from the fungus *Helminthosporium siccans*[237] and the carotenoid alloxanthin (**164**) isolated from algae and marine organisms.[149]



(162)



(163)



(164)

2.3.13 CONJUGATED ENYNES

2.3.13.1 Preparation of conjugated enynes

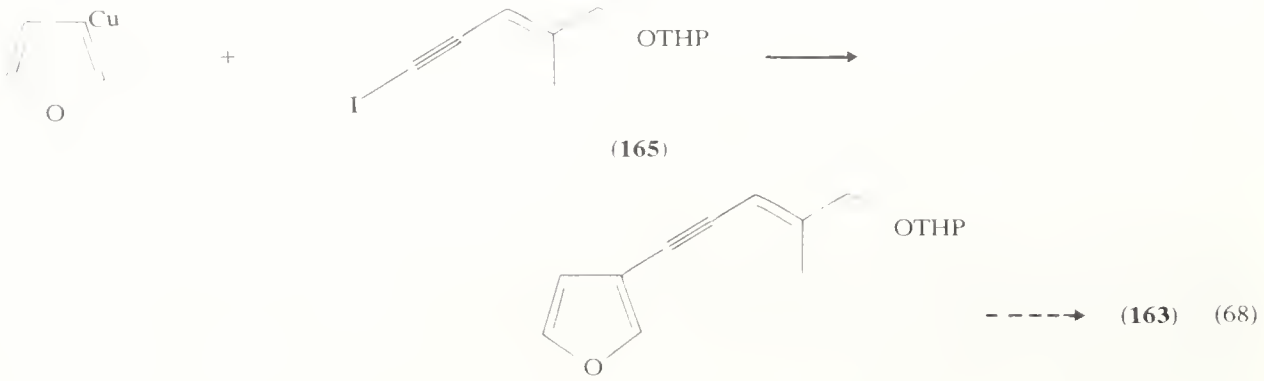
(i) From conjugated diynes

Mono-hydroboration of constitutionally symmetrical conjugated diynes using disiamylborane, followed by protonolysis of the intermediate vinylborane, leads to the corresponding *cis*-enynes in high yield.[8] Terminal *cis*-enynes are obtained by the selective hydrogenation of terminal diynes protected as their trimethylsilyl derivatives;[204b] the reduction of terminal diynes using sodium in liquid ammonia produces *trans*-enynes.[205a]

(ii) By coupling reactions of acetylenic with vinylic systems

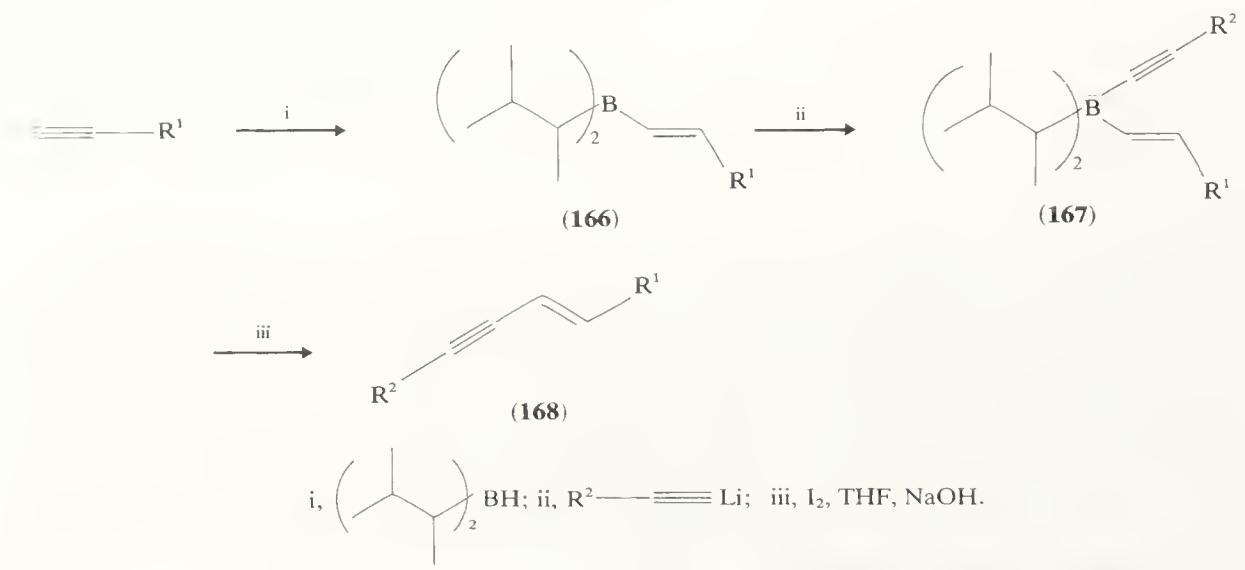
The coupling of acetylenic Grignard reagents with vinyl halides in the presence of cobalt chloride leading to enynes has been known for a long time.[238,239] In more recent years, the scope of this approach to enynes has been widened with the use of *cis*- and

trans-vinyl copper reagents, which are shown to couple with 1-haloalkynes under mild conditions, leading to constitutionally homogeneous *cis*- and *trans*-enynes.[240] The coupling reaction between 2-furylcopper and the iodoacetylene (**165**) provided a key reaction in the recently described[236b] synthesis of the sesquiterpene freelingyne (**163**) (equation 68).



(68)

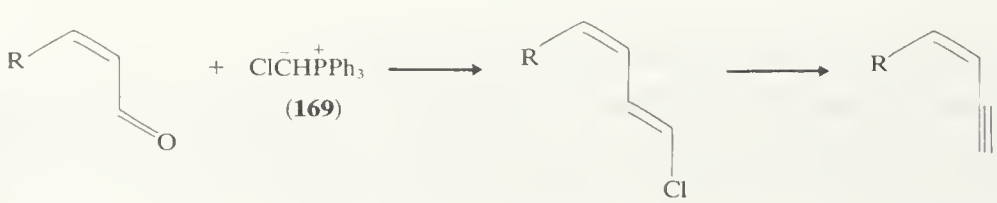
The reaction of lithium acetylides with vinyldialkylboranes (**166**) produces intermediate vinyldialkylalkynylborates, *viz.* (**167**), which on subsequent treatment with iodine and sodium hydroxide give rise to enynes (**168**) by migration of the vinyl group from boron to the acetylenic carbon (Scheme 29).[241]



SCHEME 29

(*iii*) *By the Wittig reaction*

Wittig reactions between aldehydes and the phosphonium salt from propargyl bromide at −50 °C in liquid ammonia produce largely *cis*-enynes,[242] whereas use of the trimethylsilyl-protected phosphonium salt and butyl-lithium as base leads to the corresponding *trans*-enyne.[242] *cis*-Enynes are also produced[243] by Wittig condensation between *cis*-α,β-unsaturated aldehydes and the ylide (**169**) followed by dehydrochlorination (equation 69).

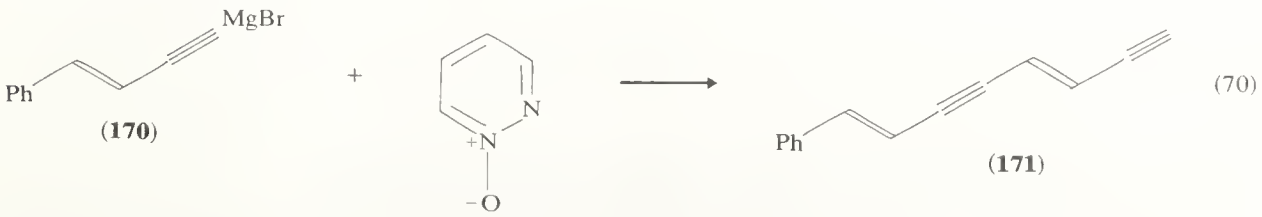


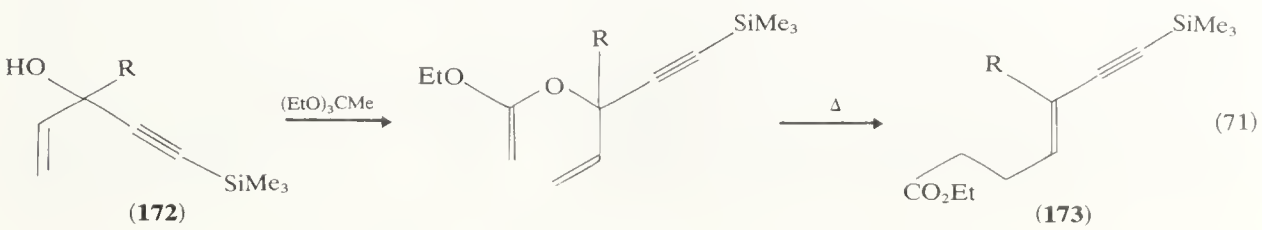
(69)

(iv) Other methods

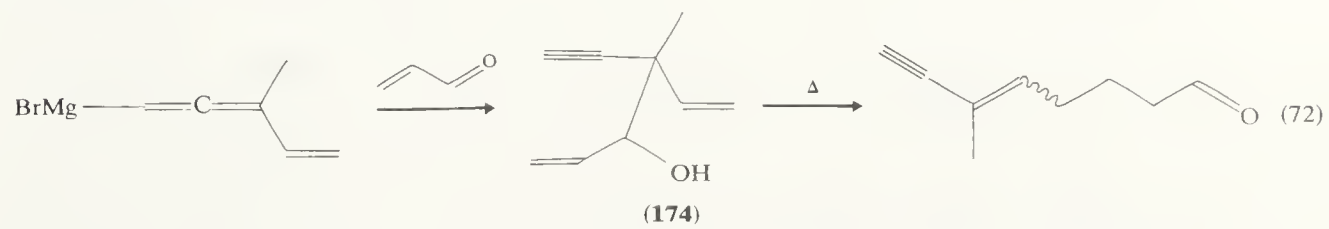
The coupling of terminal acetylenes in acetic acid in the presence of a cuprous salt leads to enynes (Straus coupling); vinylacetylene is manufactured on a large scale from acetylene by this procedure. A number of enynes can be prepared by dehydration of β-hydroxyacetylenes, themselves easily available from reaction of acetylides with epoxides. The dehydration of α-hydroxyacetylenes also produces conjugated enynes, and, in some cases, the dehydrohalogenation of unsaturated dihalides has provided a useful method for the preparation of simple enynes, *e.g.* the preparation of vinylacetylene from butadiene.

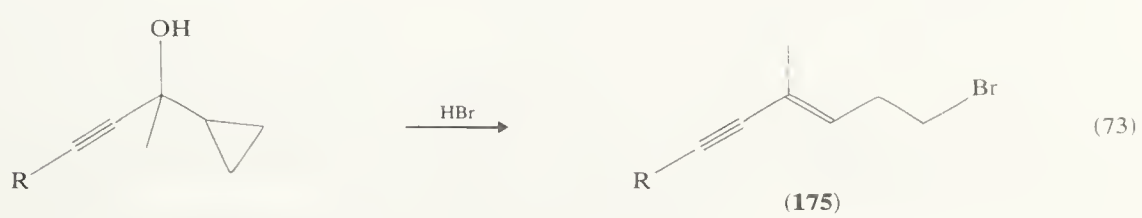
Grignard reagents react with pyridazine 1-oxide to produce terminal enynes[244], *e.g.* (**170**) → (**171**)[245] in equation (70), and the orthoester Claisen rearrangement of alkynyl allylic alchohols has been shown to lead to *trans*-enynes, *e.g.* (**172**) → (**173**)[246] in equation (71).





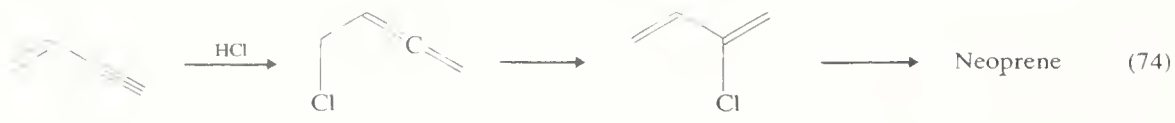
Mixtures of *cis*- and *trans*-enynes are obtained *via* the Cope rearrangement of dienynols (**174**)[247] (equation 72), whereas *trans*-enynes of type (**175**) are produced when α-cyclopropylacetylenic carbinols are treated with $HBr–ZnBr_2$ in the presence of dicobalt octacarbonyl[229] (equation 73).





2.3.14 REACTIONS OF CONJUGATED ENYNES

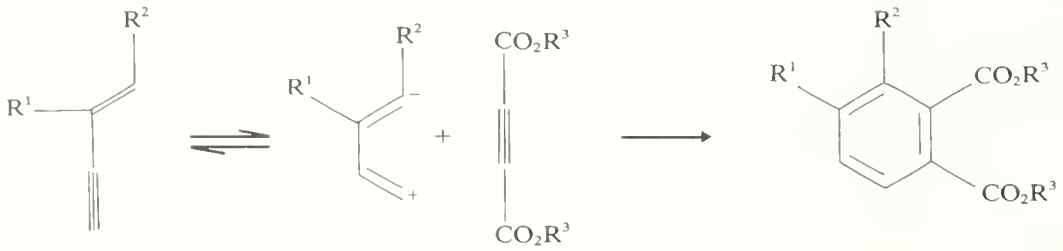
Conjugated enynes display reactivity characteristic of both alkenes and acetylenes. Thus, the double bond is preferentially attacked by peroxy acids, and hydrations in the presence of mercuric salts lead to methyl vinyl ketones. Vinylacetylene undergoes 1,4-addition of hydrogen chloride, leading to the allene (**176**) which readily rearranges to give 2-chlorobuta-1,3-diene, the monomer for neoprene (equation 74).



(74)

(176)

Diels–Alder reactions between conjugated enynes and dienophiles are accompanied by hydride shifts and may proceed *via* zwitterionic dienes of the type (**177**) (equation 75).



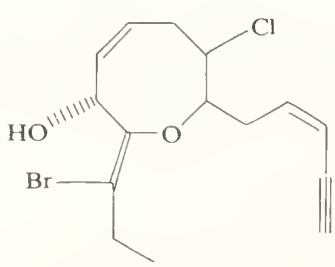
(75)

(177)

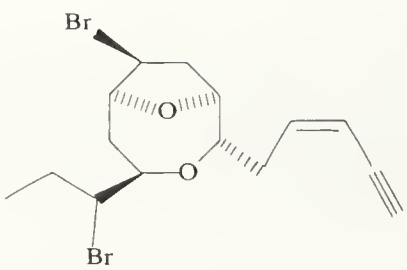
2.3.15 NATURALLY OCCURRING CONJUGATED ENYNES

A number of novel enyne cyclic bromoethers have been found in seaweed *Laurencia* in the past few years, *e.g.* (**178**)–(**180**),[235,248] and more recently structurally related compounds, *e.g.* (**181**), have been isolated from the sea hare *Aplysia*;[249] the latter compounds undoubtedly come from the algae on which the mollusc feeds.

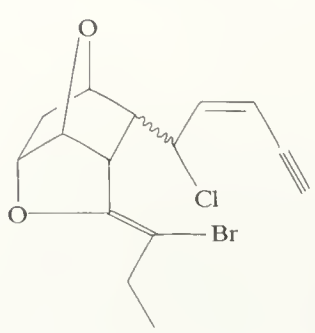
The enyne isohistrionicotoxin (**109**) and related metabolites are found in skin of the arrow poison frog *Dendrobates histrionicus*,[150] and several enynes accompany polyacetylenes and allenes in *Compositae*.[152]



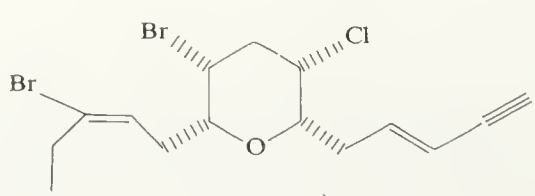
(178)



(179)



(180)



(181)

References

1. 'Our Industry Petroleum', British Petroleum, London, 1970.
2. R. F. Garwood, 'Unsaturated Acyclic Hydrocarbons', in 'Rodd's Chemistry of Carbon Compounds', 2nd edn., ed. S. Coffey, Elsevier, Amsterdam, 1964, vol. IA.

3. 'Methods in Organic Chemistry', vol. 5, part 1d, 'Open chain and cyclic polyenes, enynes', 4th edn., in 'Methoden der Organischen Chemie (Houben-Weyl)', ed. E. Muller, Thieme, Stuttgart, 1973.
4. M. Cais, 'Conjugated Dienes', in 'The Chemistry of Alkenes', ed. S. Patai, Interscience, New York, 1964.
5. 'Aliphatic Chemistry', Specialist Periodical Reports, The Chemical Society, London, 1971–1977, vols. 1–5.
6. 'General and Synthetic Methods', Specialist Periodical Report, The Chemical Society, London, 1977, vol. 1.
7. D. Holme, E. R. H. Jones, and M. C. Whiting, *Chem. and Ind. (London)*, 1956, 928.
8. G. Zweifel and N. L. Polston, *J. Amer. Chem. Soc.*, 1970, **92,** 4068.
9. Kh. V. Balyan, A. A. Petrov, and Yu. I. Porfiryeva, *Zhur. obshchei Khim.*, 1957, **27,** 365.
10. *K. Eiter, Fortsch. Chem. Forsch.*, 1970, **28,** 204 and refs. therein.
11. G. Wilke and H. Muller, *Annalen*, 1960, **629,** 222.
12. G. Zweifel and R. L. Miller, *J. Amer. Chem. Soc.*, 1970, **92,** 6678.
13. Y. Yamamoto, H. Yatagai, and I. Moritani, *J. Amer. Chem. Soc.*, 1975, **97,** 5606.
14. G. Zweifel, N. L. Polston, and C. C. Whitney, *J. Amer. Chem. Soc.*, 1968, **90,** 6243.
15. E. Negishi and T. Yoshida, *J.C.S. Chem. Comm.*, 1973, 606.
16. R. C. Larock, *J. Org. Chem.*, 1976, **41,** 2241.
17. (a) H. C. Brown, T. Hamaoka, and N. Ravindran, *J. Amer. Chem. Soc.*, 1973, **95,** 5786, 6456; (b) G. Zweifel and C. C. Whitney, *ibid.*, 1967, **89,** 2753; (c) J. F. Normant, C. Chuit, G. Cahiez, and J. Villieras, *Synthesis*, 1974, 803.
18. M. F. Semmelhack, P. M. Helquist, and J. D. Gorzynski, *J. Amer. Chem. Soc.*, 1972, **94,** 9234.
19. G. M. Whitesides and C. P. Casey, *J. Amer. Chem. Soc.*, 1966, **88,** 4541.
20. T. Cohen and T. Poeth, *J. Amer. Chem. Soc.*, 1972, **94,** 4363.
21. G. Cahiez, D. Bernard, and J. F. Normant, *Synthesis*, 1976, 245; *J. Organometallic Chem.*, 1976, **113,** 99; J. F. Normant, G. Cahiez, C. Chuit, and J. Villieras, *ibid.*, 1974, **77,** 269.
22. R. B. Banks and H. M. Walborsky, *J. Amer. Chem. Soc.*, 1976, **98,** 3732.
23. E. I. Negishi and S. Baba, *J.C.S. Chem. Comm.*, 1976, 596; *J. Amer. Chem. Soc.*, 1976, **98,** 6729.
24. H. A. Dieck and R. F. Heck, *J. Org. Chem.*, 1975, **40,** 1083.
25. E. J. Corey, C. U. Kim, R. H. K. Chen and M. Takeda, *J. Amer. Chem. Soc.*, 1972, **94,** 4395.
26. F. Naf and P. Degen, *Helv. Chim. Acta*, 1971, **54,** 1939.
27. H. von Brachel and U. Bahr, in 'Methoden der Organischen Chemie (Houben-Weyl)', Thieme, Stuttgart, 1970, vol. 5, p. 590.
28. I. T. Harrison and B. Lythgoe, *J. Chem. Soc.*, 1958, 843.
29. L. Barlow and G. Pattenden, *J.C.S. Perkin I*, 1976, 1029.
30. B. Lythgoe, T. A. Moran, M. E. N. Nambudiry, and S. Ruston, *J.C.S. Perkin I*, 1976, 2386 and refs. therein.
31. G. Pattenden and B. C. L. Weedon, *J. Chem. Soc. (C)*, 1968, 1984, and refs. therein.
32. A. H. Davidson and S. Warren, *J.C.S. Perkin I*, 1976, 639.
33. L. Crombie, P. Hemesley, and G. Pattenden, *J. Chem. Soc. (C)*, 1969, 1016.
34. A. Butenandt, E. Hecker, M. Hopp, and W. Koch, *Annalen*, 1962, **658,** 39.
35. G. Egloff and G. Hulla, *Chem. Rev.*, 1945, **36,** 63.
36. C. W. Spangler and T. W. Hartford, *Synthesis*, 1976, 108.
37. M. R. Short, *J. Org. Chem.*, 1972, **37,** 2201.
38. A. Rüttimann, A. Wick, and A. Eschenmoser, *Helv. Chim. Acta*, 1975, **58,** 1450.
39. (a) W. G. Dauben, D. J. Hart, J. Ipaktschi, and A. P. Kozikowski, *Tetrahedron Letters*, 1973, 4425; (b) F. Bohlmann and C. Zdero, *Chem. Ber.*, 1973, **106,** 3779.
40. P. L. Fuchs, *Tetrahedron Letters*, 1974, 4055.
41. F. Jung, M. Molin, R. Van Den Elzen, and T. Durst, *J. Amer. Chem. Soc.*, 1974, **96,** 935.
42. S. D. Turk and R. L. Cobb, in '1,4-Cycloaddition Reactions', ed. J. Hamer, Academic, New York, 1967.
43. B. F. Nesbitt, P. S. Beevor, R. A. Cole, R. Lester and R. G. Poppi, *Tetrahedron Letters*, 1973, 4669; *Nature New Biol.*, 1973, **244,** 208.
44. D. Bellus and C. D. Weis, *Tetrahedron Letters*, 1973, 999.
45. G. O. Schenk, W. Hartmann and R. Steinmetz, *Chem. Ber.*, 1963, **96,** 498.
46. *e.g.* C. A. Coulson, 'Valence', Oxford University Press, 1965.
47. M. S. Kharasch, E. T. Margolis and F. R. Mayo, *J. Org. Chem.*, 1937, **1,** 393.
48. W. G. Young, R. L. Meier, J. Vinograd, H. Bollinger, L. Kaplan, and S. L. Linden, *J. Amer. Chem. Soc.*, 1947, **69,** 2046.
49. E. N. Frankel and R. O. Butterfield, *J. Org. Chem.*, 1969, **34,** 3930.
50. K. Kawakami, T. Mizoroki and A. Ozaki, *Chem. Letters*, 1976, 847.
51. N. L. Bauld, *J. Amer. Chem. Soc.*, 1962, **84,** 4347.
52. G. Zweifel, K. Nagase, and H. C. Brown, *J. Amer. Chem. Soc.*, 1962, **84,** 183, 190.
53. H. C. Brown and E. Negishi, *J. Amer. Chem. Soc.*, 1967, **89,** 5477; *Chem. Comm.*, 1968, 594.
54. H. Wollweber, 'Diels–Alder Reactions', Thieme, Stuttgart, 1972
55. A. S. Onischenko, 'Diene Synthesis', Davey, New York, 1964.
56. W. Carruthers, in 'Some Modern Methods of Organic Synthesis', Cambridge University Press, 1971.
57. J. Sauer, *Angew. Chem. Internat. Edn.*, 1966, **5,** 211.
58. S. Ranganathan, D. Ranganathan and A. K. Mehrotra, *J. Amer. Chem. Soc.*, 1974, **96,** 5261.
59. W. G. Dauben and A. P. Kozikowski, *J. Amer. Chem. Soc.*, 1974, **96,** 3664.

60. W. G. Dauben and H. O. Krabbenhoft, *J. Amer. Chem. Soc.*, 1976, **98,** 1992.
61. (a) S. Danishefsky and T. Kitahara, *J. Amer. Chem. Soc.*, 1974, **96,** 7807; *J. Org. Chem.*, 1975, **40,** 538; (b) S. Danishefsky, R. McKee, and R. K. Singh, *ibid.*, 1976, **41,** 2934.
62. B. M. Trost and A. J. Bridges, *J. Amer. Chem. Soc.*, 1976, **98,** 5017.
63. I. Fleming and A. Percival, *J.C.S. Chem. Comm.*, 1976, 681; M. J. Carter and I. Fleming, *ibid.*, 1976, 679.
64. (a) T. Cohen, A. J. Mura, D. W. Shull, E. R. Fogel, R. J. Ruffner, and J. R. Falck, *J. Org. Chem.*, 1976, **41,** 3218; (b) M. E. Jung and C. A. McCombs, *Tetrahedron Letters*, 1976, 2935.
65. J. W. Cornforth, B. V. Milborrow, and G. Ryback, *Nature*, 1965, **206,** 715.
66. E. Demole, C. Demole, and D. Berthet, *Helv. Chim. Acta*, 1973, **56,** 265.
67. R. G. Carlson, *Ann. Reports Medicin. Chem.*, 1974, **9,** 270.
68. W. Oppolzer, R. Achini, E. Pfenninger, and H. P. Weber, *Helv. Chim. Acta*, 1976, **59,** 1186.
69. T. Kametani, H. Nemoto, and K. Fukumoto, *J.C.S. Chem. Comm.*, 1976, 400.
70. G. Fráter, *Tetrahedron Letters*, 1976, 4517.
71. J. Auerbach and S. M. Weinreb, *J. Org. Chem.*, 1975, **40,** 3311.
72. W. C. Herndon, *Chem. Rev.*, 1972, **72,** 157.
73. R. B. Woodward and R. Hoffmann, *Angew. Chem. Internat. Edn.*, 1969, **8,** 781.
74. P. C. Jain, Y. N. Mukerjee, and N. Anand, *J. Amer. Chem. Soc.*, 1974, **96,** 2996.
75. (a) Z. Stojanac, R. A. Dickinson, N. Stojanac, R. J. Woznow, and Z. Valenta, *Canad. J. Chem.*, 1975, 616; (b) N. Stojanac, A. Sood, Z. Stojanac and Z. Valenta, *ibid.*, 1975, 619.
76. K. N. Houk and R. W. Strozier, *J. Amer. Chem. Soc.*, 1973, **95,** 4094.
77. N. T. Anh and J. Seyden-Penne, *Tetrahedron*, 1973, **29,** 3259.
78. P. V. Alston and R. M. Ottenbrite, *J. Org. Chem.*, 1975, **40,** 1111.
79. (a) D. H. R. Barton, A. A. L. Gunatilaka, T. Nakanishi, H. Patin, D. A. Widdowson, and B. R. Worth, *J.C.S. Perkin I*, 1976, 821; (b) D. H. R. Barton and H. Patin, *ibid.*, 1976, 829.
80. (a) E. J. Corey and G. Moinet, *J. Amer. Chem. Soc.*, 1973, **95,** 7185; (b) C. P. Casey and C. R. Cyr, *ibid.*, 2248.
81. T. H. Whitesides, R. W. Arhart, and R. W. Slaven, *J. Amer. Chem. Soc.*, 1973, **95,** 5792.
82. A. J. Pearson, *Tetrahedron Letters*, 1975, 3617.
83. G. S. Hammond, N. J. Turro, and R. S. H. Liu, *J. Org. Chem.*, 1963, **28,** 3297.
84. (a) R. H. S. Liu and G. S. Hammond, *J. Amer. Chem. Soc.*, 1964, **86,** 1892; (b) K. J. Crowley, *Proc. Chem. Soc.*, 1962, 334.
85. M. Elliott, *J. Chem. Soc.*, 1964, 888.
86. M. J. Devos, L. Hevesi, P. Bayet, and A. Krief, *Tetrahedron Letters*, 1976, 3911; M. Sevrin, L. Hevesi, and A. Krief, *ibid.*, 1976, 3915.
87. C. A. Bertelo and J. Schwartz, *J. Amer. Chem. Soc.*, 1976, **98,** 262.
88. J. P. Neilan, R. M. Laine, N. Cortese, and R. F. Heck, *J. Org. Chem.*, 1976, **41,** 3455.
89. W. E. Billups, J. H. Cross, and C. V. Smith, *J. Amer. Chem. Soc.*, 1973, **95,** 3438.
90. G. Pattenden, *J. Chem. Soc.* (*C*), 1970, 1404.
91. H. Achenbach and J. Witzke, *Angew. Chem. Internat. Edn.*, 1977, **16,** 191.
92. (a) B. L. Shaw and M. C. Whiting, *J. Chem. Soc.*, 1954, 3217; (b) B. C. L. Weedon, *Chem. and Ind.* (*London*), 1953, 1388.
93. J. N. Labovitz, C. A. Henrick, and V. L. Corbin, *Tetrahedron Letters*, 1975, 4209.
94. K. Mori, *Tetrahedron*, 1974, **30,** 3807.
95. R. G. Riley, R. M. Silverstein, J. A. Katzenellenboger, and R. S. Lenox, *J. Org. Chem.*, 1974, **39,** 1957.
96. L. Crombie, *J. Chem. Soc.*, 1955, 999.
97. J. I. Okogun and D. E. U. Ekong, *J.C.S. Perkin I*, 1974, 2195.
98. 'Pyrethrum, the Natural Insecticide', ed. J. E. Casida, Academic, New York 1973.
99. D. Marshall and M. C. Whiting, *J. Chem. Soc.*, 1957, 537; J. Gripenberg, *Acta Chem. Scand.*, 1952, **6,** 580.
100. A. G. Andrews, C. L. Jenkins, M. P. Starr, J. Shepherd, and H. Hope, *Tetrahedron Letters*, 1976, 4023.
101. H. Fischer, in 'The Chemistry of Alkenes', ed. S. Patai, Interscience, New York, 1964.
102. P. Cadiot, W. Chodkiewicz and J. Rauss-Godineau, *Bull. Soc. chim. France*, 1961, 2176.
103. D. R. Taylor, *Chem. Rev.*, 1967, **67,** 317.
104. R. Rossi and P. Diversi, *Synthesis*, 1973, 25.
105. 'Organic Functional Group Preparations', ed. S. R. Sandler and W. Karo, Academic, New York, 1971, vol. 2.
106. (a) K. Griesbaum, *Angew. Chem. Internat. Edn.*, 1966, **5,** 933; (b) G. Zweifel, *Intra-Sci. Chem. Reports*, 1973, 181.
107. (a) D. J. Pasto, G. F. Hennion, R. H. Shults, A. Waterhouse, and S.-K. Chou, *J. Org. Chem.*, 1976, **41,** 3496; (b) A. Claesson, I. Tämnefors, and L. I. Olsson, *Tetrahedron Letters*, 1975, 1509; (c) M. Kalli, P. D. Landor, and S. R. Landor, *J.C.S. Perkin I*, 1973, 1347.
108. P. Crabbé, E. Barreiro, J.-M. Dollat, and J. L. Luche, *J.C.S. Chem. Comm.*, 1976, 183; *Tetrahedron Letters*, 1975, 4615.
109. C. Descoins, C. A. Henrick, and J. B. Siddall, *Tetrahedron Letters*, 1972, 3777.
110. J. H. Wotiz, *J. Amer. Chem. Soc.*, 1951, **73,** 693; T. L. Jacobs and R. D. Wilcox, *ibid.*, 1964, **86,** 2240.
111. (a) J. Meinwald and L. Hendry, *Tetrahedron Letters*, 1969, 1657; (b) S. W. Russell and B. C. L. Weedon, *Chem. Comm.*, 1969, 85.

112. A. A. Petrov and V. A. Kormer, *J. Gen. Chem. U.S.S.R.*, 1960, **30,** 231, 3846.
113. J. S. Cowie, P. D. Landor, S. R. Landor, and N. Punja, *J.C.S. Perkin I*, 1972, 2197.
114. W. von E. Doering and P. M. LaFlamme, *Tetrahedron*, 1958, **2,** 75.
115. W. R. Moore and H. R. Ward, *J. Org. Chem.*, 1962, **27,** 4179.
116. L. Skattebøl, *Acta. Chem. Scand.*, 1963, **17,** 1683.
117. W. R. Moore and J. B. Hill, *Tetrahedron Letters*, 1970, 4553.
118. L. Brandsma and E. Mugge, *Rec. Trav. chim.*, 1973, **92,** 628.
119. H. Nozaki, T. Aratani, T. Toraya, and R. Noyori, *Tetrahedron*, 1971, **27,** 905.
120. J. Cymerman Craig and M. Moyle, *Proc. Chem. Soc.*, 1963, 56; *J. Chem. Soc.*, 1963, 5356.
121. G. Buono, *Tetrahedron Letters*, 1972, 3257.
122. P. J. Stang and R. J. Hargrove, *J. Org. Chem.*, 1975, **40,** 657.
123. T. H. Chan and W. Mychajlowskij, *Tetrahedron Letters*, 1974, 171.
124. M. Baran Marszak, M. Simalty, and A. Seuleiman, *Tetrahedron Letters*, 1974, 1905.
125. H. J. Bestmann and F. Seng, *Tetrahedron*, 1965, **21,** 1373.
126. S. Musierowicz, A. Wróblewski, and H. Krawczyk, *Tetrahedron Letters*, 1975, 437.
127. D. Michelot and G. Linstrumelle, *Tetrahedron Letters*, 1976, 275; *cf. J.C.S. Chem. Comm.*, 1975, 561.
128. P. A. Grieco, M. Meyers, and R. S. Finkelhor, *J. Org. Chem.*, 1974, **39,** 119.
129. K. J. Crowley, *Proc. Chem. Soc.*, 1964, 17.
130. J. H. Wotiz, in 'Chemistry of Acetylenes' ed. H. G. Viehe, Dekker, New York, 1969.
131. J. K. Crandall and W. W. Conover, *J.C.S. Chem. Comm.*, 1973, 340.
132. T. Greibrokk, *Tetrahedron Letters*, 1973, 1663.
133. J. K. Crandall, W. W. Conover, J. B. Komin, and W. H. Machleder, *J. Org. Chem.*, 1974, **39,** 1723.
134. S.-H. Dai and W. R. Dolbier, *J. Org. Chem.*, 1972, **37,** 950.
135. J. E. Baldwin and R. H. Fleming, *Fortsch. Chem. Forsch.*, 1970, **15,** 281.
136. L. Crombie, P. A. Jenkins, and D. A. Mitchard, *J.C.S. Perkin I*, 1975, 1081.
137. L. Crombie, P. A. Jenkins, and J. Roblin, *J.C.S. Perkin I*, 1975, 1090.
138. B. Rambeck and H. Simon, *Angew. Chem. Internat. Edn.*, 1974, **13,** 609.
139. M. M. Bhagwat and D. Devaprabhakara, *Tetrahedron Letters*, 1972, 1391.
140. B. L. Shaw and A. J. Stringer, *Inorg. Chim. Acta Rev.*, 1973, **7,** 1.
141. (a) S. Otsuka, A. Nakamura, T. Yamagata, and K. Tani, *J. Amer. Chem. Soc.*, 1972, **94,** 1037; (b) R. J. De Pasquale, *J. Organometallic Chem.*, 1971, **32,** 381.
142. P. Heimbach, H. Selbeck, and E. Troxler, *Angew. Chem. Internat. Edn.*, 1971, **10,** 659.
143. R. Baker, B. N. Blackett, and R. C. Cookson, *J.C.S. Chem. Comm.*, 1972, 802.
144. P. P. Montijn, L. Brandsma, and J. F. Arens, *Rec. Trav. chim.*, 1967, **86,** 129.
145. S. Kajigaeshi, N. Kuroda, G. Matsumoto, E. Wada, and A. Nagashima, *Tetrahedron Letters*, 1971, 4887.
146. H. Westmijze, J. Meijer, and P. Vermeer, *Tetrahedron Letters*, 1975, 2923.
147. T. Yoshida, R. M. Williams, and E. Negishi, *J. Amer. Chem. Soc.*, 1974, **96,** 3688.
148. (a) F. Bohlmann and K. Kieslich, *Chem. Ber.* 1954, **87,** 1363; (b) R. Kuhn and K. Wallenfels, *ibid.*, 1938, **71,** 783.
149. B. C. L. Weedon, in 'Carotenoids', ed. O. Isler, Birkhaüser Verlag, Basel, 1971.
150. T. Tokuyama, K. Uenoyama, G. Brown, J. W. Daly, and B. Witkop, *Helv. Chim. Acta*, 1974, **57,** 2597.
151. P. D. Landor, S. R. Landor, and J. P. Leighton, *Tetrahedron Letters*, 1973, 1019.
152. F. Bohlmann, T. Burkhardt, and C. Zdero, 'Naturally Occurring Acetylenes', Academic, New York, 1973.
153. B. Witkop, *Experientia*, 1971, **27,** 1121.
154. 'Chemistry of Acetylenes', ed. H. G. Viehe, Dekker, New York, 1969.
155. R. A. Raphael, 'Acetylenic Compounds in Organic Synthesis', Butterworths, London, 1955.
156. T. F. Rutledge, 'Acetylenic Compounds', Van Nostrand-Reinhold, New York, 1968; 'Acetylenes and Allenes', Van Nostrand-Reinhold, New York, 1969.
157. L. Brandsma, 'Preparative Acetylenic Chemistry', Elsevier, New York, 1971.
158. (a) P. Savignac, J. Petrova, M. Dreux, and P. Coutrot, *Synthesis*, 1975, 535; (b) J. Villieras, P. Perriot, and J. F. Normant, *ibid.*, 1975, 458.
159. E. J. Corey and P. L. Fuchs, *Tetrahedron Letters*, 1972, 3769.
160. P. Fritsch, *Annalen*, 1894, **279,** 319; W. P. Buttenberg, *ibid.*, 1894, **279,** 324; H. Wiechell, *ibid.*, 1894, **279,** 337.
161. G. Köbrich and P. Buck, 'Synthesis of Acetylenes and Polyacetylenes by Elimination Reactions', in 'Chemistry of Acetylenes', ed. H. G. Viehe, Dekker, New York, 1969.
162. J. Klein and E. Gurfinkel, *Tetrahedron*, 1970, **26,** 2127.
163. C. M. Wong and T.-L. Ho, *Synth. Comm.*, 1974, **4,** 25.
164. J. Tsuji, H Takahashi, and T. Kajimoto, *Tetrahedron Letters*, 1973, 4573.
165. (a) T. Mukaiyama, H. Nambu, and T. Kumamoto, *J. Org. Chem.*, 1964, **29,** 2243, (b) F. Ramirez, R. B. Mitra, and N. B. Desai, *J. Amer. Chem. Soc.*, 1960, **82,** 2651, 2652; *cf.* D. P. Bauer and R. S. Macomber, *J. Org. Chem.*, 1976, **41,** 2640.
166. (a) E. C. Taylor, R. L. Robey, and A. McKillop, *Angew. Chem. Internat. Edn.*, 1972, **11,** 48; (b) E. C. Taylor, R. L. Robey, D. K. Johnson, and A. McKillop, *Org. Synth.*, 1976, **55,** 73.
167. (a) J. C. Montaigne, *Ann. Chim. (Paris)*, 1954, **9,** 310; (b) E. R. H. Jones, G. Eglinton, and M. C. Whiting, *Org. Synth. Coll. Vol. 4*, 1963, 755.
168. D. Felix, R. K. Muller, U. Horn, R. Joos, J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta*, 1972, **55,** 1276.

169. J. Wislicenus and M. Henze, *Annalen*, 1900, **313,** 243.
170. (a) S. Trippett and D. M. Walker, *J. Chem. Soc.*, 1959, 3874; (b) G. Markl, *Chem. Ber.*, 1961, **94,** 3005.
171. E. J. Corey and R. H. Wollenberg, *J. Amer. Chem. Soc.*, 1974, **96,** 5581.
172. W. Ziegenbein, 'Synthesis of Acetylenes and Polyacetylenes by Substitution Reactions', in 'Chemistry of Acetylenes', ed. H. G. Viehe, Dekker, New York, 1969.
173. W. Beckmann, G. Doerjer, E. Logemann, C. Merkel, G. Schill, and C. Zürcher, *Synthesis*, 1975, 423.
174. M. M. Midland, *J. Org. Chem.*, 1975, **40,** 2250.
175. H. C. Brown, J. A. Sinclair, M. M. Midland, A. Suzuki, N. Miyaura, S. Abiko, and M. Itoh, *J. Amer. Chem. Soc.*, 1973, **95,** 3080; *cf.* K. Yamada, N. Miyaura, M. Itoh, and A. Suzuki, *Tetrahedron Letters*, 1975, 1961.
176. M. Naruse, K. Utimoto, and H. Nozaki, *Tetrahedron*, 1974, **30,** 2159.
177. M. M. Midland, J. A. Sinclair, and H. C. Brown, *J. Org. Chem.*, 1974, **39,** 731.
178. P. Cadiot and W. Chodkiewicz, 'Couplings of Acetylenes', in 'Chemistry of Acetylenes', ed. H. G. Viehe, Dekker, New York, 1969.
179. (a) L. Cassar, *J. Organometallic Chem.*, 1975, **93,** 253; (b) H. A. Dieck and F. R. Heck, *ibid.*, 1975, **93,** 259; (c) K. Sonogashira, Y. Tohda, and N. Hagihara, *Tetrahedron Letters*, 1975, 4467.
180. S. Bhanu and F. Scheinmann, *J.C.S. Chem. Comm.*, 1975, 817.
181. R. J. Bushby, *Quart. Rev.*, 1970, **24,** 585.
182. C. A. Brown and A. Yamashita, *J. Amer. Chem. Soc.*, 1975, **97,** 891; *J.C.S. Chem. Comm.*, 1976, 959.
183. F. Sondheimer, D. A. Ben-Efraim, and Y. Gaoni, *J. Amer. Chem. Soc.*, 1961, **83,** 1682 and refs. therein.
184. D. R. Taylor, *Chem. Rev.*, 1967, **67,** 317.
185. G. F. Hennion, J. J. Sheehan, and D. E. Maloney, *J. Amer. Chem. Soc.*, 1950, **72,** 3542.
186. (a) G. F. Hennion, R. B. Davis, and D. E. Maloney, *J. Amer. Chem. Soc.*, 1949, **71,** 2813; (b) M. Apparu and R. Glenat, *Bull. Soc. chim. France*, 1968, 1113.
187. E. Winterfeldt, 'Ionic Additions to Acetylenes', in 'Chemistry of Acetylenes', ed. H. G. Viehe, Dekker, New York, 1969.
188. K. E. Schulte, J. Reisch and W. Herrmann, *Naturwiss.*, 1963, **50,** 332.
189. M. Julia, 'Free Radical Additions to Acetylenes' in 'Chemistry of Acetylenes', ed. H. G. Viehe, Dekker, New York, 1969.
190. E. I. Heiba and R. M. Dessau, *J. Amer. Chem. Soc.*, 1967, **89,** 2238.
191. G. Stork, S. Malhotra, H. Thompson, and M. Uchibayashi, *J. Amer. Chem. Soc.*, 1965, **87,** 1148.
192. (a) G. Zweifel, G. M. Clarke, and N. L. Polston, *J. Amer. Chem. Soc.*, 1971, **93,** 3395; (b) H. C. Brown and G. Zweifel, *Org. Reactions*, 1963, **13,** 1.
193. G. Zweifel, R. P. Fisher, J. T. Snow, and C. C. Whitney, *J. Amer. Chem. Soc.*, 1971, **93,** 6309.
194. H. C. Brown, T. Hamaoka, and N. Ravindran, *J. Amer. Chem. Soc.*, 1973, **95,** 6456; *cf.* H. C. Brown, D. H. Bowman, S. Misumi, and M. K. Unni, *ibid.*, 1967, **89,** 4531.
195. J. J. Eisch and M. W. Foxton, *J. Org. Chem.*, 1971, **36,** 3520.
196. G. Zweifel and R. B. Steele, *J. Amer. Chem. Soc.*, 1967, **89,** 2754, 5085; G. Zweifel and C. C. Whitney, *ibid.*, 1967, **89,** 2753.
197. (a) A. Pelter, C. R. Harrison, C. Subrahmanyam, and D. Kirkpatrick, *J.C.S. Perkin I*, 1976, 2435; A. Pelter, T. W. Bentley, C. R. Harrison, C. Subrahmanyam, and R. J. Laub, *ibid.*, 1976, 2419; (b) A. Pelter, K. J. Gould, and C. R. Harrison, *ibid.*, 1976, 2428.
198. M. Naruse, T. Tomita, K. Utimoto, and H. Nozaki, *Tetrahedron Letters*, 1973, 795.
199. H. Gutmann and H. Lindlar, 'Partial Catalytic Hydrogenation of Acetylenes', in 'Chemistry of Acetylenes', ed. H. G. Viehe, Dekker, New York, 1969.
200. E. N. Marvell and T. Li, *Synthesis*, 1973, 457.
201. R. R. Schrock and J. A. Osborn, *J. Amer. Chem. Soc.*, 1976, **98,** 2143.
202. C. A. Brown and V. K. Ahuja, *J.C.S. Chem. Comm.*, 1973, 553.
203. P. W. Chum and S. E. Wilson, *Tetrahedron Letters*, 1976, 15.
204. (a) H. M. Schmidt and J. F. Arens, *Rec. Trav. chim.*, 1967, **86,** 1138; (b) A. B. Holmes, R. A. Raphael, and N. K. Wellard, *Tetrahedron Letters*, 1976, 1539.
205. (a) N. A. Dobson and R. A. Raphael, *J. Chem. Soc.*, 1955, 3558; (b) K. Avasthi, S. S. Ghosh, and D. Devaprabhakara, *Tetrahedron Letters*, 1976, 4871.
206. B. Grant and C. Djerassi, *J. Org. Chem.*, 1974, **39,** 968.
207. F. Näf, R. Decorzant, W. Thommen, B. Willhalm, and G. Ohloff, *Helv. Chim. Acta*, 1975, **58,** 1016.
208. H. Gopal and A. J. Gordon, *Tetrahedron Letters*, 1971, 2941.
209. S. Wolfe, W. R. Pilgrim, T. F. Garrard, and P. Chamberlain, *Canad. J. Chem.*, 1971, **49,** 1099.
210. J. E. Shaw and J. J. Sherry, *Tetrahedron Letters*, 1971, 4379.
211. R. Fuks and H. G. Viehe, 'Cyclic Compounds from Acetylenes', in 'Chemistry of Acetylenes', ed. H. G. Viehe, Dekker, New York, 1969.
212. D. D. Coffman, P. L. Barrick, R. D. Cramer, and M. S. Raasch, *J. Amer. Chem. Soc.*, 1949, **71,** 490.
213. D. Seebach, *Chem. Ber.*, 1964, **97,** 2953.
214. J. H. Lukas, F. Baardman, and A. P. Kouwenhoven, *Angew. Chem. Internat. Edn.*, 1976, **15,** 369.
215. D. Becker, L. R. Hughes, and R. A. Raphael, *J.C.S. Chem. Comm.*, 1974, 430; L. R. Hughes and R. A. Raphael, *Tetrahedron Letters*, 1976, 1543.
216. S. R. Wilson and R. B. Turner, *J. Org. Chem.*, 1973, **38,** 2870.
217. L. H. Klemm and P. S. Santhanam, *J. Heterocyclic Chem.*, 1972, **9,** 423.

218. J. Bastide, J. Hamelin, F. Texier, and Y. Vo Quang, *Bull Soc. chim. France*, 1973, 2555.
219. T. Kauffmann, *Angew. Chem. Internat. Edn.*, 1974, **13,** 627.
220. N. T. Castellucci and C. E. Griffin, *J. Amer. Chem. Soc.*, 1960, **82,** 4107.
221. P. M. Maitlis, *Pure Appl. Chem.*, 1972, **30,** 427.
222. (a) W. Reppe, O. Schlichting, K. Klager, and T. Toepel, *Annalen*, 1948, **560,** 1; (b) G. Schröder, 'Cyclooctatetraene', Verlag Chemie, Weinheim, 1965.
223. J. R. Leto and M. F. Leto, *J. Amer. Chem. Soc.*, 1961, **83,** 2944.
224. A. J. Chalk and R. A. Jerussi, *Tetrahedron Letters*, 1972, 61.
225. K. P. C. Vollhardt and R. G. Bergman, *J. Amer. Chem. Soc.*, 1974, **96,** 4996.
226. W. Brenner and P. Heimbach, *Annalen*, 1975, 660.
227. D. M. Singleton, *Tetrahedron Letters*, 1973, 1245.
228. R. L. Funk and K. P. C. Vollhardt, *J. Amer. Chem. Soc.*, 1976, **98,** 6755.
229. K. M. Nicholas and R. Pettit, *Tetrahedron Letters*, 1971, 3475; *cf.* C. Descoins and D. Samain, *ibid.*, 1976, 745.
230. G. Eglinton and W. McCrae, *Adv. Org. Chem.*, 1963, **4,** 225.
231. A. S. Hay, *J. Org. Chem.*, 1962, **27,** 3320.
232. U. Fritzsche and S. Hunig, *Tetrahedron Letters*, 1972, 4831.
233. R. Eastmond and D. R. M. Walton, *Tetrahedron*, 1972, **28,** 4591; *cf.* B. F. Coles and D. R. M. Walton, *Synthesis*, 1975, 390.
234. (a) A. Pelter, R. Hughes, K. Smith, and M. Tabata, *Tetrahedron Letters*, 1976, 4385; (b) J. A. Sinclair and H. C. Brown, *J. Org. Chem.*, 1976, **41,** 1078.
235. G. Pattenden, 'Naturally Occurring Polyolefinic and Polyacetylenic Compounds', in 'Aliphatic Chemistry', Specialist Periodical Reports, The Chemical Society, London, 1973–1977, vols. 2–5.
236. (a) R. A. Massy-Westropp, G. D. Reynolds and T. M. Spotswood, *Tetrahedron Letters*, 1966, 1939; (b) D. W. Knight and G. Pattenden, *J.C.S. Perkin I*, 1975, 641.
237. K. Ishibashi, K. Nose, T. Shindo, M. Arai, and H. Mishima, *Ann. Reports Sankyo Res. Labs.*, 1968, **20,** 76.
238. (a) H. K. Black, D. H. S. Horn, and B. C. L. Weedon, *J. Chem. Soc.*, 1954, 1704; (b) R. F. Garwood, E. Oskay and B. C. L. Weedon, *Chem. and Ind. (London)*, 1962, 1684.
239. J. Burdon, P. L. Coe, C. R. Marsh, and J. C. Tatlow, *Chem. Comm.*, 1967, 1259.
240. J. F. Normant, A. Commercon, and J. Villieras, *Tetrahedron Letters*, 1975, 1465.
241. E. Negishi, G. Lew, and T. Yoshida, *J.C.S. Chem. Comm.*, 1973, 874.
242. K. Eiter and H. Oediger, *Annalen*, 1965, **682,** 62.
243. E. J. Corey and R. A. Ruden, *Tetrahedron Letters*, 1973, 1495.
244. G. Okusa, M. Kumagai, and T. Itai, *Chem. Pharm. Bull. (Japan)*, 1969, **17,** 2502.
245. L. Crombie, N. A. Kerton, and G. Pattenden, unpublished results.
246. K. A. Parker and R. W. Kosley, *Tetrahedron Letters*, 1975, 691.
247. M. L. Roumestant, P. Place, and J. Gore, *Tetrahedron Letters*, 1976, 677.
248. H. H. Sun, S. M. Waraszkiewicz, and K. L. Erickson, *Tetrahedron Letters*, 1976, 3021 and 4227.
249. D. J. Vanderah and F. J. Schmitz, *J. Org. Chem.*, 1976, **41,** 3480.

2.4

Aromaticity

P. J. GARRATT
University College London

2.4.1 HISTORICAL INTRODUCTION 215
2.4.2 ELECTRONIC THEORIES OF BENZENE 218
2.4.3 CRITERIA FOR AROMATICITY 221
2.4.3.1 Thermodynamic properties 221
2.4.3.2 Structural properties 222
2.4.3.3 Magnetic properties 224
2.4.3.4 Other criteria 227
2.4.4 ANTI-AROMATICITY 228
2.4.4.1 Thermodynamic properties 229
2.4.4.2 Structural properties 229
2.4.4.3 Magnetic properties 230
2.4.4.4 Other properties 231
2.4.5 THEORETICAL DEFINITIONS OF AROMATICITY 231
2.4.5.1 Semi-empirical calculations and Dewar resonance energy 232
2.4.5.2 Valence bond calculations and application of the resonance method 233
2.4.5.3 Bond localization 233
2.4.5.4 Relationship of energetic and bond localization criteria 234
2.4.6 AROMATIC TRANSITION STATES 235

2.4.1 HISTORICAL INTRODUCTION

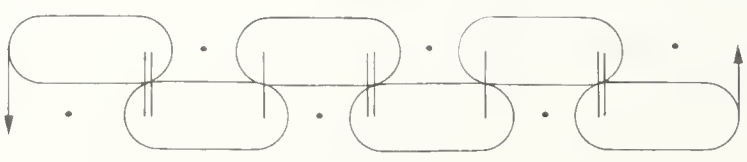
The generic name 'aromatic' was given originally to a structurally diverse collection of compounds which had one common property, a fragrant odour. The fragrance was an important proviso, since many organic compounds smell. The discovery of benzene by Faraday in 1825 may be considered to institute the constitutional study of aromatic compounds.[1] Faraday treated the liquid obtained by compressing oil gas to a sequence of fractional distillation and low-temperature crystallization, and isolated a compound which boiled at 186 °F and had a melting point of 42 °F. He found the density of the vapour, showed the composition was CH, and by combustion deduced the molecular formula as $(CH)_6$.[2] Faraday examined the behaviour of benzene with halogens, showing that it reacted with chlorine in the light but not in the dark, and he also found that it reacted with nitric and sulphuric acids, but not with potassium. Benzene was first synthesized by Mitscherlich in 1833 by the decarboxylation of benzoic acid.[3]

The properties of benzene are in striking contrast to another CH hydrocarbon, acetylene, discovered by Edmund Davy, cousin of the more famous Humphry, in 1836.[4] Acetylene, or ethyne, is a colourless flammable gas and is extremely reactive. Benzene, though flammable, is relatively inert and was, until its carcinogenic properties became of

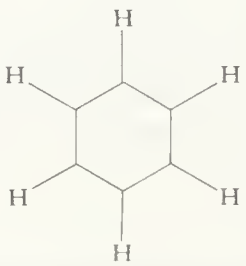
more environmental concern, used as a solvent for numerous chemical reactions. Further, it was found that in substituted benzenes the phenyl 'radical', C_6H_5, could pass unchanged through a variety of chemical transformations carried out on the attached side chain. The inertness of this highly unsaturated 'radical' was an intriguing mystery to chemists in the middle of the nineteenth century, and the constitution of aromatic compounds has for more than 100 years provided one of the major stimuli for the development and testing of theories of chemical structure.

Besides substituted benzenes, a variety of substances were discovered or synthesized which fitted into the aromatic classification but in which more extensive unsaturation was apparent. Coal tar provided a range of these compounds,[5] and naphthalene (C_5H_4), anthracene (C_7H_5), and phenanthrene (C_7H_5) were characterized early on. The empirical formulae revealed the continuing depletion of hydrogen and also indicated that constitutional isomerism can occur in the latter two compounds. However, little progress could be made until the late 1850's when the idea of molecular weight was clarified[6] and the concept of tetravalent carbon was advanced. The formulae of Couper and Kekulé then allowed structures to be drawn for aliphatic compounds and provided a rationale for constitutional isomerism; however, unsaturation remained unexplained. The subsequent adoption of the multiple bond between carbon atoms supplied structures for ethylene and acetylene and also provided an explanation for their high reactivity through the tendency of carbon to saturate its four valencies. The enigma of benzene and its analogues deepened — unsaturated but inert! Why were these compounds not readily saturated? Were the carbon atoms already tetravalent? What, simply, was the structure of benzene?

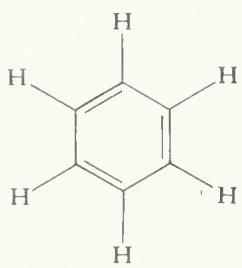
It was into this historical context that Kekulé in 1865 supplied his inspired solution that benzene was a cyclic system.[7] The earliest formula used by Kekulé to depict benzene was (**1**), in which the carbon atoms are represented by ellipsoids, the alternate double and single bonds by lines, the residual affinities (unsatisfied valences) by dots, and arrows indicate the closing of the chain. Hydrogen atoms can now be attached to the six residual affinities. A simple hexagonal representation (**2**) followed and this was then modified to introduce the double and single bonds as in (**3**), the representation from which the current Kekulé benzene structure (**4**) is derived.[8]



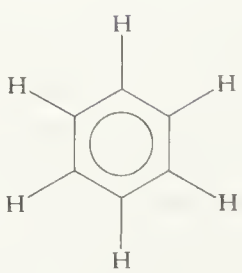
(**1**)



(**2**)



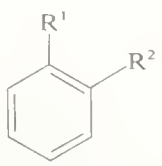
(**3**)



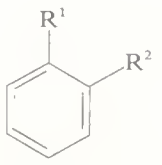
(**4**)

Certain observations can be made immediately about the Kekulé benzene structure. All of the carbon and all of the hydrogen atoms are equivalent. This prediction was verified for benzene by the investigations of Ladenburg and of Wroblensky.[9] The hexagonal formula requires that there are three isomeric disubstituted benzenes, 1,2- (**5**), 1,3- (**6**), and 1,4- (**7**), and three isomers were observed. Ladenburg pointed out that a problem

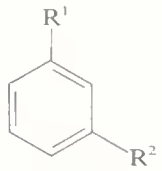
now arises with the Kekulé representation: there should actually be two types of 1,2-disubstituted benzene, (**5a**) and (**5b**) (and also when $R^1 \neq R^2$ there should be two types of 1,3-disubstituted benzene). To meet this objection Kekulé suggested that the double bonds in benzene were interchanging, thus interconverting (**5a**) and (**5b**), and he provided a mechanical model for this process. This proposal resembles the later concept of resonance.



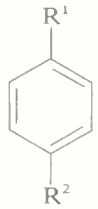
(**5a**)



(**5b**)

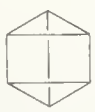


(**6**)

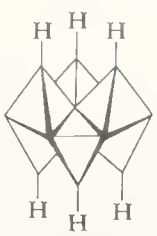


(**7**)

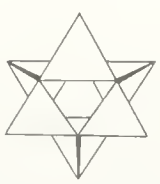
Although Kekulé's formula provided a rationale for some of the properties of benzene, it did not explain its lack of reactivity. The structure contained three double bonds and there appeared to be no reason why these should not readily undergo addition reactions. Yet such reactions were comparatively rare, the majority of products being derived from substitution of a hydrogen atom. A variety of other structures were suggested which attempted to account for the inert character of benzene. Ladenburg[10] proposed the prism formula (**8**), firstly as a planar and later as a three-dimensional construct, which he believed overcame the problem of two 1,2-disubstituted derivatives and in which all the carbons are tetravalent. Claus[11] suggested (**9**) which, if not planar, introduces grave geometric problems. The introduction of the tetrahedral arrangement of the carbon valencies by van't Hoff and Le Bel led to a variety of formulae derived from the tetrahedron, such as (**10**) by Körner and (**11**) by Thiele. Some of these formulae appeared to explain the inertness of benzene better than that of Kekulé, but all were abandoned for other reasons.


(**8**)


(**9**)



(**10**)


(**11**)

Besides these approaches, attempts were also made to modify the Kekulé structure to indicate, if not explain, the lack of reactivity. Armstrong, Lothar Meyer, and Baeyer all introduced formulae, using various symbolic representations, in which the six unsaturated valencies pointed towards the centre of the hexagon, for example as in (**12**). Bamburger made a significant contribution to the understanding of the nature of aromatic compounds when he suggested that the important characteristic of such formulae was the number of these valencies, *i.e. six*.[12] Using this concept he was able to account not only for the structures of benzene and naphthalene (**13**), but also of pyrrole (**14**) where the nitrogen atom was considered to be pentavalent and to contribute two free valencies to the sextet.[13]


(**12**)

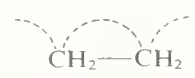

(**13**)

(**14**)

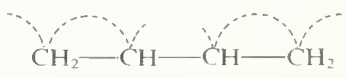
(**15**)

The concept of the aromatic sextet clearly originated with Bamberger, and he enunciated lucidly its importance in explaining the difference in basicity of pyrrole and

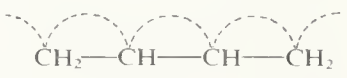
pyrrolidine (**15**). A subsequent major theoretical contribution was made by Thiele using his theory of partial valency, which had been developed to explain 1,4-addition to dienes.[14] Multiple bonds were assumed to have partial valencies, indicated by dotted lines, as shown for ethylene (**16**). Linking two multiple bonds by a single carbon–carbon bond gave a formula such as (**17a**) for butadiene in which the central valencies can be satisfied, leaving partial valencies only on the terminal atoms as in (**17b**). If three such double bonds were introduced into a ring then all of the partial valencies can be satisfied as in (**18**) and the molecule should no longer exhibit the properties of a polyalkene. An explanation for the inertness of benzene was thus provided. Unfortunately, Thiele's theory predicts that any ring compound of alternate double and single bonds should be stabilized. The synthesis of cyclo-octatetraene (**19**) by Willstätter and his co-workers[15] showed that this compound behaves like a polyene and caused Thiele's theory to be abandoned. It is amusing to consider that a combination of Bamberger's insistence on *six* with Thiele's theory of partial valency provides a convincing explanation for the stability of benzene and its analogues. Piquance is added to this conjunction in that Thiele had already provided evidence that *six* was a magic number, since cyclopentadiene gave an anion (**20**) whereas cycloheptatriene did not. However, interest in the constructs of our own imagination often precludes a more objective view of the situation. Thiele explained this difference on the basis of his partial valency theory, suggesting that cycloheptatriene (**21**) was homoaromatic![16]



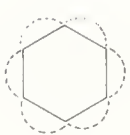
(**16**)



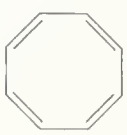
(**17a**)



(**17b**)

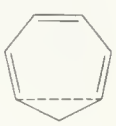


(**18**)



(**19**)

(**20**)



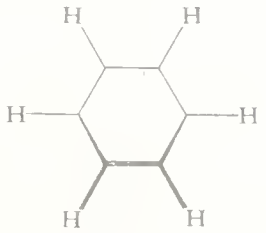
(**21**)

2.4.2 ELECTRONIC THEORIES OF BENZENE

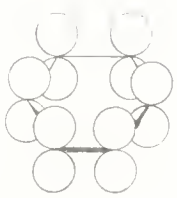
The synthesis of the cyclopentadienyl anion and of cyclo-octatetraene, coming at the beginning of the twentieth century, coincided with a reawakening of interest in the nature of matter. The discovery of the electron, radioactivity, and the atomic nucleus initiated a ferment of activity and the advances made in this area were soon applied to the structure of molecules. The theories of Kossel, Langmuir, Lewis, and others allowed a formal description of bonding involving the electron, and Lewis's octet theory, ascribing eight as a magic number for the valence electron shell around atoms, was particularly fruitful. In 1925 Armit and Robinson[17] re-enunciated Bamberger's hexacentric theory in electronic terms, suggesting that, like the octet, the aromatic sextet was an arrangement of electrons of particular stability. As with the octet, the reason why six, rather than four or eight, electrons should be the stable configuration was not understood. At about the same time Ingold[18] suggested that besides the Kekulé constitutions, the *para*-bonded Dewar benzene constitutions might also contribute to the ground state of benzene and a resonance picture for benzene was produced.

Further insight into the problem of aromaticity and the structure of benzene now had to await the development of wave-mechanics in the 1920's. In 1930, Hückel,[19] on the basis of the molecular orbital method, advanced the first explanation for the stability of the aromatic sextet. Benzene contains too many electrons for a complete solution to the wave equation, but Hückel, following the method of Heitler and London, was able to simplify the problem by separating the electrons into two types, those in orbitals symmetric about the intermolecular axis, the σ-electrons, and those non-symmetric around the internuclear

axis, the π-electrons. If the two 1*s* electrons of carbon are ignored as not contributing to the bonding, then 30 electrons remain. Considering benzene to be a hexagon (**22**) with the six hydrogen atoms in the same plane as the carbon atoms, then 24 of the electrons are used in forming σ-bonds. The problem of the aromaticity of benzene then devolves on to the six remaining electrons, which are in π-orbitals (**23**) and which are considered to be energetically separate from the σ-electrons.



(**22**)



(**23**)

Hückel determined the energy levels for these orbitals by the linear combination of atomic orbitals (LCAO) method, introducing a number of simplifying approximations (the Hückel approximations) which form the basis of the Hückel molecular orbital method. When the calculations are carried out, six molecular orbitals are produced from the combination of the six atomic orbitals. Three of these orbitals are of lower energy than the atomic orbitals from which they were formed and three are of higher energy (Figure 1). The energy of the orbitals is given in terms of α, the coulomb integral of an electron in a carbon $2p$ atomic orbital, and β, the resonance integral, the energy of interaction between two $2p$ atomic orbitals. The stability of benzene can now be explained. Each orbital can accommodate two electrons with anti-parallel spins, and there are three bonding orbitals, so that all six π-electrons are bonding.

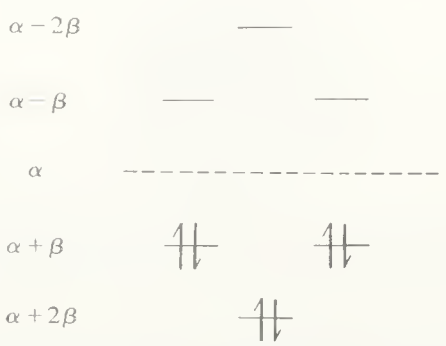


Figure 1 The energy levels in benzene

The six π-molecular orbitals of benzene are represented in Figure 2. The lowest-energy $\alpha+2\beta$ bonding orbital has no nodes, and the two degenerate $\alpha+\beta$ bonding orbitals each have one node. The degenerate $\alpha-\beta$ antibonding orbitals have two nodes, and the $\alpha-2\beta$ orbital, three nodes. The total π-electron density (ψ^2) for the six electrons in the three bonding orbitals is shown in Figure 3, in which the π-electron density is arranged symmetrically above and below the ring plane.

The Hückel theory explains the stability of the aromatic sextet. What does it predict about the eight π-electrons of cyclo-octatetraene? The problem is approached in exactly the same manner, the eight-membered ring being assumed to be planar and the eight π-electrons treated separately from those in the σ framework. The energy levels of the eight molecular orbitals which result are shown in Figure 4. Three orbitals are bonding, three are antibonding, and two are non-bonding, *i.e.* they have the same energy, α, as the original atomic orbitals. Six electrons can go into bonding orbitals, but two electrons must go into non-bonding orbitals. Further, by application of Hund's rule, the electrons in the non-bonding orbitals should be unpaired with parallel spin, and planar cyclo-octatetraene

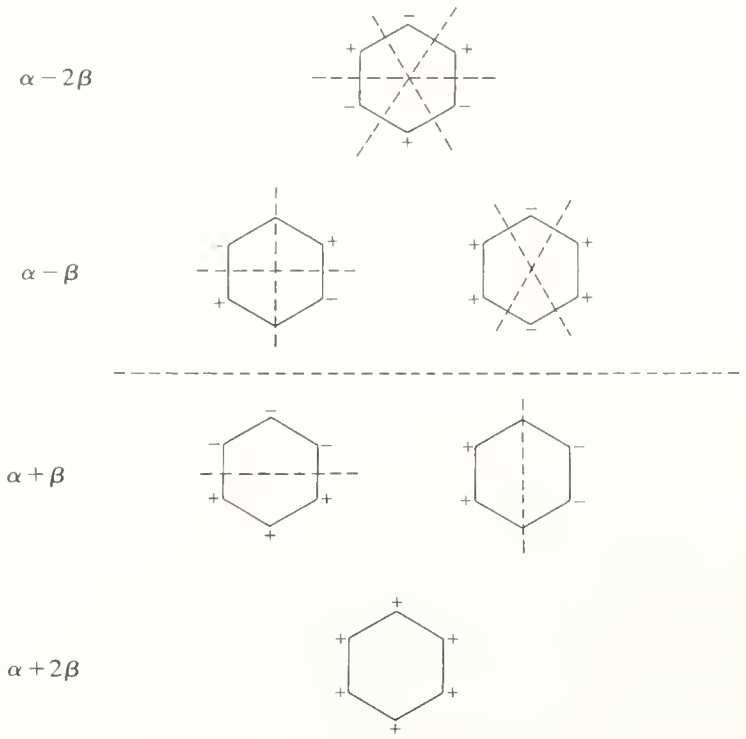


Figure 2 The six π-orbitals of benzene showing the phase of the orbital at each carbon atom and the nodal planes

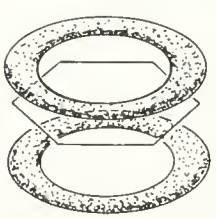


Figure 3 The π-electron density (ψ^2) resulting from the introduction of the six π-electrons into the three bonding molecular orbitals

is thus predicted to be a triplet diradical. Thus, Hückel theory demonstrates that there is a profound difference between the electronic configurations of the six and eight π-electron monocyclic systems, and it vindicates the concept of the aromatic sextet. However, the theory does predict that planar cyclo-octatetraene will be stabilized by 1.66β compared with four isolated double bonds, and this is close to the value of 2.0β predicted for benzene.

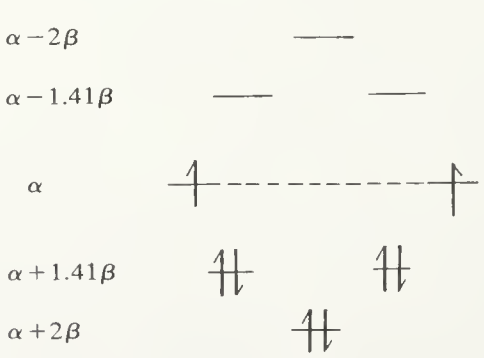
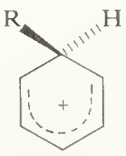


Figure 4 The energy levels in cyclo-octatetraene

The difference in the electronic energy levels for benzene and cyclo-octatetraene can be generalized for planar, cyclic systems and has been formulated as the Hückel rule: planar, monocyclic conjugated systems with $4n+2$ π-electrons will be aromatic, whereas those systems with $4n$ π-electrons will be non-aromatic. The Hückel rule can be applied to charged as well as neutral systems; it explained the stability of the cyclopentadienyl anion and predicted the stability of the cycloheptatrienyl cation.[19]

The Hückel rule provides a simple, theoretically based method of predicting whether a monocyclic system will be aromatic or not. For such a prediction to be verified, criteria must be adopted by which the aromaticity of a compound can be determined. In the preceding discussion the properties characteristic of an aromatic system were seen to be inertness and the retention of type, as exemplified by the preference of substitution over addition reactions. The inertness of the system is a measure of the difference in free energy between the ground state and the transition state, and it is being compared with this difference in an alkene. Replacement of hydrogen by another group on the benzene ring may clearly affect either the ground-state or transition-state energy, and a decrease or increase in the rate of reaction may occur. The observation of substitution rather than addition is related to the subsequent fate of the transition state complex, which is presumably closely related to the Wheland intermediate (**24**). This may either eliminate a proton to restore the aromatic sextet or add a nucleophile to give the addition product. Again, the replacement of hydrogen by another group will influence the fate of the transition-state complex, and addition products may become important. As a consequence of these difficulties in using reactivity as a criterion for the aromatic nature of a molecule, consideration has turned to the ground-state properties of the system as a judge of its aromaticity. These properties will be examined in the next section.



(**24**)

2.4.3 CRITERIA FOR AROMATICITY

A variety of physical properties have been used as criteria to determine the presence or absence of aromatic character in a compound. Some of these properties are, in principle, applicable to any system, others only to systems of a particular type; most involve ground-state properties, but some depend on the difference between ground and excited states.

2.4.3.1 Thermodynamic properties

When an acyclic alkane is burnt the heat of combustion can be partitioned between the various bonds and the average value for a bond of a particular type determined. Thus combustion of methane will give an average value for the bond energy of the carbon–hydrogen bond, and combustion of ethane, taken in conjunction with the data derived from methane, will give a bond energy for the carbon–carbon bond. When these empirical bond energies are applied to other alkanes, it is found that heats of formation can be quite accurately estimated by adding the empirical energies contributed by the individual bonds. By the same method, average bond energies can be assigned to multiple bonds, and again it is found that these energies are additive, giving accurate heats of formation for other compounds containing multiple bonds.[20]

When the bond energies derived for the alkanes and alkenes are applied to benzenoid systems, it is found that the additive relationship no longer holds. In these cases the heats

of formation derived from the empirical bond energies are considerably different from those determined experimentally. Thus the heat of formation of gaseous benzene, obtained from the heat of combustion of benzene and the heats of formation of the products of combustion, carbon dioxide and water, is found to be 4343 kJ mol^{-1}, whereas the calculated heat of formation, taking the derived energies for six C—H, three C—C, and three C=C bonds, is 4180 kJ mol^{-1}. Thus benzene is 163 kJ mol^{-1} more stable than would be predicted from the additive bond data. This difference in energy between the calculated and observed heat of formation is called the *resonance energy* of benzene. The calculated heat of formation was made for cyclohexatriene, an unknown molecule with alternate double and single bonds, and the 163 kJ mol^{-1} is thus supposed to represent the stabilization of benzene, with its six equivalent C—C bonds, over the structure with alternate double and single bonds.[20]

A similar value for the resonance energy can be obtained by comparing the heats of hydrogenation of benzene and cyclohexene. If each of the double bonds of cyclohexatriene is considered to be like a double bond of cyclohexene, then cyclohexatriene would be expected to have three times the heat of hydrogenation of cyclohexene, *i.e.* 358.5 kJ mol^{-1}. The experimentally determined heat of hydrogenation of benzene is 150.4 kJ mol^{-1} less than this value, and can again be assigned to the difference in energy between benzene and cyclohexatriene.

Although the heat of combustion (or hydrogenation) of benzene is a measurable quantity, the resonance energy is not. As we have seen, it arises from the difference between the found and the predicted heat of combustion based on the model cyclohexatriene. However, cyclohexatriene is not a real system, and we must decide how satisfactory our model of cyclohexatriene is likely to be. Dewar and Schmeising[21] have argued cogently that taking the values of bond energies from cyclohexene and transferring them to cyclohexatriene is not very meaningful. This can be most readily seen by considering the hydrogenation model. Hydrogenation of cyclohexene involves the following C—C bond changes: one sp^2–sp^2 alkene C=C bond to a C—C alicyclic sp^3–sp^3 C—C bond, and two sp^2–sp^3 C—C bonds to sp^3–sp^3 C—C bonds. In cyclohexatriene, hydrogenation would convert three sp^2–sp^2 alkene C=C bonds and three sp^2–sp^2 C—C bonds into six sp^3–sp^3 bonds. Thus, transferring the values from cyclohexene will not duplicate the changes in cyclohexatriene, and the process may well be energetically different. Similar arguments apply to the combustion data.

There is a further problem involved in the conversion of cyclohexatriene into benzene, which is summarized in Figure 5. The single bonds in cyclohexatriene must be shortened and the double bonds lengthened to give the symmetric hexagonal Kekulé structure (Figure 5, route c). Delocalization of the π-electrons over the σ framework now gives benzene. The partition of resonance energy between bond length changes and delocalization requires an estimate of the energy change with change of bond length. This has been done by examining the variation of heat of formation with bond length and bond order. Allowing the electrons to delocalize (Figure 5, route d) would then give the value for 2β predicted by the Hückel theory.

Thus there are two problems in using the resonance energy as a measure of the aromaticity of a system. The first arises from the uncertainty in estimating the heat of formation of the hypothetical cyclohexatriene, and the second is how to partition the value obtained between σ-bond compression and π-delocalization. One solution of the first, more serious, problem is to provide a different model system from which to compute the energy of the non-aromatic molecule. Such a model, which appears to be more satisfactory, is discussed below (see Section 2.4.5.1).

2.4.3.2 Structural properties

The early chemical investigations of benzene showed that all of the carbon and all of the hydrogen atoms were equivalent (see Section 2.4.1). It could also be inferred, though

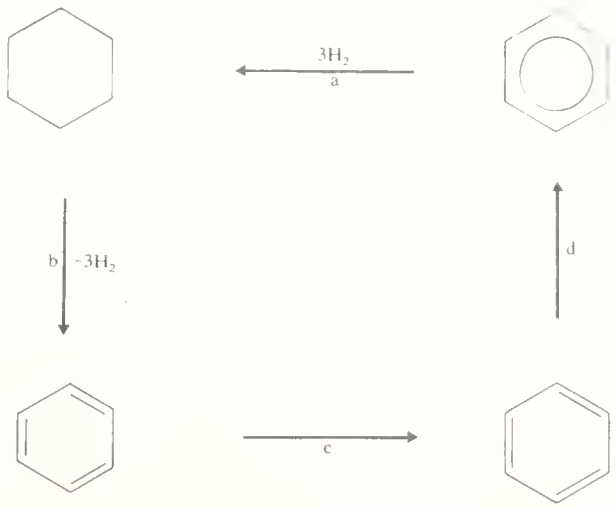


Figure 5

on less secure grounds, that all of the C—C bonds were equivalent, since only one *ortho* and one *meta* disubstituted derivative were formed. The actual physical confirmation of this equivalence for benzene was made much later by electron and neutron diffraction,[22] spectroscopic,[23] and X-ray crystallographic[24a,24b] methods. The bond lengths in benzene are now known with considerable accuracy from the rotational Raman spectrum,[25] which gives values of 139.7 pm for the C—C bonds and 108.4 pm for the C—H bonds. The equivalence of bond lengths thus becomes a plausible criterion for determining the aromaticity of a compound, and aromatic compounds could be defined as 'cyclic, conjugated systems in which all the C—C and all the C—H bonds are equivalent.' There is an immediate problem with such a definition since benzene and the monocyclic ions $C_3H_3^+$, $C_5H_5^-$, $C_7H_7^+$, and $C_9H_9^-$ are the only systems which would be aromatic by this criterion. However, a distinct difference between aromatic and non-aromatic compounds can be expected; the non-aromatic compounds will show an alternation of bond lengths corresponding to alternate double and single bonds, whereas the aromatic systems will not. Substituted benzenes and polycyclic systems will not exhibit bond equivalence, but these compounds should not show bond alternation.

In hexamethylbenzene, the first system in which the symmetric hexagonal structure of the benzene ring was demonstrated,[26] all of the ring C—C bonds are equivalent (139 pm) and the molecule, like benzene, has $\mathbf{D}_{6h}$ symmetry. In naphthalene, anthracene, and pyrene, although all the bonds are not of the same length, the range is small (136–145 pm) and there is no bond alternation.[24b]

A property related to these structural criteria is the *ortho* H–H coupling constant in the ^{1}H n.m.r. spectrum.[27a] It has been shown for a variety of fused benzenoid hydrocarbons that the *ortho* coupling constant, J, varies in a simple linear manner with the π-bond order P such that

$$J = 12.7\,P - 1.1\ \text{Hz} \qquad (1)$$

The values of J for a number of benzenoid hydrocarbons are given in Table 1, together with the derived values from the π-bond orders. Günther and co-workers[27b] have used the values of the *ortho* coupling constants in the benzene rings of benzannelated annulenes to estimate the aromaticity of the annulene ring (see Chapter 2.6).

The properties of benzene are unique; it is the only monocyclic unsaturated system, excluding its hexasubstituted derivatives, which can attain the correct bond angle of 120° without bond strain or the intrusion of hydrogens into the ring cavity. Its i.r. and Raman spectra substantiate the symmetric $\mathbf{D}_{6h}$ structure;[23] thus there are only the four allowed fundamental frequencies in the i.r. spectrum in the gaseous state, and the seven allowed frequencies in the Raman spectrum. The preparation of deuteriated benzenes allowed the assignment of the bands to different vibrations, and also the calculation of the force

TABLE 1

ortho Coupling Constants in Polycyclic Aromatic Hydrocarbons[a]

Compound	C—C *bond*	*P* π-*bond order*	J_{exp}	J_{calc}
Benzene	1,2	0.667	8.0	7.4
Naphthalene	1,2	0.725	8.1	8.1
	2,3	0.603	6.4	6.6
Anthracene	1,2	0.738	8.3	8.3
	2,3	0.586	6.5	6.3
Pyrene	1,2	0.670	7.6	7.4

[a] Data from N. Jonathan, S. Gordon, and B. P. Dailey, *J. Chem. Phys.*, 1962, **36**, 2443.

constants for ring deformations. Benzene much more easily undergoes out-of-plane than in-plane distortion,[23] the twisting moment being only one-fifth that of ethylene. Analysis of the electronic spectrum (see Section 2.4.3.4) shows that benzene is also planar in the excited state.[28]

The direct transfer of the structural properties of benzene, particularly those associated with its high symmetry, to other systems will often require that these properties are suitably modified. Nevertheless, structural criteria, such as the absence of bond alternation, do form a useful test with which to estimate the aromatic character of an unsaturated system.

2.4.3.3 Magnetic properties

The measurement of the magnetic anisotropy of crystals of low symmetry, together with a knowledge of the arrangement of the molecules within the crystal, allows for the calculation of the magnetic anisotropy of single molecules. When this method was applied to aromatic molecules, it was found that the diamagnetic susceptibility was much greater in the direction normal to the plane of the molecule than in the direction parallel to this plane. A qualitative explanation of the anisotropy of the diamagnetic susceptibility can be made by assuming that when the molecule is introduced into the magnetic field, Larmor precession of the π-electrons occurs in orbitals extending over many nuclei. This precession of the electrons will occur in such a direction as to induce a magnetic field, H^i, which will oppose the applied field, H^0, and the resulting field for benzene is shown in Figure 6.

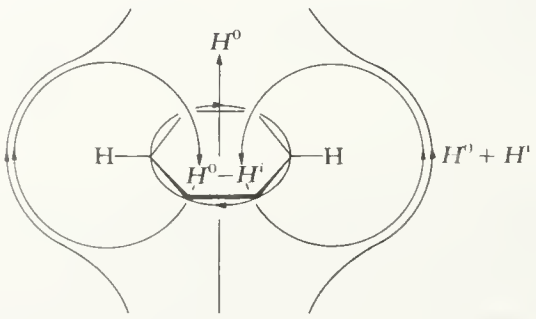


Figure 6

If the excess molecular susceptibility in the plane perpendicular to the plane parallel is defined by ΔK_M, then

$$\Delta K_M = \Delta K_{M_{perpendicular}} - \Delta K_{M_{parallel}} \quad (2)$$

where $K_{M_{parallel}}$ is the mean susceptibility in the two parallel, orthogonal directions. ΔK_M

can be related to the radius of the circular orbit of equivalent mean plane in which precession is allowed.

Values of K_M for a number of aromatic molecules are given in Table 2. Quantitative calculations have been made, using both semi-classical[29] and quantum mechanical[30] methods, and these are in reasonably good agreement with the experimental values. Later calculations, made in order to account for the lack of correlation of the predicted and experimental values of the ^{1}H n.m.r. chemical shifts based on this model, indicated that only part of ΔK_M is due to the circulation of electrons over the molecular framework, about 30% of the anisotropy being attributed to localized contributions.[31]

TABLE 2

Diamagnetic Anisotropies of Conjugated Hydrocarbons[a]

Compound	ΔK_M	ΔK_M *per ring*
Benzene	54.0	54
Naphthalene	114.0	57
Phenanthrene	166.0	55.2
Chrysene	225.2	56.3
Pyrene	232.9	58.2
Durene	61.5	61.5
Hexamethylbenzene	61.9	61.9

[a] Values from K. Lonsdale, *Proc. Roy. Soc.*, 1937, **A159,** 149.

Within the context of organic chemistry, diamagnetic anistropy would seem a useful criterion to indicate the presence of aromaticity. However, the method is difficult to apply and only a small number of molecules, mainly monocyclic and polycyclic benzenoid systems, have been examined. A method of overcoming many of the experimental difficulties is to examine the bulk diamagnetic susceptibility, which should be higher for an aromatic system than for similar model systems in which delocalization of the electrons does not occur. The problem with such a measurement is that a model system must again be found in which the ring current is absent and for which the diamagnetic bulk susceptibility can be measured or calculated. The availability of more reliable values for the Pascal constants of the susceptibilities of the component parts has allowed more accurate estimates of the susceptibilities of model systems, and the method has been revived by Dauben and his associates.[32]

The diamagnetic exaltation, Λ, is the difference between the experimentally determined molar susceptibility χ_M and the calculated susceptibility $\chi_{M'}$ of the model system.

$$\Lambda = \chi_M - \chi_{M'} \tag{3}$$

The diamagnetic exaltations of a number of conjugated systems are collected in Table 3. From this table it can be seen that cyclohexene and cyclohexa-1,3-diene have susceptibilities close to the calculated value, and consequently Λ is small, whereas the calculated and measured values for benzene are very different, and Λ is large and positive. The value for cyclo-octatetraene is close to the calculated value, indicating that it is non-aromatic.

The induced magnetic field produced by the circulating electrons when introduced into an external magnetic field can be expected to influence the chemical shift of the protons in the ^{1}H n.m.r. spectrum. Pople[31] utilized this model in an attempt to account quantitatively for the deshielding of aromatic compared with olefinic protons in the spectrum. The circulating π-electrons were treated as a magnetic dipole situated at the centre of the ring, and the induced magnetic field so produced deshielded the ring proton by 0.14 p.p.m. This model was improved by Waugh and Fessenden,[33] and by Bovey and Johnson,[34] who substituted current loops, similar to those used by Pauling, for the point dipole.

TABLE 3

Diamagnetic Exaltation in Conjugated Hydrocarbons[a]

Compound	χ_M (-10^{-6} cm^3 mol^{-1})	$\chi_{M'}$ (-10^{-6} cm^3 mol^{-1})	Λ
Cyclohexene	57.5	58.3	−0.8
Cyclohexa-1,3-diene	48.6	49.3	−0.7
Benzene	54.8	41.1	13.7
Naphthalene	91.9	61.4	30.5
Azulene	91.0	61.4	29.6
Chrysene	167	102	65
1,6-Methano[10]annulene	111.9±0.4	75.1	36.8
Pyrene	155	98	57
trans-15,16-Dimethyl-15,16-dihydropyrene	210±15	129	81

[a] Values from H. J. Dauben, J. D. Wilson, and J. L. Laity, in 'Nonbenzenoid Aromatics', ed. J. P. Snyder, Academic, New York, 1971, vol. 2, p. 182.

McWeeny[35] used a quantum mechanical model related to that which London had used in his treatment of diamagnetic anisotropy. It was found that in all of these models a term for localized atomic contributions had to be made in order to obtain satisfactory agreement with experiment, and it was subsequently concluded that such corrections were also required for satisfactory agreement of the model with the experimental magnetic susceptibilities.

The total anisotropy, $\Delta\chi$, is the sum of the anisotropies of the σ-bonds, $\Delta\chi^{\sigma}$, the localized p π-electron, $\Delta\chi^{p}$, and the London contribution to the ring current, χ^{L}:

$$\Delta\chi = \Delta\chi^{\sigma} + \Delta\chi^{p} + \Delta\chi^{L} \tag{4}$$

In order to correctly predict nuclear magnetic chemical shifts, it was found that χ^{L} had to have a value of -30×10^{6} cm^3 mol^{-1}, which was considerably smaller than the value previously used to calculate the diamagnetic anisotropy.

The correlation between the ^{1}H n.m.r. chemical shifts and the ring current allows the proton chemical shift to be used as a criterion of aromaticity. Again, suitable model compounds are required, such that the proton chemical shift in benzene may be compared with the olefinic proton in cyclohexene and cyclohexadiene. However, in the larger cyclic conjugated systems in which some of the protons are *inside* the ring cavity and are consequently *shielded*, the chemical shift difference between the inner and outer protons can be determined and the need for a model system is removed. The use of the n.m.r. criterion to determine the aromaticity of the annulenes and related systems is discussed in Chapter 2.6. Attempts have been made to quantify the chemical shifts with the degree of aromaticity, but such quantification does not seem reliable.

The bulk diamagnetic anisotropy of benzene can also be demonstrated in an n.m.r. experiment: if two compounds are dissolved in benzene, one of which complexes with the benzene and the other does not, then the chemical shift difference between protons in the two compounds will be different from that when they are dissolved in an inert solvent.[36] The ability of benzene to cause specific chemical shifts has been exploited as a means of identifying protons at specific sites in complex molecules.[37] The same effect should be observed for other compounds with ring currents when these are used as n.m.r. solvents, and this could provide a measure of diamagnetic anisotropy. When cyclo-octaterraene was used as an n.m.r. solvent, no anomalous shifts were observed for dissolved compounds when compared with the shifts in neat solvents, and cyclo-octatetraene therefore does not appear to sustain any type of ring current.[38] This method suffers from the disadvantages that a large amount of compound is required, and that it should be either a liquid or very soluble in an inert solvent. Few examples of the use of this technique have, therefore, been reported.

The lack of additivity of magnetic rotatory power (Faraday effect) has also been used as a diagnostic test for a delocalized system.[39]

2.4.3.4 Other criteria

(i) Electron spectra

Benzene has a very characteristic electronic spectrum with an intense band at 185 nm and weak bands at 200 and 260 nm. The short-wavelength band is assigned to an allowed $^1A_{1g} \rightarrow {}^1E_{1u}$ transition, the 260 nm band to a forbidden $^1A_{1g} \rightarrow {}^1B_{2u}$ transition, and the 200 nm band is now generally agreed to arise from a $^1A_{1g} \rightarrow {}^1B_{1u}$ transition. The non-allowed transitions are observed as weak bands because of vibrational coupling to other allowed transitions. Comparison of the spectrum of benzene with fused polycyclic benzenoid systems is difficult, as these systems have lower symmetries, but a number of attempts have been made to classify the bands in polycyclic systems. The classifications of Clar,[40] Jones,[41] and Klevens and Platt[42] are the best known. For a particular type of annelation, it is possible to predict the spectrum and to deduce the effects of further annelation at different positions. Within a group of molecules, the electronic spectrum is often an excellent indication of the way in which the system has been perturbed, but it does not appear to be a useful general criterion for aromaticity.

(ii) Photoelectron (PE) spectra

Photoelectron spectroscopy provides a convenient method of determining the ionization potential (IP) of electrons in a molecule.[43] The character of the electron type, π or σ, can also be deduced, and this technique could be diagnostic for aromatic character, provided an arbitrary standard could be agreed. The technique provides valuable information within a group of related molecules; thus in monosubstituted benzenes, electron-withdrawing groups cause an increase in the ionization potential, whereas electron-donating groups cause a decrease. If mesomeric charge transfer is possible, as with substituents such as OH and NH_2 having lone pairs of electrons, then a large decrease in IP is observed, although the groups are inductively electron withdrawing. The spectra of azabenzenes and of polycyclic systems have been reported, the former having similar ionization potentials to the corresponding benzenoid systems.

There is some dispute regarding the assignment of the ionization potentials to orbitals in many cases and the spectra do not fit the theoretical models. Recent results suggest that this is due to deficiencies in the semi-empirical methods of calculation which have been used.[44]

At the present time, PE spectra appear to be more useful in studying the changes of IP in a series of related molecules than as an absolute criterion of aromatic character.

(iii) pK Values

With charged species, such as the cyclopentadienyl anion (**20**) or the cycloheptatrienyl (tropylium) cation (**25**), the thermodynamic stability with regard to the corresponding conjugate acid or base may serve as a criterion to determine whether the species is aromatic. In the case of anions, the stabilizations of the anion will be seen in the increased acidity of the hydrocarbon, whereas with cations it is seen in the ease of hydride abstraction or resistance to hydrolysis:

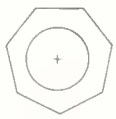
$$RH + B^- \rightleftharpoons R^- + BH \quad (5)$$

$$RH + A^+ \rightleftharpoons R^+ + AH \quad (6)$$

$$R^+ + H_2O \rightleftharpoons ROH + H^+ \quad (7)$$

The acidities of a series of hydrocarbons, expressed as pK_a values, are given in Table 4.

(20)



(25)

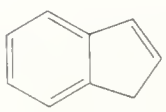
TABLE 4

Acidities of Hydrocarbons[a]

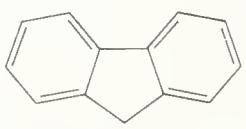
Hydrocarbon	pK_a
Cyclohexane	51
Cyclopropane	46
Cycloheptatriene	36
Triphenylmethane	31.5
Fluorene (**27**)	22.9
Indene (**26**)	18.5
Cyclopentadiene	15
Fluoradene (**28**)	11

[a] E. Buncel, 'Carbanions: Mechanistic and Isotopic Aspects', Elsevier, Amsterdam, 1975.

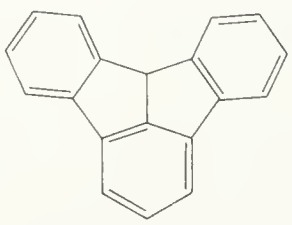
From Table 4 it can be seen that cyclopentadiene is 20 orders of magnitude more acidic than cycloheptatriene, and considerably more acidic than triphenylmethane. Benzoannulation of cyclopentadiene causes a decrease in acidity, as in indene (**26**) and fluorene (**27**), but fluoradene (**28**), which has two alternative fluorene contributors, is more acidic.



(26)



(27)



(28)

(29)

The stabilities of a series of carbocations, based on equation (7) and reported as pK_{R^+} values, are tabulated in Table 5. From the table it can be seen (*i*) that both the cyclopropenium (**29**) and tropylium (**25**) ions are very stable, (**25**) having a comparable acidity to acetic acid, and (*ii*) that the cyclopropenium ion is stabilized by alkyl, and to a lesser extent, aryl groups.

TABLE 5

pK_{R^+} Values for Some Carbocations

Substrate	pK_{R^+}	*Ref.*
$Pr^n_2C_3H^+ ClO_4^-$	2.7	a
$Ph_3C_3^+ Br$	3.1	a
$(p\text{-}MeOC_6H_4)_2PhC_3^+ Br^-$	5.2	a
$C_7H_7^+ Br$	5.3	b
$(p\text{-}MeOC_6H_4)_3C_3^+ Br^-$	6.5	a
$Pr^n_3C_3^+ ClO_4^-$	7.2	a

[a] R. Breslow, H. Höver, and H. W. Chang, *J. Amer. Chem. Soc.*, 1962, **84**, 3168. [b] W. von E. Doering and L. H. Knox, *J. Amer. Chem. Soc.*, 1954, **76**, 3203.

2.4.4 ANTI-AROMATICITY

We have attempted so far to distinguish between aromatic and non-aromatic compounds, and to provide criteria by which such a distinction can be made. In the middle

1960s it was suggested, on the basis of experimental and theoretical observations, that there could be a third group of compounds which are anti-aromatic systems, *i.e.* they are *destabilized* by delocalization.[45,46] Thus it was found that the cyclopropenyl anion (**30**) was less stable than the cyclopropanyl anion (**31**), although the former is an allylic anion,[47] and it was suggested that delocalized, square-planar cyclobutadiene (**32**) is less stable than the localized rectangular form (**33**).[46,48]

The concept of anti-aromaticity appears, at first sight, rather strange, but it must be remembered that the properties of the molecule are being compared with a model system. The anti-aromatic molecule will thus be in its ground state, but this will be of a higher energy than would be calculated or found for a model system. The ground state of the cyclopropenyl anion is of a higher energy than those of the model systems, the cyclopropanyl and allyl anions.[47] Cyclobutadiene will likewise be in its ground state, but this will be of higher energy than the model system.[48] Anti-aromatic compounds can be expected to have antithetical properties to aromatic compounds, and the criteria discussed in Section 2.4.3 should be applicable, but the observations reversed! In the succeeding parts of this section these criteria will be re-examined.

(**30**)

(**31**)

(**32**)

(**33**)

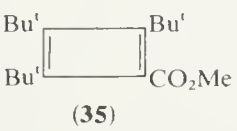
(**34**)

2.4.4.1 Thermodynamic properties

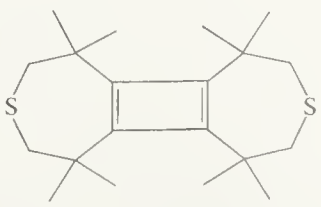
Anti-aromatic compounds might be expected to have *negative* resonance energy. There are, at the present time, no thermodynamic measurements on anti-aromatic compounds. Theoretical calculations have been carried out on the cyclopropenyl anions, cyclobutadiene, and the cyclopentadienium cation (**34**), and each of these compounds is predicted to be less stable than the corresponding acyclic analogue.[47–49] For a more detailed discussion of compounds (**30**)–(**34**), see Chapter 2.6.

2.4.4.2 Structural properties

Since anti-aromatic compounds are destabilized by conjugation, alternation of single and double bonds is to be expected, and also distortion from planarity. The i.r. spectrum of cyclobutadiene is consistent with it having a square ground state,[50] whereas two derivatives, methyl tri-t-butylcyclobutadienecarboxylate (**35**)[51] and the tricyclic compound (**36**)[52] have been examined by X-ray crystallographic methods and have approximately rectangular structures with alternate double and single bonds. Cyclo-octatetraene is a non-planar system with alternating double and single bonds and is, on the basis of a variety of criteria, non-aromatic rather than anti-aromatic. An X-ray crystallographic analysis of [16]annulene (**37**) showed that it has alternate double and single bonds, but that it deviates little from planarity.[53] The magnetic properties of (**37**) suggest it has some anti-aromatic character.



(**35**)



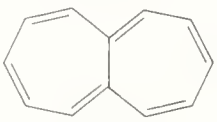
(**36**)

(**37**)

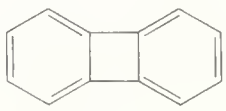
2.4.4.3 Magnetic properties

In the Hückel model for a $4n$ system, two electrons are in degenerate non-bonding orbitals with unpaired spins (Section 2.4.2). In order to remove the degeneracy, the molecule will undergo a distortion so that one orbital increases and one decreases in energy (pseudo-Jahn–Teller effect), and the electrons will become paired in the orbital of lower energy. Since the orbitals were degenerate, magnetic transitions between them are allowed, and since the energy difference is small, the probability of such a transition will be high. Consequently, when the molecule is introduced into a magnetic field, mixing of the excited and ground states will occur. This mixing results in a *paramagnetic* field which will have opposite consequences to the diamagnetic fields discussed earlier. Paramagnetism in benzene will be small because magnetic transitions between the occupied and unoccupied orbitals are forbidden, and the energy difference is large.[54]

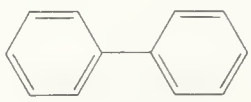
As a consequence of the large paramagnetic effect in $4n$ annulenes, the bulk magnetic susceptibility will be reduced *below* that expected, and a negative magnetic exaltation, $-\Lambda$, should be observed. The magnetic susceptibilities of a few $4n$ π-electron mono- and poly-cyclic systems have been reported,[32] and these are tabulated in Table 6. Unlike cyclo-octatetraene, which has a value close to that calculated, [16]annulene (**37**) and heptalene (**38**) show negative diamagnetic exaltations, and that for biphenylene (**39**) is much less than that for biphenyl (**40**). Thus compounds (**37**) and (**38**) can be considered to be anti-aromatic while biphenylene (**39**) has an anti-aromatic component.



(38)



(39)



(40)

TABLE 6

Diamagnetic Exaltation in $4n$ π-Electron Systems[a]

Compound	χ_M (-10^{-6} cm^3 mol^{-1})	$\chi_{M'}$ (-10^{-6} cm^3 mol^{-1})	Λ
Cyclo-octene[b]	80.5±0.6	81.0	−0.5
Cyclo-octa-1,3,5-triene[b]	65.1±0.8	64	1.1
Cyclo-octatetraene	53.9	54.8	−0.9
[16]Annulene (**38**)	105±2	110	−5
Biphenyl[b]	103.3	77.1	26.2
Biphenylene (**40**)	88±3	74	15
Heptalene (**39**)	72±7	78.2	−6

[a] Values from H. J. Dauben, J. D. Wilson, and J. L. Laity, in 'Nonbenzenoid Aromatics', ed. J. P. Snyder, Academic, New York, 1971, vol. 2. [b] Model system for comparison.

The paramagnetic term can be expected to affect the ^{1}H n.m.r. chemical shifts.[54] Whereas with the diamagnetic ring current the induced field opposed the applied field, in the paramagnetic case the induced field will enhance the applied field. The protons inside the ring will thus be deshielded and those outside the ring will be shielded, the opposite situation to that in aromatic systems. These differences are summarized in Table 7. Systems in which the outer protons are shifted downfield and the inner protons upfield have been termed *diatropic*, those in which the outer protons are shifted upfield and the inner protons downfield, *paratropic*, and those in which the two types of protons are not shifted from each other, *atropic*.[55] These designations are intended to describe the observed magnetic effects exhibited by the molecule, but in most cases the magnetic properties will be in accord with the designations of aromatic, anti-aromatic, and non-aromatic. The use of this magnetic criterion has been extensive because of the ease with which the measurements are taken and numerous examples are given in Chapter 2.6.

TABLE 7

Comparison of Magnetic Properties of $4n$ and $4n+2$ π-Electron Systems

System	Predominant magnetic term	^1H n.m.r. chemical shift		Type
		Outer protons	Inner protons	
$4n+2$	Diamagnetic	Downfield (deshielded)	Upfield (shielded)	Diatropic
$4n$	Paramagnetic	Upfield (shielded)	Downfield (deshielded)	Paratropic

2.4.4.4 Other properties

Only a few electronic spectra of anti-aromatic compounds have been taken and these have not been sufficiently studied to be used for diagnostic purposes. The $4n$ annulenes have their principal maximum absorption at shorter wavelength than the near-neighbours in the $4n+2$ series,[56] but a general analysis of the spectra is lacking.

PE spectra of anti-aromatic systems have yet to be reported.

pK values have been used to indicate the anti-aromaticity of anions. Thus cycloheptatriene is much less basic than cyclopentadiene (Table 4) and the cyclopropenyl anion is less stable than the cyclopropanyl or allyl anions.[47]

2.4.5 THEORETICAL DEFINITIONS OF AROMATICITY

As was pointed out in Section 2.4.2, Hückel theory accounts for the difference between $4n+2$ and $4n$ monocyclic π-electron systems, but it predicts that all of these systems, with the exception of cyclobutadiene, will be stabilized compared with a non-delocalized model system. These results are expressed in a graphical form in Figure 7. It can be seen that at small values of n, the $4n$ and $4n+2$ systems form two series, with the $4n+2$ systems more stabilized than the $4n$, but at higher values of N the two series converge. The Hückel theory does not adequately explain the lack of stability of the lower members of the $4n$ series and, in particular, it does not predict the anti-aromatic behaviour described in Section 2.4.4. The inadequacy of the Hückel calculations stimulated the study of these molecules by more sophisticated methods.

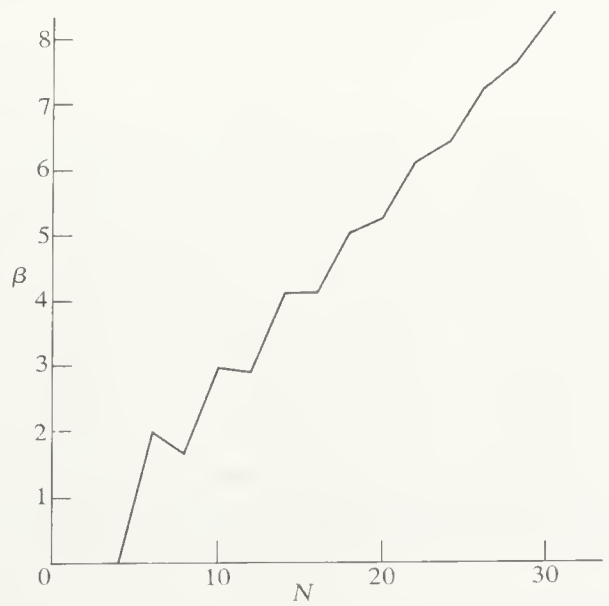


Figure 7 The delocalization energy (in β) calculated by the HMO method for monocyclic conjugated systems with N carbon atoms

2.4.5.1 Semi-empirical calculations and Dewar resonance energy

The major problem with the Hückel method is that it uses one-electron Hamiltonians and interactions of the electrons are not treated. Pople,[57a] and Pariser and Parr,[57b] introduced a method which used the many-electron Hamiltonian, together with a number of simplifications, which allows the formulation of a series of equations comparable with those used in the Hückel theory but includes terms representing electronic interaction. This self-consistent field (SCF) treatment, using parameters originally suggested by Pariser and Parr,[57b] is known as the Pople–Pariser–Parr (PPP) approximation. The theory was applied to benzene in the original publications,[57] and it has been used extensively to calculate a variety of molecular properties. Chung and Dewar[58] applied the PPP method to benzene and related molecules and showed that the heats of formation could be reasonably estimated. The method was modified to take into account less idealized geometries and it was found that all of the small $4n$ annulenes were destabilized compared with model systems.[59] It was also shown that alicyclic polyenes have additive bond energies, thus allowing values to be assigned to the C=C and C—C bonds in these systems.[59] Dewar and de Llano[60] utilized these values to obtain the heats of formation of polyenes which were used as model systems with which to compare the heats of formation of the delocalized molecule. These calculations gave a considerably lower resonance energy, 83.7 kJ mol^{-1}, to benzene than had previously been accepted on the basis of a model with ethylene 'double' and ethane 'single' bonds. The resonance energy values based on the acyclic polyene model have been called 'Dewar-resonance energies' (DRE).[61]

In these calculations, two changes have been made with respect to the older Hückel calculations. Firstly, the PPP method has replaced the Hückel theory, and secondly a new model system has been used to calculate the resonance energy. It now appears that the second change was the more significant (though the additivity was revealed by the PPP calculation on acyclic polyenes), since it has been shown that when the Dewar acyclic polyene model is used as reference, satisfactory values for heats of formation and resonance energies can be obtained with the simple Hückel method.[62] The values for the heats of formation and Dewar resonance energies calculated by the PPP[60] and Hückel methods[62] are given in Table 8.

TABLE 8

Comparison of Calculated and Observed Heats of Formation of Conjugated Hydrocarbons from Atoms

Compound	ΔH(eV)		
	Calc.[a] *PPP*	*Calc.*[b] *Hückel*	*Observed*
Benzene	57.16	57.14	57.16
Naphthalene	90.61	90.59	90.61
Anthracene	123.89	123.95	123.93
Phenanthrene	124.22	124.14	124.20
Azulene	89.47	90.13	89.19
Pyrene	138.62	138.60	138.88
Triphenylene	157.94	157.79	157.76
Biphenyl	109.75	—	109.76
Biphenylene	104.87	104.67	102.00

[a] Values from M. J. S. Dewar and C. de Llano, *J. Amer. Chem. Soc.*, 1969, **91**, 789. [b] Values from L. J. Schaad and B. A. Hess, *J. Amer. Chem. Soc.*, 1972, **94**, 3068.

Dewar resonance energy appears to provide a theoretically based method for defining aromaticity; an unsaturated cyclic system which has a positive DRE will be aromatic, a

system with a negative DRE will be anti-aromatic, and a system with zero — or approximately zero — DRE will be non-aromatic. Such a definition has the merit that it does not require testing, but it may be considered to have the disadvantage of not predicting the chemical properties of the system. Nevertheless, this seems a considerable advance on previous theoretical methods, one advantage being that, given the model system, the method of calculation does not appear crucial.[61]

Schaad and Hess[62] have suggested that the resonance energy per π-electron (REPE) could be used as an index of aromaticity. They defined the REPE by the equation

$$\text{REPE} = \frac{E_\pi - E_{\text{ref}}}{N}$$

where E_π is the total π-energy, E_{ref} the energy of the reference system, and N the number of the π-electrons. The values of E_π for the delocalized molecule and E_{ref} for the acyclic polyene were both calculated by the Hückel method. Compounds with REPE > 0 are aromatic, with REPE $= 0$ are non-aromatic, and with REPE < 0 are anti-aromatic. Clearly, since REPE is a continuous function, there will not be large differences in properties of molecules with REPE close to zero. Similar indices have been used by other workers.[63]

2.4.5.2 Valence bond calculations and application of the resonance method

The preceding theoretical discussions have been made on the basis of the MO method. The valence bond (VB) method was formulated in the early 1930s and, as has been repeatedly pointed out, if extended calculations are carried out the two methods are equivalent. The VB method had the initially attractive advantage that it uses structures familiar to the organic chemist and it can be formulated in an even simpler version, the resonance theory, which was extensively illustrated by Pauling[20] and Wheland.[20] In resonance theory, only Kekulé structures are enumerated and thus a large variety of alternative bond-paired structures are ignored. Because of the gross simplification made, the resonance theory has been relegated to a role at an elementary level in structure theory, but a number of workers have recently suggested that by enumerating Kekulé structures with a bias towards those which are important contributors to the resonance hybrid, valid predictions about the properties of compounds can be made.[64,65]

2.4.5.3 Bond localization

The preceding theoretical criteria have all been based on the increase in thermodynamic stability of the aromatic system compared with a non-aromatic model. Theoretical criteria related to other phenomena have also been advanced, and one of some interest is based on the concept of bond fixation.[66] Two types of bond fixation have been described, the first of which leaves the symmetry of the σ-bond framework unaltered whereas the second reduces it. If one considers a molecule such as fulvene (**41**), a structure for the σ-framework can be drawn with all bonds equal and which has $\mathbf{C}_{2v}$ symmetry (Figure 8). The π-bond orders for fulvene can now be calculated, and it is found that there are large differences between formal single and double bonds in the energetically most favoured structure, and fulvene is best represented by the single valence bond structure (**41a**). Examination of (**41a**) shows that it also has $\mathbf{C}_{2v}$ symmetry, and so the symmetry of the original σ-system has been unaltered by bond fixation. This type of bond fixation is called first-order, and it derives from the first term in the Taylor series. If we now consider pentalene (**42**), the σ-framework has $\mathbf{D}_{2h}$ symmetry. Computing the π-bond orders for pentalene it is found that either of the two structures (**42a**) and (**42b**) is favoured, and the molecule will interchange between the two forms. Structures (**42a**) and (**42b**) have less

symmetry than the original σ-bond structure, two C_2 axes being lost, and this type of bond fixation is called second-order and arises from higher terms in the Taylor series. Cyclobutadiene (**33**) similarly has second-order bond fixation, the two rectangular structures (**33a**) and (**33b**) having $\mathbf{D}_{2h}$, and the σ-structure $\mathbf{D}_{4h}$, symmetry. When this analysis is applied to benzene, it is found to have neither first- nor second-order bond fixation.

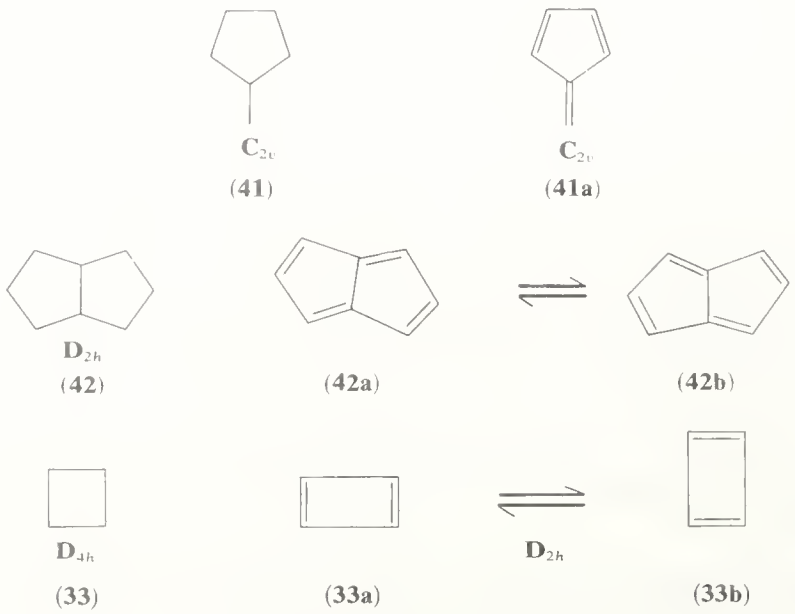


Figure 8

It has been suggested that bond fixation, derived in this way, could be used as a theoretical criterion of aromaticity. Aromatic molecules would be those which do not exhibit either first- or second-order bond fixation. This idea has received some critical comment,[67] it being inferred that benzene would be the one aromatic neutral molecule by this criterion, but the concept of bond fixation does lead to useful predictions regarding the reactive sites in molecules.[68]

2.4.5.4 Relationship of energetic and bond localization criteria

The definition of aromaticity based on Dewar resonance energy and the concept of bond localization, which have been developed in the preceding sections, can be combined pictorially as in Figure 9. Whereas aromatic compounds, such as benzene, will have a

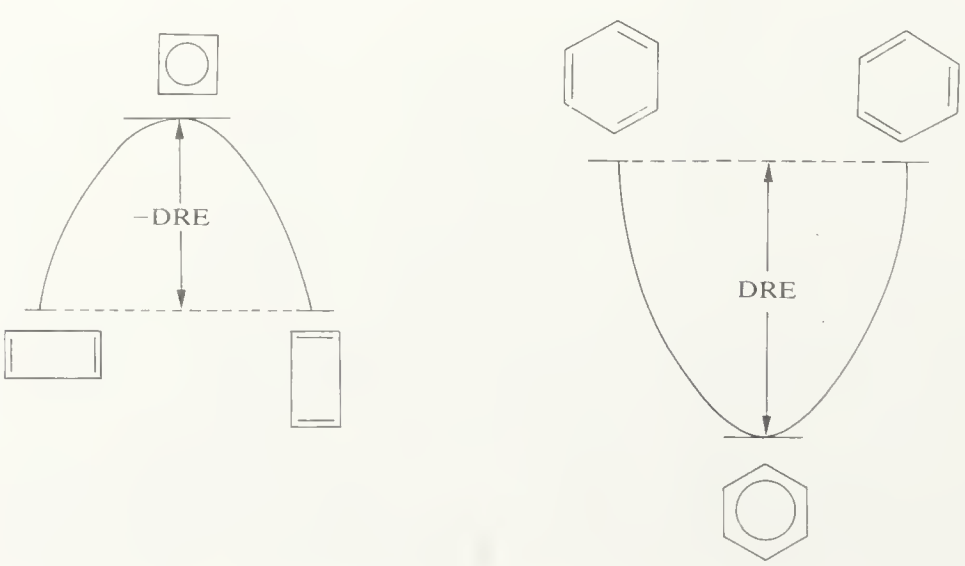


Figure 9

positive DRE with the delocalized molecule at lower energy than the localized model system, anti-aromatic molecules, such as butadiene, will have a negative DRE, with the localized structures at lower energy than the delocalized structure. The negative DRE in these latter systems will approximate to the activation energy needed to convert the planar, localized molecule into the other bond isomer.

2.4.6 AROMATIC TRANSITION STATES

The cyclic delocalization of electrons over a number of atoms has been shown to increase the stability of the system, provided that there are sufficient bonding and non-bonding molecular orbitals to accommodate these electrons in a closed shell. Such an electronic arrangement would also be expected to lower the transition state of a reacting molecule or molecules. Aromatic transition states can be expected to facilitate reactions.

The Hückel model for planar, monocyclic conjugated systems involves the linear combination of atomic *p*-orbitals with an even number of nodes. Thus the lowest MO of benzene had no nodes, the next degenerate pair of MOs, two nodes, the next pair of MOs, four nodes, and the highest MO, six nodes. It is also possible to formulate arrays of atomic *p*-orbitals with an odd number of nodes, and these would involve an odd number of phase changes. Such an array of orbitals with one phase change is shown in Figure 10. Its topology resembles a Möbius strip, *i.e.* a band twisted so that it has one continuous surface. Heilbronner[69] first drew attention to the Möbius arrangement and showed that it led to a different ordering of levels compared with the system with a Hückel perimeter, and that an annulene with $4n$ π-electrons would have a closed shell if arranged in a Möbius manner, whereas a $4n+2$ annulene would have an open shell. Although no examples of a ground-state molecule with a Möbius orbital array have yet been discovered, this concept has found considerable utility in predicting the likely organization of the transition states for a variety of reactions.

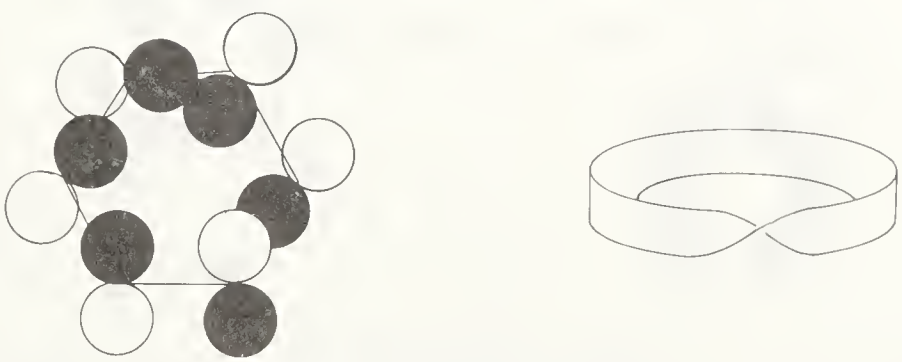
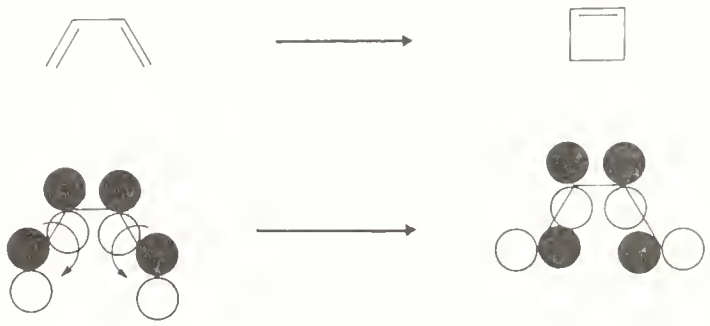


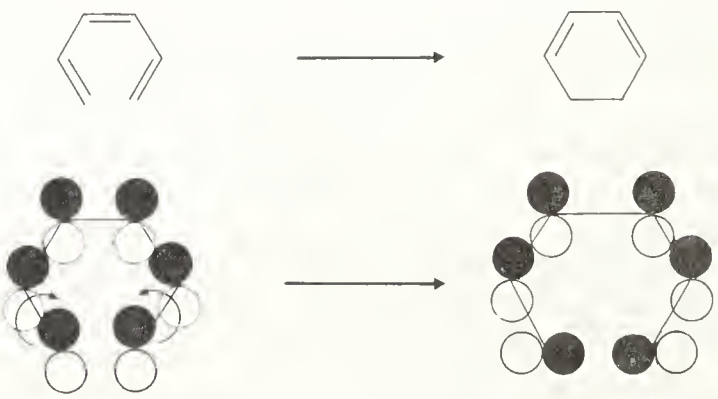
Figure 10

Dewar[70] and Zimmerman[71] have both shown that the stereochemistry and allowedness of pericyclic reactions[72] can be deduced by examining the array of atomic orbitals in the transition state. Ground-state reactions will be expected to proceed *via* Hückel transition states if $4n+2$ π-electrons are involved and by Möbius transition states if $4n$ π-electrons are involved. This can be illustrated for the electrocyclic ring closure of butadiene and hexatriene (Figure 11). The ground-state orbitals and those for both the Hückel and Möbius transition states are illustrated in the figure. Butadiene has four electrons, and these can enter low-lying orbitals in the Möbius transition state, whereas two electrons have to enter a non-bonding pair of orbitals in the Hückel transition state. Conrotatory ring closure of butadiene to cyclobutene will therefore be the preferred mode *via* the allowed Möbius transition state. For hexatriene, the Hückel transition state is of lower energy and disrotatory ring closure is preferred.

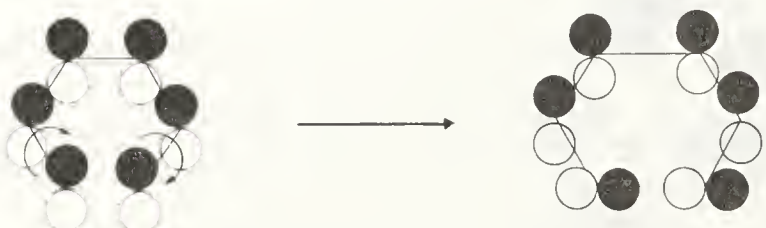


Hückel 4π disrotatory forbidden

Möbius 4π conrotatory allowed



Hückel 6π disrotatory allowed



Möbius 6π conrotatory forbidden

Figure 11

For photochemical reactions the first excited state of the reactant must be correlated with the ground state of the product. Now for butadiene the orbital into which the electron is excited correlates with an anti-bonding orbital in the Möbius transition state but with a non-bonding orbital in the Hückel state, and the latter reaction mode, with disrotatory ring closure, is preferred. This preference is reversed in hexatriene, which reacts *via* a Möbius transition state with conrotatory closure on irradiation. These predictions assume that the energies of the appropriately populated Hückel or Möbius system will be similar in energy to that of the excited reactant when it is close to the crossing point at which it is transformed to the ground-state product.

The concept of the aromatic transition state can be applied to the other types of

pericyclic reactions. In the Diels–Alder cycloaddition, a 4π-diene reacts with a 2π-dienophile *via* a 6π-electron transition state. A lowering of the transition state energy is therefore expected (Figure 12).

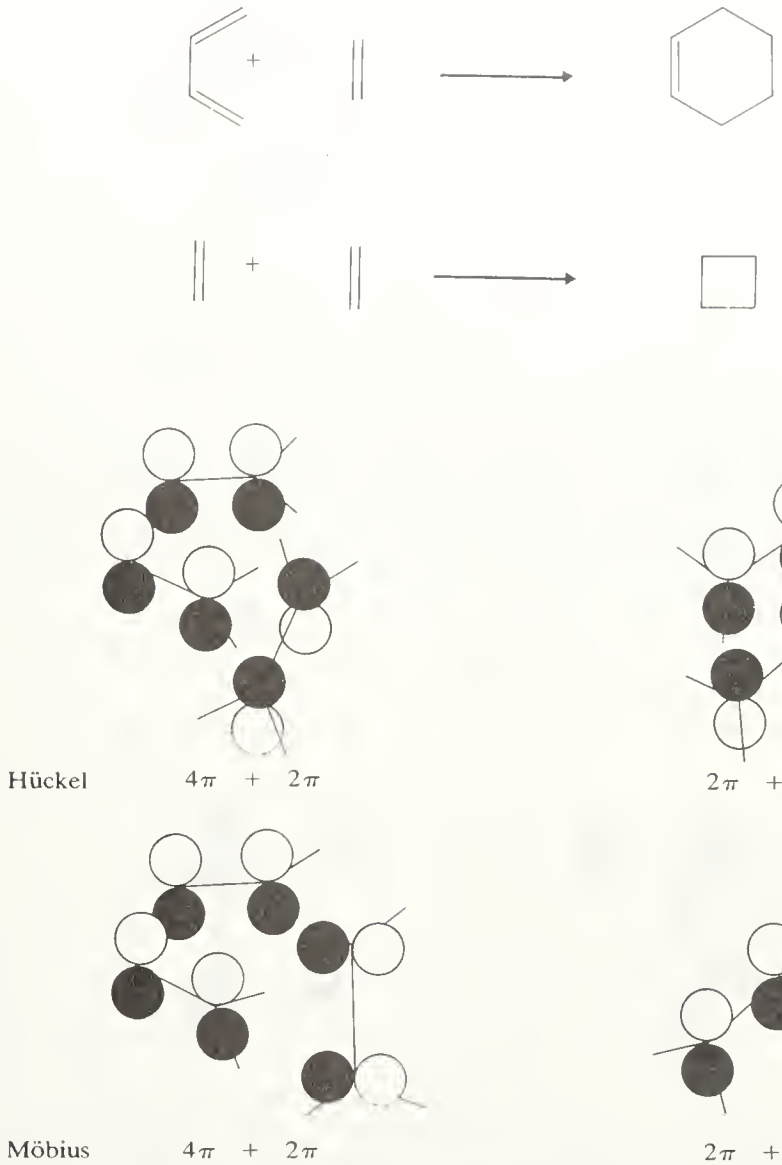


Figure 12

The cycloaddition of two olefins involves the combination of two 2π-systems in a 4π-electron transition state, and this should increase its energy (Figure 12). Clearly, for a ground-state dimerization of an olefin the two molecules must adopt a Möbius array, as shown. Photochemically the requirements are reversed, and $2\pi+2\pi$ photodimerizations are well known, proceeding by Hückel transition states, whereas photochemical $4\pi+2\pi$ cycloadditions are not.

Sigmatropic reactions involve rearrangements which have as a component the cleavage and formation of σ-bonds, and again this type of reaction can be concerted if an aromatic transition state is involved. In the sigmatropic 1,5-hydrogen shift, the hydrogen atom will be transferred on the same side of the diene, *i.e.* suprafacially. This can be considered to have a 6π-electron transition state involving the five p-orbitals on the five carbon atoms and the s-orbital on hydrogen (Figure 13).

A 1,3-sigmatropic hydrogen shift would involve a 4π-electron transition state, and the Möbius array preferred requires that the hydrogen atom be transferred from one face to

Figure 13

the other of the allyl system, *i.e.* antarafacially. Such a situation is stereochemically disfavoured.

The Cope reaction involves a [3,3]-sigmatropic shift, and this also involves a 6π-electron transition state. It has been found that the Cope reaction proceeds by a chair-like rather than a boat-like transition state, and this can also be explained by the nature of the transition state since the boat-like state involves two four-membered 4π-electron rings and consequently will be destabilized (Figure 14).

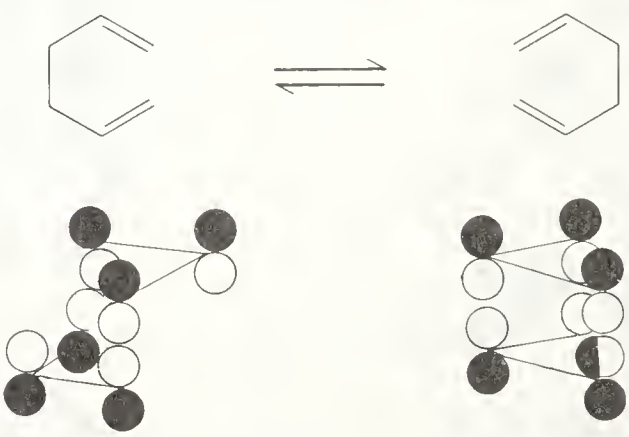


Figure 14

The correlation described between the MOs of the reactants and the products was first clearly enunciated for pericyclic reactions by Woodward and Hoffmann.[72] These authors originally used frontier orbital theory as the description, and later they and other workers employed orbital correlation methods resulting in the introduction of the principle of conservation of orbital symmetry. The predictions of all three descriptive methods will be the same for the simpler cases, and the general predictions have been enunciated in the form of a set of rules, the Woodward–Hoffmann rules.

References

1. M. Faraday, *Phil. Trans. Roy. Soc.*, 1825, 440.
2. Using the equivalent weight concepts current at the time, Faraday expressed the empirical formula as C_2H and the molecular formula as C_6H_3.
3. E. Mitscherlich, *Ann. Phys.*, 1833, **29,** 231.
4. E. W. Davy, *Trans. Roy. Irish Acad.*, 1839, **18,** 80.
5. 'There's hardly a thing a man can name
   Of beauty or use in life's small game,
   But you can extract in alembro or jar
   From the physical basis of black coal tar'
   Punch

6. See J. R. Partington, 'A History of Chemistry', Macmillan, London, 1964, vol. 4, p. 488 *et seq.*
7. A. Kekulé, *Bull. Soc. chim. France*, 1865, **3,** 98; *Bull. Acad. Roy. Belg.*, 1865, **19,** 551; *Annalen*, 1866, **137,** 129.
8. See J. P. Snyder, in 'Nonbenzenoid Aromatics', ed. J. P. Snyder, Academic, New York, 1969, vol. 1, p. 1; Ref. 6, p. 553 *et seq.*
9. See ref. 6, p. 802; E. Wroblewsky, *Ann. Chem. Pharm.*, 1878, **192,** 196.
10. A. Ladenburg, *Ber.*, 1869, **2,** 140, 272.
11. A. Claus, *Ber.*, 1882, **15,** 1405.
12. E. Bamberger, *Annalen*, 1890, **257,** 1; *Ber.*, 1891, **24,** 1758; *Annalen*, 1893, **273,** 373.
13. 'das Axiom zu Grunde legt ein centrischen (potentielles) Valenzsystem. Kann nur als *hexa*centrisches bestehen', in Ref. 12, Bamberger's italics.
14. J. Thiele, *Annalen*, 1899, **306,** 87.
15. R. Willstätter and E. Waser, *Ber.*, 1911, **44,** 3423; R. Willstätter and M. Heidelberger, *Ber.*, 1913, **46,** 517.
16. J. Thiele, *Annalen*, 1901, **319,** 226.
17. J. W. Armit and R. Robinson, *J. Chem. Soc.*, 1925, **127,** 1604.
18. C. K. Ingold, *J. Chem. Soc.*, 1922, **121,** 1133.
19. E. Hückel, *Z. Phys.*, 1931, **70,** 204; 'Grundzüge der Theorie Ungesattigter und Aromatischer Verbindungen', Verlag Chemie, Berlin, 1938.
20. See L. Pauling, 'The Nature of the Chemical Bond', 3rd edn., Cornell University Press, New York, 1960; G. Wheland, 'The Theory of Resonance and its Application to Organic Chemistry', Wiley, New York, 1944.
21. M. J. S. Dewar and H. N. Schmeising, *Tetrahedron*, 1960, **11,** 96.
22. P. L. F. Jones, *Trans. Faraday Soc.*, 1935, **31,** 1036; R. Wierl, *Amer. Phys.*, 1931, **8,** 521; V. Schomaker and L. Pauling, *J. Amer. Chem. Soc.*, 1939, **61,** 1769; G. E. Bacon, N. A. Curry, and S. A. Wilson, *Proc. Roy. Soc.*, 1964, **A279,** 98.
23. C. K. Ingold, *Proc. Roy. Soc.*, 1938, **A169,** 149; 'Structure and Mechanism in Organic Chemistry', 2nd edn., Cornell University Press, New York, 1971.
24. (a) E. G. Cox, D. W. J. Cruickshank, and J. A. S. Smith, *Proc. Roy. Soc.*, 1958, **A247,** 1; G. J. Piermarini, A. D. Mighell, C. E. Weir, and S. Block, *Science*, 1969, **165,** 1250; R. Fourme, D. André, and M. Renaud, *Acta Cryst.* 1971, **B27,** 1275; (b) 'Tables of Interatomic Distances and Configurations in Molecules and Ions', ed. L. E. Sutton, The Chemical Society, London, Special Publication, No. 11 (1958), Supplement, No. 18 (1965); 'Molecular Structure and Dimensions', ed. O. Kennard *et al.*, International Union of Crystallography, 1972, vol. 1A.
25. A. Langseth and B. P. Stoicheff, *Canad. J. Phys.*, 1956, **34,** 350.
26. K. Lonsdale, *Proc. Roy. Soc.*, 1929, **A123,** 494.
27. (a) J. W. Emsley, J. Feeny, and L. H. Sutcliffe, 'High Resolution Nuclear Magnetic Resonance Spectroscopy', Pergamon, Oxford, 1966, vol. 2, p. 772; (b) H. Günther, A. Shyoukh, D. Cremer, and K. H. Frisch, *Tetrahedron Letters*, 1974, 781.
28. J. H. Callomon, T. M. Dunn, and I. M. Mills, *Phil. Trans.* 1966, **A259,** 499.
29. L. Pauling, *J. Chem. Phys.*, 1936, **4,** 673.
30. F. London, *Compt. rend.*, 1937, **205,** 28; *J. Chem. Phys.*, 1937, **5,** 837.
31. J. A. Pople, *J. Chem. Phys.*, 1956, **24,** 1111.
32. H. J. Dauben, J. D. Wilson, and J. L. Laity, in 'Nonbenzenoid Aromatics', ed. J. P. Snyder, Academic, New York, 1971, vol. 2, p. 167.
33. J. S. Waugh and R. W. Fessenden, *J. Amer. Chem. Soc.*, 1957, **79,** 846.
34. C. E. Johnson and F. A. Bovey, *J. Chem. Phys.*, 1958, **29,** 1012.
35. R. McWeeny, *Proc. Phys. Soc.*, 1951, **64A,** 261, 921; 1952, **65A,** 839; 1953, **66A,** 714.
36. W. G. Schneider, *J. Phys. Chem.*, 1962, **66,** 2653.
37. See N. S. Bhacca and D. H. Williams, 'Application of NMR Spectroscopy in Organic Chemistry', Holden Day, New York, 1964, p. 159.
38. F. A. L. Anet and G. E. Schenck, *J. Amer. Chem. Soc.*, 1971, **93,** 556.
39. J.-F. Labarre and F. Crasnier, *Topics Current Chem.*, 1971, **24,** 33.
40. See E. Clar, 'Polycyclic Hydrocarbons', Academic, London, 1964, vols. 1 and 2.
41. R. N. Jones, *Chem. Rev.*, 1947, **41,** 353.
42. H. B. Klevens and J. R. Platt, *J. Chem. Phys.*, 1949, **17,** 470.
43. D. W. Turner, *Adv. Phys. Org. Chem.*, 1966, **4,** 31; S. D. Worley, *Chem. Rev.*, 1971, **71,** 295.
44. E. Heilbronner and A. Schmelzer, *Helv. Chim. Acta*, 1975, **58,** 936.
45. R. Breslow, *Chem. Eng. News*, 1965, **43,** XXVI, 90; *Angew. Chem. Internat. Edn.*, 1968, **7,** 565; *Pure Appl. Chem.* 1971, **28,** 111; *Accounts Chem. Res.*, 1973, **6,** 393.
46. M. J. S. Dewar, *Adv. Chem. Phys.*, 1965, **8,** 121.
47. R. Breslow, J. M. Brown, and J. J. Gajewski, *J. Amer. Chem. Soc.*, 1967, **89,** 4383.
48. M. J. S. Dewar, 'Molecular Orbital Theory of Organic Chemistry', McGraw-Hill, New York, 1969.
49. M. Saunders, R. Berger, A. Jaffe, J. M. McBride, J. O'Niell, R. Breslow, J. M. Hoffman, C. Perchonock, E. Wasserman, R. S. Hutton, and V. J. Kuck, *J. Amer. Chem. Soc.*, 1973, **95,** 3017; W.-D. Stohrer and R. Hoffmann, *ibid*, 1972, **94,** 1661.
50. G. Maier, H.-G. Hartan, and T. Sayrac, *Angew. Chem. Internat. Edn.*, 1976, **15,** 226.
51. L. T. J. Delbaere, M. N. G. James, N. Nakamura, and S. Masamune, *J. Amer. Chem. Soc.*, 1975, **97,** 1973.
52. H. Irngartinger and H. Rodewald, *Angew. Chem. Internat. Edn.*, 1974, **13,** 740.
53. S. M. Johnson, I. C. Paul, and G. S. D. King, *J. Chem. Soc.* (*B*), 1970, 643.

54. J. A. Pople and K. G. Untch, *J. Amer. Chem. Soc.*, 1966, **88,** 4811; F. Baer, H. Kuhn, and W. Regel, *Z. Naturforsch.*, 1967, **22a,** 103; H. C. Longuet-Higgins, in 'Aromaticity', The Chemical Society, Lindon, Special Publications, 1967, No. 21, p. 109.
55. P. J. Garratt, 'Aromaticity', McGraw-Hill, London, 1971.
56. P. J. Garratt and K. Grohmann, in 'Methoden der Organischen Chemie (Houben-Weyl)', ed. E. Müller, Verlag Chemie, Stuttgart, 1972, vol. 5/1d, p. 534.
57. (a) J. A. Pople, *Trans. Faraday Soc.*, 1953, **49,** 1375; (b) R. Pariser and R. G. Parr, *J. Chem. Phys.*, 1953, **21,** 466, 767.
58. A. L. H. Chung and M. J. S. Dewar, *J. Chem. Phys.*, 1965, **42,** 756.
59. M. J. S. Dewar and G. J. Gleicher, *J. Amer. Chem. Soc.*, 1965, **87,** 685, 692.
60. M. J. S. Dewar and C. de Llano, *J. Amer. Chem. Soc.*, 1969, **91,** 789.
61. N. C. Baird, *J. Chem. Educ.*, 1971, **48,** 509; however, for an earlier calculation using an acyclic molecule as a model compound, see R. Breslow and E. Mohacsi, *J. Amer. Chem. Soc.*, 1963, **85,** 431.
62. L. J. Schaad and B. A. Hess, *J. Chem. Educ.*, 1974, **51,** 640.
63. See D. Lewis and D. Peters, 'Facts and Theories of Aromaticity', Macmillan, London, 1975; H. P. Figeys, *Tetrahedron*, 1970, **26,** 5225; J. Kruszewski and T. M. Krygowski, *Canad. J. Chem.*, 1975, **53,** 945; J. Aihara, *J. Amer. Chem. Soc.*, 1976, **98,** 2750; I. Gutman, M. Milun, and N. Trinajstić, *ibid.*, 1977, **99,** 1692.
64. W. C. Herndon, *J. Chem. Educ.*, 1974, **51,** 10.
65. C. F. Wilcox, *J. Amer. Chem. Soc.*, 1969, **91,** 2732.
66. G. Binsch, in 'Jerusalem Symposia on Quantum Chemistry and Biochemistry', ed. E. D. Bergmann and B. Pullman, Israel Academy of Science and Humanities, Jerusalem, Israel, 1971, vol. 3, p. 25.
67. Ref. 6, p. 33.
68. G. Binsch, *Naturwiss.*, 1973, **60,** 369.
69. E. Heilbronner, *Tetrahedron Letters*, 1964, 1923.
70. M. J. S. Dewar, *Tetrahedron*, 1966, suppl. 8, 75.
71. H. E. Zimmerman, *Accounts Chem. Res.*, 1971, **4,** 272.
72. R. B. Woodward and R. Hoffmann, 'The Conservation of Orbital Symmetry', Academic, New York, 1970.

2.5

Arenes and their Reactions

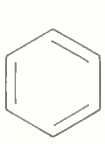
H. HEANEY
University of Technology, Loughborough

2.5.1 INTRODUCTION 241
2.5.2 NOMENCLATURE 242
2.5.3 PHYSICAL PROPERTIES OF ARENES 246
2.5.4 COMMERCIAL PREPARATIONS OF ARENES 248
2.5.5 CYCLOTRIMERIZATIONS OF ACETYLENES 250
2.5.6 ELECTROPHILIC ADDITION-WITH-ELIMINATION REACTIONS OF ARENES 254
2.5.6.1 Mechanisms of aromatic nitrations 254
2.5.6.2 Kinetic isotope effects 263
2.5.6.3 Reactions involving ipso *protonation* 264
2.5.6.4 Metallations 266
2.5.6.5 Group IV electrophiles 268
2.5.6.6 *Group V electrophiles* 284
2.5.6.7 Group VI electrophiles 287
2.5.6.8 Group VII electrophiles 291
2.5.7 DIRECTIVE EFFECTS IN ELECTROPHILIC ADDITION-WITH-ELIMINATION REACTIONS 298
2.5.8 RADICAL HALOGENATION ON THE SIDE CHAINS OF ARENES 303
2.5.9 ADDITIONS TO ARENES 305
2.5.9.1 The reduction of arenes 305
2.5.9.2 Thermal cycloadditions of arenes 309
2.5.9.3 Photocycloadditions of monocyclic arenes 315
2.5.9.4 Photochemical reactions of polycyclic arenes 319
2.5.10 PHOTOISOMERIZATIONS OF ARENES 322
2.5.11 THE OXIDATION OF ARENES 324
2.5.12 REACTIONS OF ARENES WITH SINGLET OXYGEN 330
2.5.13 THE PREPARATION OF BI- AND POLY-ARYLS 331
2.5.14 INTRAMOLECULAR PHOTOCYCLIZATIONS LEADING TO POLYCYCLIC ARENES 338
2.5.15 INTRAMOLECULAR CYCLIZATIONS OF DISUBSTITUTED ARENES 344
2.5.16 CYCLOPHANES 345
2.5.17 CONFORMATION AND CHIRALITY IN ARENES 349
2.5.18 AZULENE AND NON-BENZENOID ARENES 353

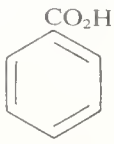
2.5.1 INTRODUCTION

The first isolation and identification of benzene (**1**) was reported by Faraday in 1825. He examined the volatile liquid obtained from compressed oil gas, which was itself

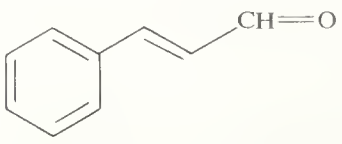
obtained by the pyrolysis of whale oil. The material had a melting point of 42 °F (5.5 °C) and the composition CH. The same liquid was obtained by Mitscherlich in 1833 by the decarboxylation of benzoic acid (**2**) with lime.[1] Mitscherlich assigned the correct molecular formula, C_6H_6, as a result of vapour density measurements. Coal-tar naphtha was not investigated in any detail until about 1847, when Mansfield found that it was a more convenient source of benzene. The structural problem and the frustrations concerning the formulation of benzene, the parent hydrocarbon of the organic molecules known as *aromatic compounds*, has been discussed in Chapter 2.4. The physical criteria which are now used to define aromaticity are also considered in that section. The term 'aromatic' was originally applied to these compounds because many had a pleasant odour.[2] Benzoic acid (**2**) was, in 1833, chiefly known as a constituent of a fragrant medicinal resin obtained from *Styrax benzoin*, a tree which grows in Sumatra. Similarly, cinnamaldehyde (**3**) and vanillin (**4**) were isolated from cinnamon and vanilla, respectively. The designation aromatic has been retained, but it is the concept of aromaticity which is of fundamental importance.



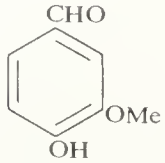
(**1**)



(**2**)



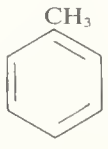
(**3**)



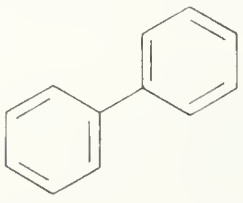
(**4**)

2.5.2 NOMENCLATURE

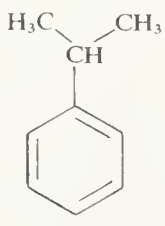
Aromatic hydrocarbons are given the generic name 'arene' (ArH) in order to distinguish them from, for example, alkenes. The IUPAC rules for organic nomenclature[3] allow for the fact that many trivial names have become so much a part of the chemical literature that it would not be sensible to replace them with more systematic names. Thus toluene is retained for methylbenzene (**5**) and biphenyl for phenylbenzene (**6**). Because of the six-fold symmetry of benzene, there is no requirement to number the compounds (**5**) and (**6**). Several of the more important monocyclic hydrocarbons are listed below, with the appropriate numbering and with their more systematic names shown in brackets.



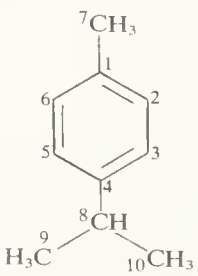
(**5**)



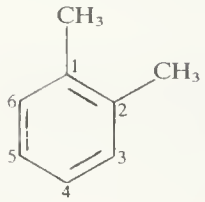
(**6**)



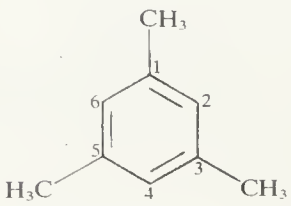
(**7**) Cumene
(Isopropylbenzene)



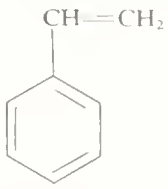
(**8**) *p*-Cymene
(4-Isopropyl-1-methylbenzene)



(**9**) *o*-Xylene
(1,2-Dimethylbenzene)

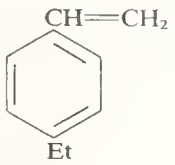


(**10**) Mesitylene
(1,3,5-Trimethylbenzene)

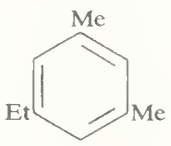


(**11**) Styrene
(Vinylbenzene)

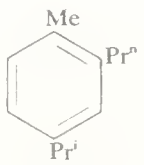
Other substituted monocyclic aromatic hydrocarbons are named as derivatives of benzene, or of one of the accepted alternatives, as long as the substituent introduced is not identical with one that is already present. So the compound (**12**) is correctly named as 4-ethylstyrene (or *p*-ethylstyrene), (**13**) as 5-ethyl-*m*-xylene, and (**14**) as 2-propyl-*p*-cymene. On the other hand, the compound (**15**) is correctly named as *p*-divinylbenzene (or 1,4-divinylbenzene) but not as 4-vinylstyrene. Similarly, (**16**) is 1,2,3-trimethylbenzene but not a methylxylene or a dimethyltoluene.



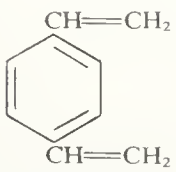
(**12**)



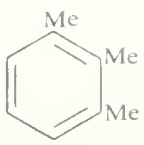
(**13**)



(**14**)



(**15**)



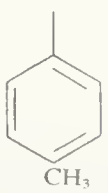
(**16**)

The generic name for a univalent aromatic hydrocarbon group is 'aryl' (Ar). Derivatives of benzene, toluene, the xylenes, cumene, and mesitylene where the additional substituent is attached to the ring may be named by using the prefixes shown below in (**17**)–(**21**). Species not listed are named as substituted phenyl groups. Certain other trivial names are used for derivatives of hydrocarbons when the substituent is attached to a side chain (see Table 1).

Ph—

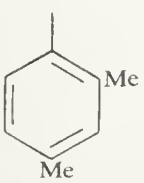
(Phenyl-)

(**17**)



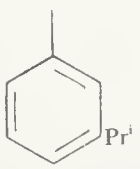
(*p*-Tolyl-)

(**18**)



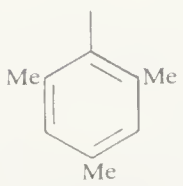
(*m*-Xylyl-)

(**19**)



(*m*-Cumenyl-)

(**20**)



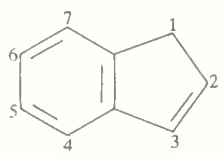
(Mesityl-)

(**21**)

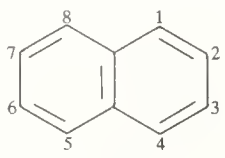
TABLE 1

$Ph—CH_2—Br$ Benzyl bromide	$Ph—CH=CH—CH_2—OH$ Cinnamyl alcohol	$Ph—\overset{\beta}{C}H_2—\overset{\alpha}{C}H_2—OH$ β-Phenethyl alcohol
$Ph—\overset{\beta}{C}H=\overset{\alpha}{C}H—Cl$ β-Styryl chloride β-Chlorostyrene	Ph_2CHOH Benzhydryl alcohol	Ph_3CCl Trityl chloride

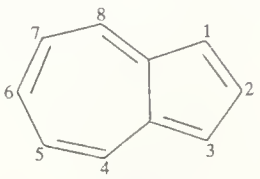
The names of polycyclic hydrocarbons which have the maximum number of non-cumulative double bonds also end in 'ene'. They include indene (**22**), naphthalene (**23**), azulene (**24**), biphenylene (**25**), phenanthrene (**26**), anthracene (**27**), fluoranthene (**28**), triphenylene (**29**), and pyrene (**30**). The appropriate numbering is shown on the formulae.



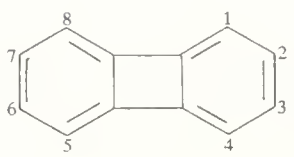
(**22**)



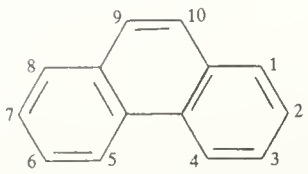
(**23**)



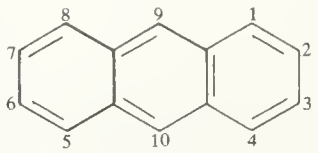
(**24**)



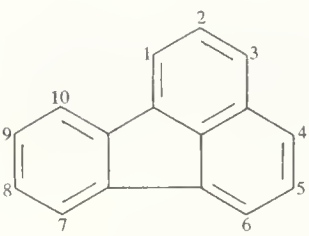
(**25**)



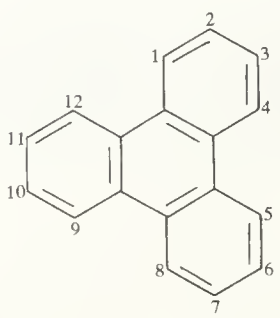
(**26**)



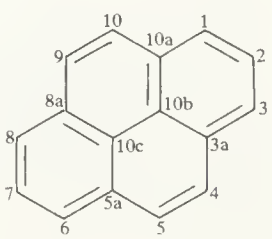
(**27**)



(**28**)



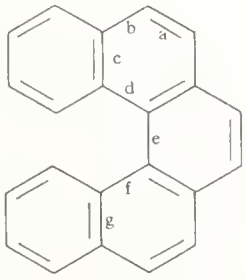
(**29**)



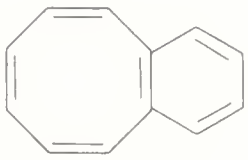
(**30**)

ortho-Fused polycyclic hydrocarbons which have no trivial name are named by prefixing, to the name of a component ring system, designations of the other components. The attached components should be as simple as possible. Thus the compound (**31**) is named dibenzophenanthrene and not naphthophenanthrene. It might be thought logical to name (**32**) as benzocyclo-octatetraene; however, when the base component is a monocyclic system the ending 'ene' signifies the maximum number of non-cumulative double bonds. Hence the compound (**32**) is correctly named benzocyclo-octene. Constitutional isomers are distinguished by using letters to denote the peripheral sides of the base component. The compound (**31**) is therefore dibenzo[*c*, *g*]phenanthrene and (**33**) benz[*a*]anthracene.

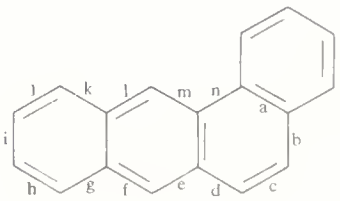
When a name applies equally correctly to two or more constitutional isomers which can be distinguished by indicating the position of one or more hydrogen atoms, this is done by modifying the name by using a locant followed by an italic uppercase *H* for each of these hydrogen atoms. Therefore the compound (**22**) is more correctly named as 1*H*-indene in order to distinguish it from 2*H*-indene (isoindene) (**34**).



(31)

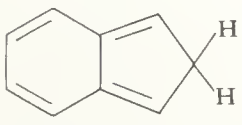


(32)

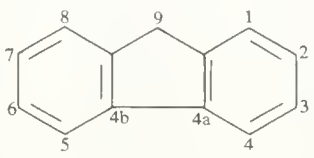


(33)

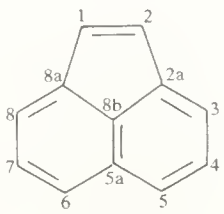
It will be evident from the examples (**22**)–(**30**) that the numbering of polycyclic ring systems follows in a clockwise direction commencing with a carbon atom not engaged in ring-fusion in the most anticlockwise position of the uppermost ring farthest to the right. Atoms which are common to two or more rings are designated by adding lower case roman letters to the number of the immediately preceding position, with interior atoms following the highest number in a clockwise sequence as in (**30**). If there is a choice, carbon atoms which are common to two or more rings take the lowest possible numbers, as in fluorene (**35**) and acenaphthylene (**36**).



(34)

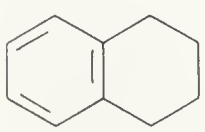


(35)

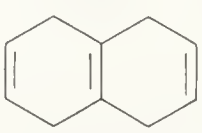


(36)

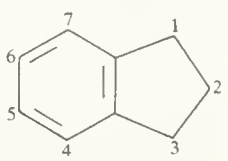
Partially or fully reduced *ortho*- and *peri*-fused polycyclic hydrocarbons are named by adding a prefix to the name of the unreduced hydrocarbon, which indicates the number of hydrogen atoms which have been added. The compounds (**37**) and (**38**) are therefore named 1,2,3,4-tetrahydronaphthalene and 1,4,5,8-tetrahydronaphthalene respectively. There are certain exceptions where trivial names are retained. These include indan (**39**) and acenaphthene (**40**).



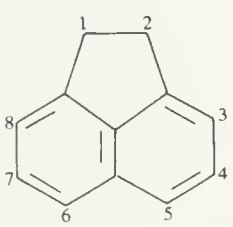
(37)



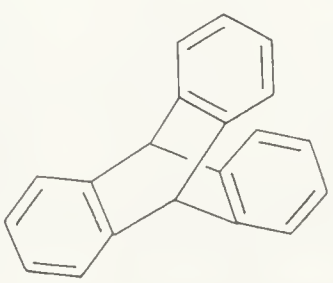
(38)



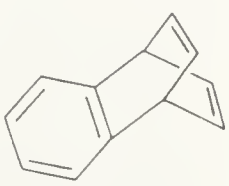
(39)



(40)



(41)



(42)

Bridged systems are named by adding a numbered prefix to the name of the parent hydrocarbon. The compound (**41**), known trivially as triptycene, is therefore correctly named 9,10-dihydro-9,10-*o*-benzenoanthracene, and benzobarrelene (**42**) as 1,4-dihydro-1,4-ethenonaphthalene.

2.5.3 PHYSICAL PROPERTIES OF ARENES

Benzene and most of the lower members of the alkylbenzene series are liquids under normal laboratory conditions. However, certain members which possess high symmetry have abnormally high melting points: see Table 2 for benzene, *p*-xylene, 1,2,4,5-tetramethylbenzene (durene), and hexamethylbenzene. Naphthalene and the higher benzologues are solids. The boiling points of mono-n-alkylbenzenes increase normally with each additional methylene group, and the branched-chain isomers have lower boiling points than the constitutionally isomeric n-alkylbenzenes. In general, the alkylbenzenes have higher boiling points than the corresponding alkylcyclohexanes. Refractive index values and specific gravities of arenes are usually high by comparison with other classes of hydrocarbons and it is possible to make use of these data in the determination of the aromatic content of petroleum distillates.

TABLE 2

Physical Constants of Some Arenes

Compound	*M.p.* (°C)	*B.p.* (°C/760 mm)	λ_{max}^{EtOH} (nm)($\log_{10}\varepsilon$)
Benzene	5.333[a]	80.10[a]	254.5 (2.31)[b]
Toluene	−94.991[a]	110.625[a]	262.0 (2.40)[b]
Ethylbenzene	−94.975[a]	136.186[a]	262.0 (2.30)[b]
o-Xylene	−25.182[a]	144.411[a]	262.5 (2.48)[b]
m-Xylene	−47.872[a]	139.103[a]	264.5 (2.48)[b]
p-Xylene	13.263[a]	138.351[a]	274.0 (2.79)[b]
Cumene	−96.035[a]	152.392[a]	260.5[e] (2.30)[b]
Mesitylene	−44.720[a]	164.716[a]	265.0 (2.34)[b]
o-Cymene	−71.540[a]	178.15[a]	264.0[e] (2.41)[b]
m-Cymene	−63.745[a]	175.14[a]	263.0[e] (2.41)[b]
p-Cymene	−67.935[a]	177.10[a]	273.8[e] (2.73)[b]
1,4-Diethylbenzene	−42.850[a]	183.752[a]	273.0[e] (2.60)[b]
1,2,4,5-Tetramethylbenzene	79.240[a]	196.80[a]	278.0[e] (2.82)[b]
Hexamethylbenzene	167[c]	263.5[c]	275.0 (2.26)[b]
Styrene	−30.628[a]	145.14[a]	282 (2.78), 292 (2.78)[b]
Indene	−1.5[a]	182.44[a]	280 (2.68), 290 (2.14)[b]
Indan	−51.411[a]	177.85[a]	260.5 (2.91), 267 (3.11), 273 (3.17)[b]
Biphenyl	69.2[a]	255.0[a]	249 (4.26)[b]
Naphthalene	80.290[a]	217.942[a]	275 (3.75), 286 (3.6), 312 (2.4), 320 (1.35)[b]
Biphenylene	112[c]	—	326 (3.47), 330 (3.49), 339 (3.79), 343 (3.76), 348 (3.58), 358 (3.97)[b]
1,2,3,4-Tetrahydronaphthalene	−35.749[a]	207.65[a]	266.5 (2.76), 274 (2.77)[b]
Anthracene	215[a]	341.2[a]	310 (3.3), 324 (3.6), 340 (3.7), 356 (4.0), 375 (4.0)[b]
Phenanthrene	99.5[a]	339.4[a]	293 (4.0), 300 (3.5), 338 (2.5), 375 (2.3)[b]
Acenaphthene	94[c]	277.9[c]	280 (3.75), 289.5 (3.80), 300 (3.60), 307 (3.44), 321 (3.19)[b]
Acenaphthylene	93[c]	265–275 (decomp)[d]	310 (3.93), 325 (3.98), 335 (3.71), 342 (3.71)[f]
Fluorene	117[c]	—	271 (4.15), 290 (3.87), 301 (3.98)[b]
Benz[*a*]anthracene	160.4[a]	437.6[a]	300 (3.9), 325 (3.8), 340 (3.8), 360 (3.6), 365 (2.7), 385 (2.8)[b]

[a] American Petroleum Institute, Project 44. [b] 'Organic Electronic Spectral Data', Interscience, New York, 1960, 1966, vols. I, II, and III.
[c] Beilstein. [d] 'Elsevier's Encyclopaedia of Organic Chemistry', Elsevier, New York, 1946, vol. 13.
[e] Determined in iso-octane. [f] Determined in benzene.

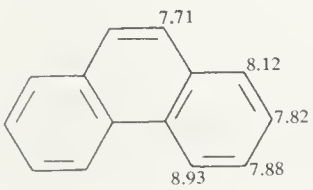
Arenes show characteristic ultraviolet absorptions.[4] Considerable fine structure is displayed in the spectrum of benzene in hexane solution and in the vapour phase. Spectra determined in hydroxylic solvents do not show the same amount of fine structure; this is

due to solvent–solute interactions. Benzene absorbs at 184 ($\log_{10}\varepsilon$ 4.77), 203.5 ($\log_{10}\varepsilon$ 3.87), and 254.5 ($\log_{10}\varepsilon$ 3.31) nm. Benzene belongs to the $\mathbf{D}_{6h}$ point group (*cf.* Section 1.2) and the intensity of the symmetry-forbidden 254 nm transition should be zero. However, vibrational distortions from hexagonal symmetry result in a small transition dipole moment which gives rise to the observed low intensity. Our understanding of the u.v. spectra of polycyclic hydrocarbons is due mainly to Clar,[5] who divided the compounds into two classes: the linear *acenes* (*e.g.* naphthalene and anthracene) and the angular *phenes* (*e.g.* phenanthrene). The acenes show the three typical bands of benzene with increased intensities and at longer wavelengths. The phenes also show the same three bands but at shorter wavelengths than the acenes with the same number of rings. The polycyclic hydrocarbon hexahelicene (*cf.* Section 1.4.5) is the classic example of the inherently chiral chromophore. We shall return to consider this compound in Section 2.5.14.

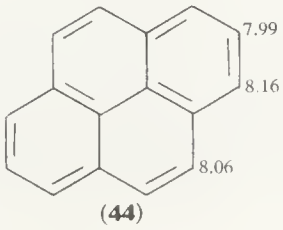
Infrared spectroscopy is also useful in establishing certain structural features which may be present in arenes.[6] The identification of substitution patterns is usually straightforward since the changes in certain regions which result from substitution is largely independent of the type of substituent introduced. Absorption in the 3100–3000 cm^{-1} range gives an indication of the presence of benzene rings (C—H stretching) which is backed up by the presence of ring breathing vibrations in the 1600–1500 cm^{-1} region. Once the presence of an aromatic ring is established, the substitution pattern can be investigated using the 2000–1660, 1250–1000, and 1000–650 cm^{-1} regions. Generally, the first of these regions is the most useful and confirmation is sought in the lowest-frequency region. The bands in the 2000–1660 cm^{-1} region are usually weak, but, by using relatively thick cells, useful results can be obtained. The Raman spectra of arenes contain several characteristic bands which can be useful where ambiguity exists.

The use of nuclear magnetic resonance spectroscopy as a probe for aromaticity has been discussed previously (Chapter 2.4). The relatively long relaxation times for aromatic ^{13}C nuclei, and the fact that alkene ^{13}C atoms resonate in the same range of chemical shifts, make precise structural assignments for aromatic systems difficult, using ^{13}C n.m.r. spectroscopy, unless suitable model compounds are available.[7] The chemical shift of the ^{13}C nuclei in benzene is 128.5 p.p.m. from tetramethylsilane while for arenes as a whole the chemical shifts range from 110 to 170 p.p.m. The theoretical treatment of aromatic chemical shifts has been dealt with extensively, and tabulations of ^{13}C substituent effects in substituted benzenes are available.

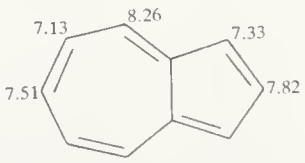
The ^{1}H n.m.r. spectra of arenes have been studied in considerable detail[8a] and reproductions of representative spectra are available.[8b] The diamagnetic anisotropy effect which results in the deshielding of the protons in benzene is emphasized in polycyclic arenes. The ring current effect is approximately additive. Thus the α-protons in naphthalene resonate at 0.35 p.p.m. to lower field than the β-protons while in anthracene the protons at position(s) 1, 4, 5, and 8 are found at 0.52 p.p.m. to lower field than the protons at position(s) 2, 3, 6, and 7. The protons at position(s) 9 and 10 in anthracene are even more deshielded (−0.92 p.p.m.) because of the deshielding effect of two benzenoid rings. Phenanthrene (**43**) is yet more complex with the protons at C-4 and C-5 being abnormally deshielded, presumably due to van der Waals effects. It is therefore relatively easy to assign resonances in angularly condensed polycyclic arenes. The chemical shifts (δ) of the protons in phenanthrene (**43**), pyrene (**44**), and azulene (**45**) are shown beside the formulae.



(**43**)



(**44**)



(**45**)

A qualitative insight into the direction and approximate magnitude of substituent effects in polysubstituted arenes can be obtained by using published substituent shift effects.[8a]

2.5.4 COMMERCIAL PREPARATIONS OF ARENES[9]

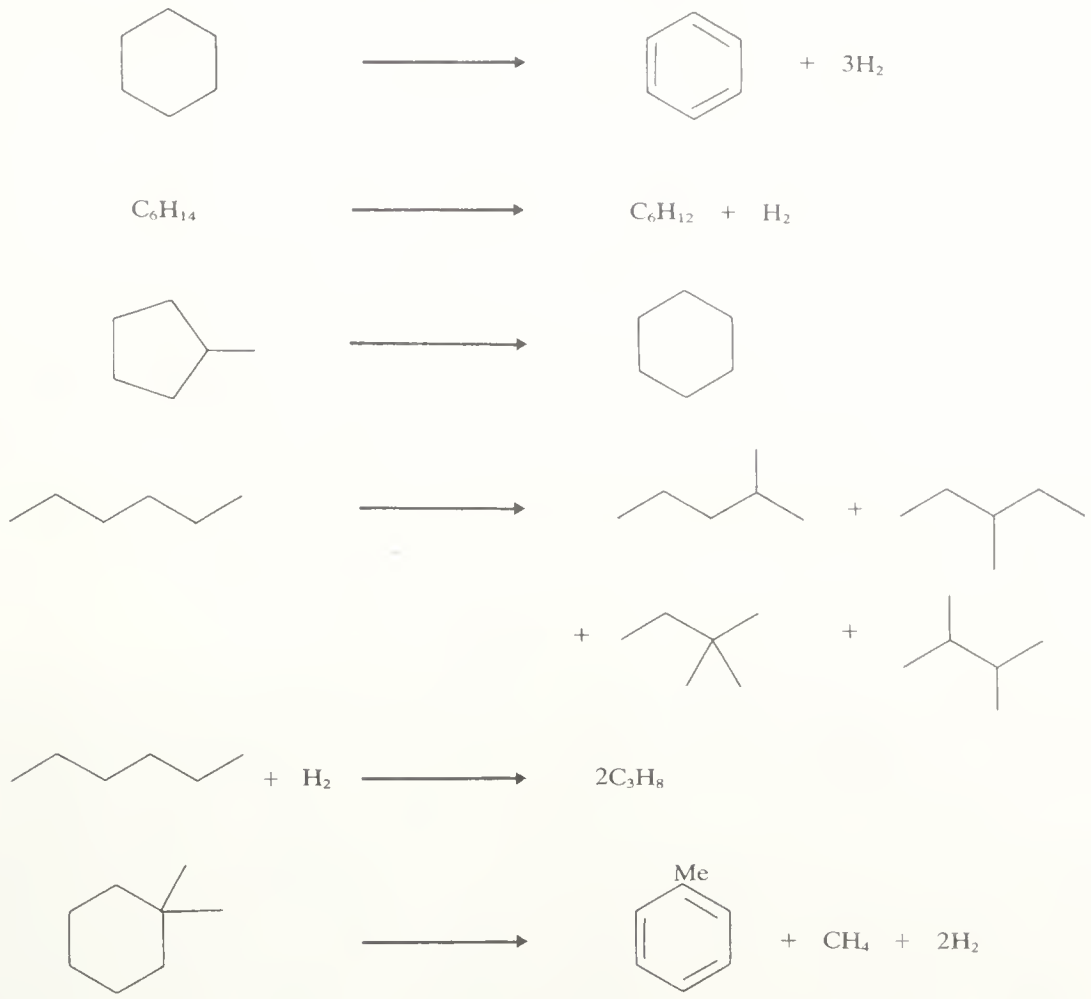
The main source of aromatic hydrocarbons used to be coal tar. However, although benzene is still obtained in worthwhile amounts from coke-oven by-products, the major source of aromatic hydrocarbons is currently petroleum. The need to conserve supplies of crude oil is at present resulting in increased research into more efficient utilization of coal as a source of arenes. Coal and lignite reserves are 76 times more plentiful than proven crude petroleum reserves.[10] The major uses of arenes are listed in Table 3.

TABLE 3
Major Chemical Uses of Arenes

Compound	*Major uses*
Benzene	Polystyrene (*via* ethylbenzene and styrene)
	Phenol (*via* cumene)
	Cyclohexane (and hence adipic acid and caprolactam)
Toluene	Benzene (by dealkylation)
	Toluene di-isocyanate
Ethylbenzene	Polystyrene (*via* styrene)
o-Xylene	Phthalate plasticizers (*via* phthalic anhydride)
m-Xylene	*o*- and *p*-Xylene by isomerization
p-Xylene	Terephthalic acid
Cumene	Phenol

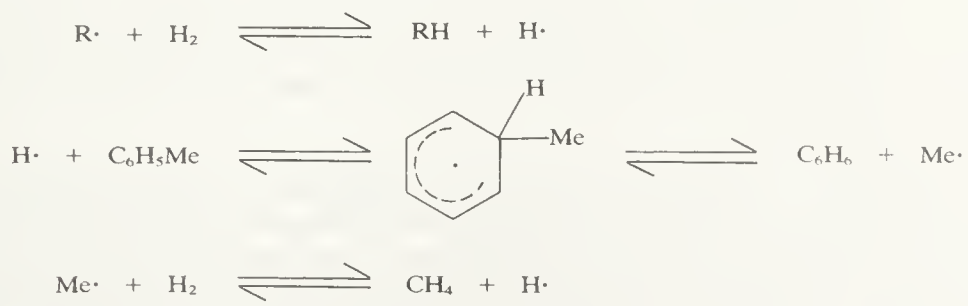
The amount of any individual compound in crude oil is, of course, low and therefore concentration must be effected before any given compound can be isolated. Distillation to give roughly a C_6–C_8 fraction can be achieved, but even then the concentration of aromatic hydrocarbons is rather low. Cyclodehydrogenation of alkanes to arenes is carried out at high temperatures and pressures in the presence of metallic catalysts. Normally the catalyst is platinum (platforming) supported on high-purity alumina. The metal provides sites on which hydrogenation–dehydrogenation reactions can occur while acidic sites on the alumina are necessary to catalyse the isomerizations. Hydrocracking reactions can occur on either type of site. The platinum is usually placed on the catalyst as chloroplatinic acid, which therefore also provides the acidic sites on the alumina. The quantity of platinum on the catalyst is between 0.3 and 1.0 wt.% and the process is operated at 500–525 °C and at pressures of between 1.0×10^6 and 4.0×10^6 N m^{-2}. The surface of the catalyst can easily be deactivated by sulphur compounds and by carbon deposits. The feedstock is therefore desulphurized to <3 p.p.m. of sulphur by weight and the reactions are carried out in the presence of hydrogen in order to avoid the deposition of carbon. Some typical reactions involved in catalytic reforming are given in Scheme 1 and reflect the complexity of the reactions which occur in addition to cyclodehydrogenation. These procedures can change a typical feedstock containing *ca.* 10% of arenes and 65% of alkanes to a reformate containing *ca.* 50–65% of arenes. In addition to the purely chemical importance of catalytic reforming, the octane rating of petroleum for use in internal combustion engines is increased significantly by an increase in the percentage of arenes.

The three major uses for benzene (see Table 3) require more benzene than is directly available from coal tar and catalytic reforming and therefore a significant amount of toluene is hydrodealkylated to benzene. The reaction can be carried out catalytically, using, for example, chromic oxide on alumina or zeolites, or thermally. Although little is known about the mechanism, it is likely that the thermal reaction occurs by a radical process (Scheme 2).



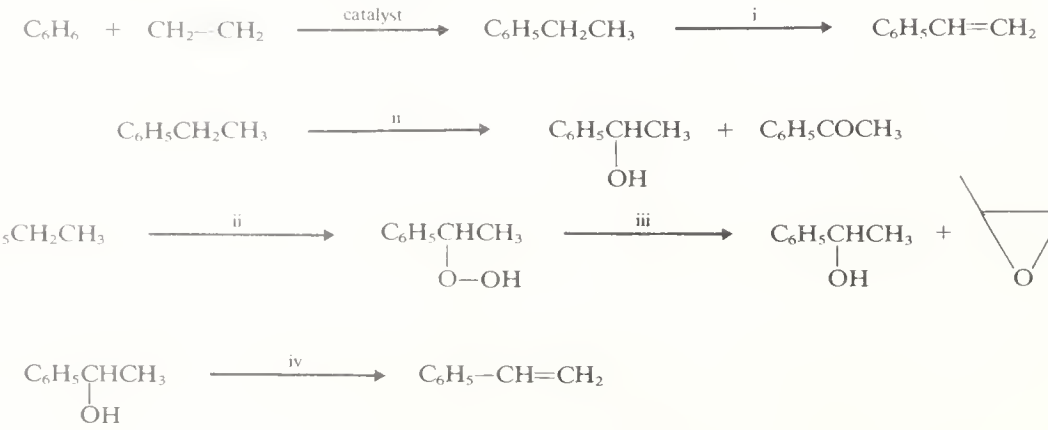
SCHEME 1

Ethylbenzene is mainly produced by the ethylation of benzene using ethylene and various catalyst systems. These include aluminium chloride in a liquid-phase reaction and phosphoric acid on Kieselguhr in a vapour-phase reaction. Boron trifluoride is also used in one process. Polyalkylation does occur (see Section 2.5.6.5) but these materials are recovered and transalkylated. The main process for converting ethylbenzene into styrene involves catalytic dehydrogenation using zinc or chromium oxide at 630 °C. Two processes which involve the initial oxidation of ethyl benzene are also used. In the first of these a manganese(II) acetate catalyst is used to produce 1-phenylethanol together with acetophenone and benzoic acid. The acetophenone is readily converted into 1-phenylethanol which is dehydrated to styrene using a titanium oxide catalyst at 300 °C. The second process involves the oxidation of ethylbenzene to its hydroperoxide. The hydroperoxide is treated with propene in a catalytic process which results in the formation of



SCHEME 2

propylene oxide and 1-phenylethanol. These processes are summarized in Scheme 3. The commercial processes for the production of cumene are essentially similar to those used to prepare ethylbenzene with the substitution of propylene for ethylene.



i, $-H_2$; ii, O_2; iii, C_3H_6; iv, $-H_2O$.

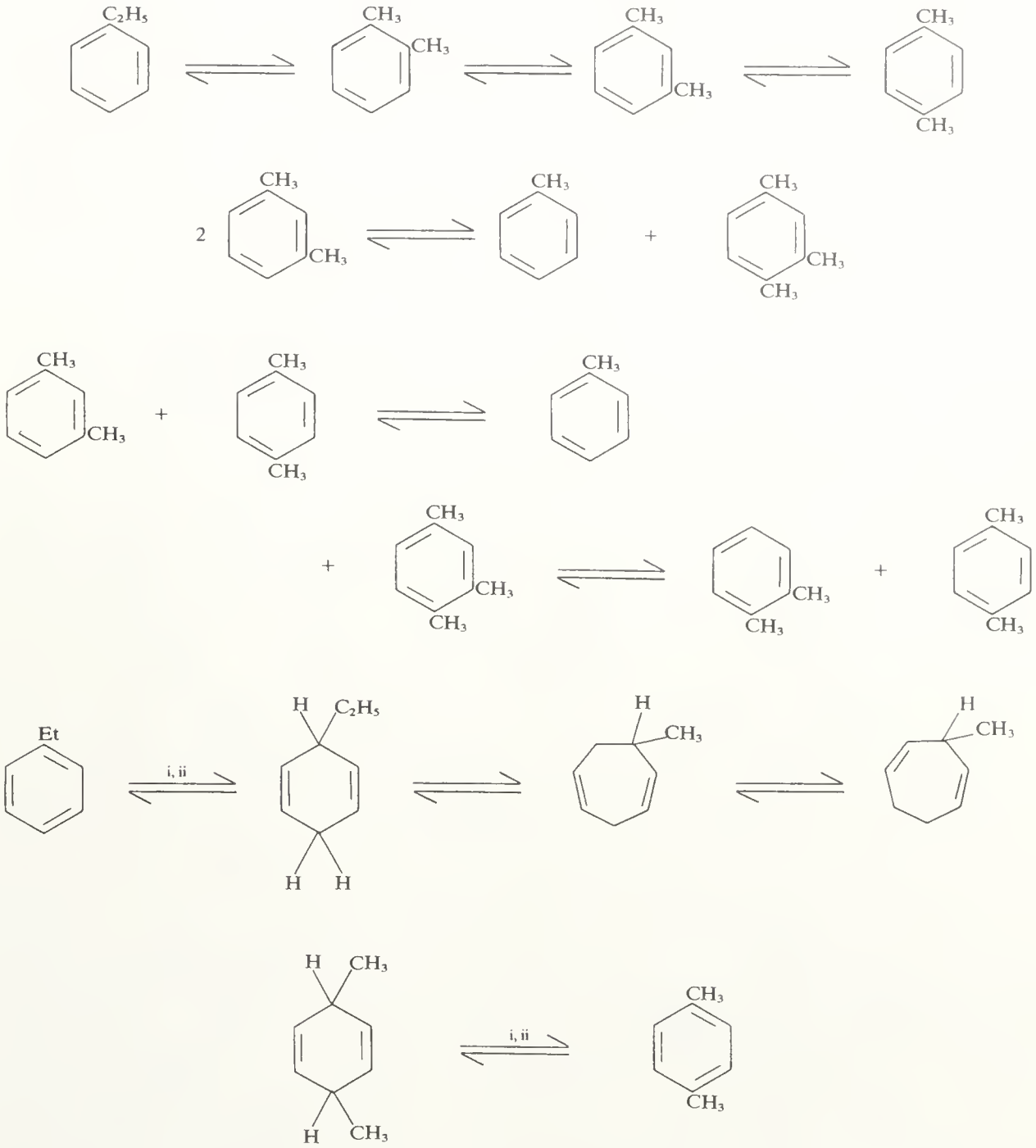
SCHEME 3

The amounts of *o*- and *p*-xylene required industrially exceeds the production from the C_8 fraction after catalytic reforming. *o*-Xylene is the only isomer which can be obtained satisfactorily by distillation and *p*-xylene is obtained by fractional crystallization (see Table 2). Unfortunately *m*-xylene is the major product in the C_8 isomer mixture and therefore much of the *m*-xylene must be isomerized towards the equilibrium composition of the three xylene isomers. Further quantities of *o*- and *p*-xylene can then be isolated. The xylenes only isomerize to ethylbenzene slowly. It has been suggested that in the presence of a silica–alumina catalyst the rearrangement of the isomeric xylenes proceeds by the stepwise migration of methyl groups around the aromatic nucleus and therefore that the direct conversion of *o*- into *p*-xylene cannot occur. There is some evidence that isomerization using zeolite catalysts occurs *via* transalkylation to trimethylbenzenes. The isomerization of ethylbenzene into the isomeric xylenes only occurs in the presence of hydrogen and a platinum catalyst. It is clear that this latter system must be used if the feedstock is rich in ethylbenzene. The sequences suggested above are summarized in Scheme 4.

2.5.5 CYCLOTRIMERIZATIONS OF ACETYLENES

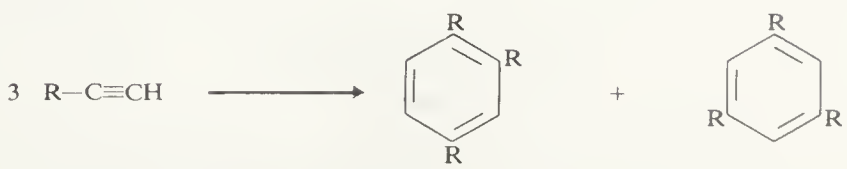
The thermal trimerization of acetylene to benzene was reported about 110 years ago.[11] In view of the highly exothermic nature of this reaction it is surprising that the process leads to a wide variety of by-products and only occurs at temperatures of *ca.* 400 °C. In 1949 the results of German war-time investigations were published[12] which showed that benzene could be produced at more reasonable temperatures by the cyclotrimerization of acetylene in the presence of a $(Ph_3P)_2Ni(CO)_2$ or $Ph_3PNi(CO)_3$ catalyst. More recently a wide range of monosubstituted acetylenes have been used successfully in the presence of transition metal catalysts.[13] Using monoalkylacetylenes, mixtures of 1,3,5- and 1,2,4-trialkylbenzenes (Scheme 5) were obtained, the precise ratios apparently being dependent on a number of factors.

α,ω-Diacetylenes have been found to undergo trimerizations in the presence of Ziegler catalysts (R_3Al–$TiCl_4$). Unfortunately the major pathway in these reactions leads to polymers, but the minor products are of interest (Scheme 6). Evidently trisubstituted benzene derivatives are the likely intermediates and it has been found that the compound (**46**) affords a mixture of cyclized monomeric products in 22% yield of which the 1,3,5-1,3,5-isomer (**47**) was isolated in 9% yield. Similarly, the hexa-acetylene (**48**) gave the layered cyclophane (**49**).

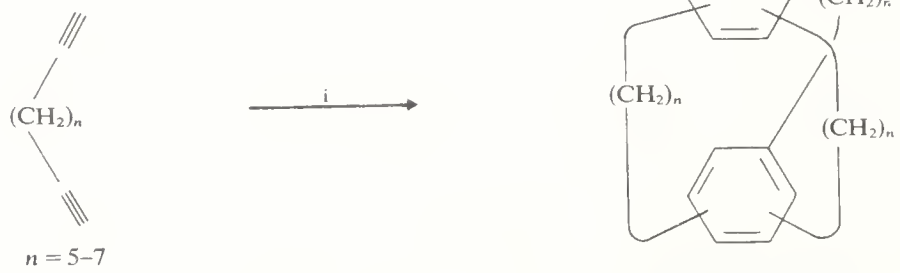


i, H_2; ii, Pt.

SCHEME 4

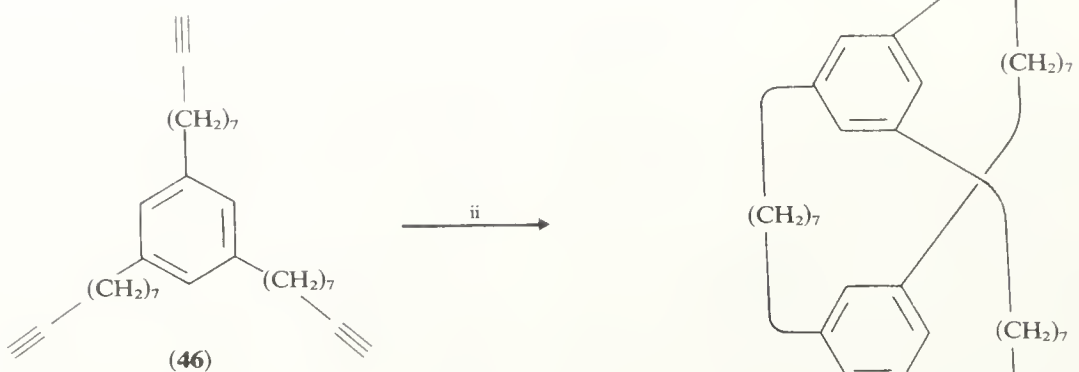


SCHEME 5



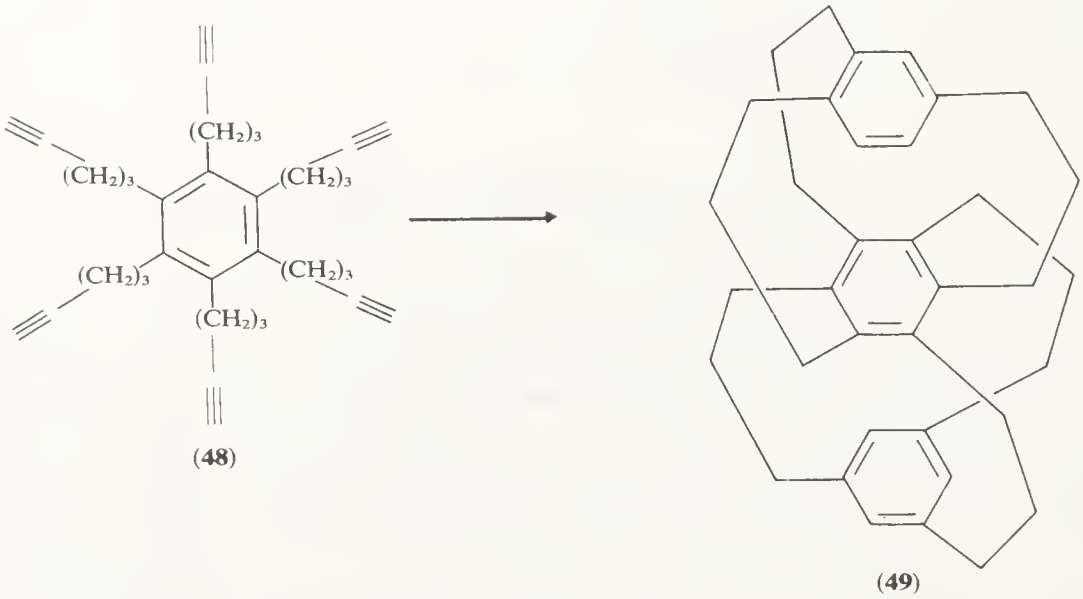
$n = 5–7$

1,2,4–1,2,4 isomer
1,3,5–1,3,5 isomer
1,2,4–1,3,5 isomer



(**46**)

(**47**)



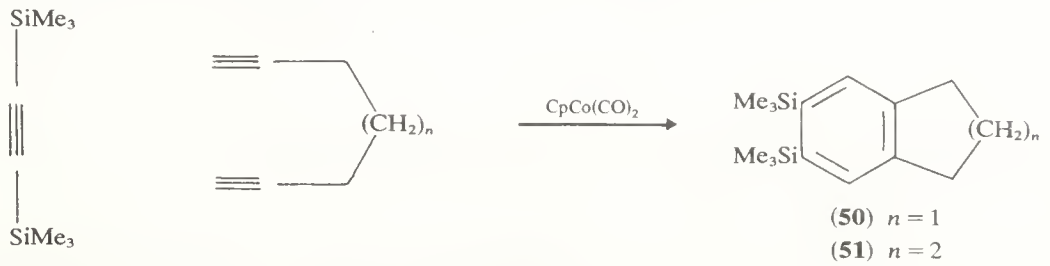
(**48**)

(**49**)

i, Et_3Al, $TiCl_4$; ii, Bu^i_3Al, $TiCl_4$.

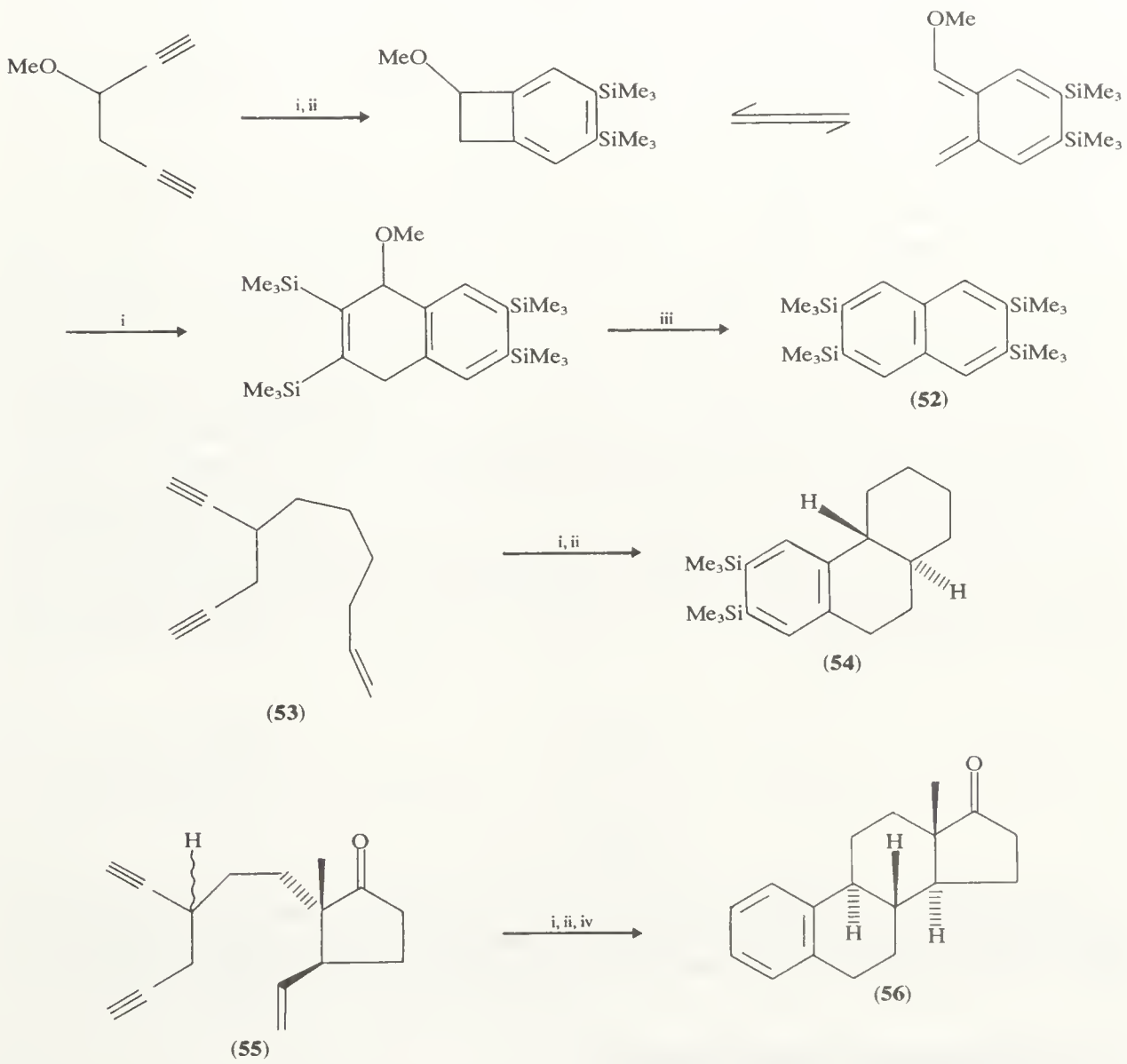
SCHEME 6

Recent results have shown that transition metal complexes catalyse the co-oligomerization of diacetylenes with monoacetylenes and can lead to the very efficient production of a wide variety of benzene derivatives.[14] Bis-trimethylsilylacetylene proved to be particularly useful as the monoacetylene component. Not only do steric problems preclude self-trimerization, but also the replacement of the trimethylsilyl residue using a wide variety of electrophiles gives effective control over substitution patterns. The indan (**50**) was obtained from hepta-1,6-diyne and the tetralin (**51**) from octa-1,7-diyne in 82 and 85% yield respectively using $CpCo(CO)_2$ as catalyst (Scheme 7).



(**50**) $n = 1$
(**51**) $n = 2$

SCHEME 7



i, $Me_3SiC{\equiv}CSiMe_3$; ii, $CpCo(CO)_2$; iii, $-MeOH$; iv, CF_3CO_2H.

SCHEME 8

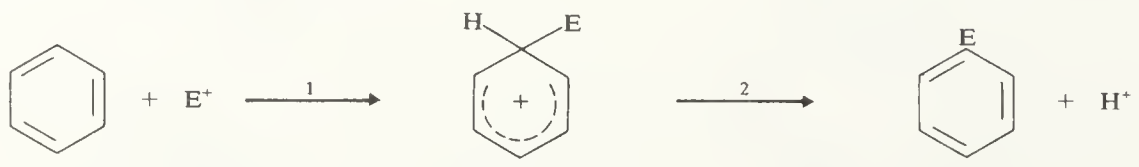
The same principle has been used in the preparation of benzocyclobutene derivatives using hexa-1,5-diynes as the diacetylene component. The known ease of opening of the four-membered ring, which gives an *o*-quinodimethane, allows the possibility of using either inter- or intra-molecular Diels–Alder reactions to produce additional rings. Thus the reaction of 3-methoxyhexa-1,5-diyne with bistrimethylsilylacetylene in the presence of $CpCo(CO)_2$ affords a one-step synthesis of 2,3,5,6-tetrakistrimethylsilylnaphthalene (**52**) as shown in Scheme 8. An intramolecular version of the same type of reaction is shown (Scheme 8) using 3-hex-5′-enylhexa-1,5-diyne (**53**), which yields the octahydrophenanthrene (**54**) in 80% yield. Similarly, the aromatic steroid oestra-1,3,5(10)-trien-17-one (**56**) was obtained in 71% yield from the diyneone (**55**).[14b]

2.5.6 ELECTROPHILIC ADDITION-WITH-ELIMINATION REACTIONS OF ARENES

Electrophilic aromatic substitutions are among the most studied of all organic chemical reactions. One can envisage two extreme mechanistic pathways. At one end is a one-step, direct substitution, while at the other extreme, multi-step processes involving discrete intermediates should be considered. A mechanism involving direct substitution would be expected to show a primary kinetic isotope effect, $k_{1H}/k_{2H} \approx 5–8$ or $k_{1H}/k_{3H} \approx 10–16$ at room temperature. In the majority of these reactions no such isotope effect is observed. Thus the rates of nitration of benzene and hexadeuteriobenzene are identical. We shall return to consider isotope effects in more detail later.

It has been noted previously (Chapter 2.2) that many additions of olefins are characteristically two-step reactions. The first step involves the attack by the olefin on an electrophile to produce a cationic intermediate. The second step produces the electrically neutral product after attack by a nucleophile. If a similar sequence were to occur with benzene for example, this would cost at least 146 kJ mol^{-1} (the difference between the resonance energy of benzene and cyclohexa-1,3-diene). Thus in the majority of reactions involving electrophiles and an aromatic substrate, an electrophile (normally a proton) is lost after the attack on the original electrophile. There is substantial evidence in favour of an essentially two-step mechanism and we can therefore regard electrophilic substitutions in aromatic systems as involving electrophilic additions followed by eliminations ($A–S_E2$).

Electrophilic addition-with-elimination reactions of arenes can be essentially irreversible (for example, nitration and bromination) or reversible (for example, sulphonation and Friedel–Crafts alkylation). We shall see that whether the reactions are reversible or not will depend in part on the relative values of the activation energies for the two steps from the cationic intermediate (σ-complex or Wheland intermediate), *i.e.* step 2 or the reverse of step 1, shown in Scheme 9.



SCHEME 9

A wide range of electrophiles react with arenes to afford substitution products. The more important of these are listed in Table 4, but not all of them will be considered in detail. Certain of the reactions listed only proceed with highly nucleophilic arenes.

2.5.6.1 Mechanisms of aromatic nitrations[15]

Direct experimental evidence is available which shows that σ-complexes do exist as stable intermediates. This does not necessarily prove that the transition states for

TABLE 4

Typical Electrophilic Addition-with-elimination Reactions of Arenes

1. Protonation, *e.g.*
   (a) $ArSO_3H + H_3O^+ \rightarrow ArH + H_2SO_4$
   (b) $ArH + D^+ \rightarrow ArD + H^+$
   (c) $ArSiMe_3 + H_3O^+ \rightarrow ArH + Me_3SiOH + H^+$

2. Metallation, *e.g.*

$$ArH + Tl(OCOCF_3)_3 \rightarrow ArTl(OCOCF_3)_2 + CF_3CO_2H$$
$$ArH + Hg(OCOCH_3)_2 \rightarrow ArHgOCOCH_3 + CH_3CO_2H$$

3. Group IV electrophiles, *e.g.*
   (a) Friedel–Crafts alkylation:

$$ArH + RCl \xrightarrow{AlCl_3} ArR + HCl$$

   (b) Chloromethylation:

$$ArH + CH_2O + HCl \xrightarrow{ZnCl_2} ArCH_2Cl$$

   (c) Aminomethylation (Mannich reaction):

$$ArH + CH_2O + Me_2NH \rightarrow ArCH_2NMe_2 + H_2O$$

   (d) Friedel–Crafts acylation:

$$ArH + RCOCl \xrightarrow{AlCl_3} ArCOR + HCl$$
$$[\text{or } (RCO)_2O]$$

   (e) Gattermann–Koch formylation:

$$ArH + CO \xrightarrow{HCl,CuCl} ArCHO$$

   (f) Gattermann formylation:

$$ArH + Zn(CN)_2 + HCl \rightarrow ArCH{=}\overset{+}{N}H_2\ Cl^- \xrightarrow{H_2O} ArCHO$$

   (g) Vilsmeier formylation:

$$ArH + HCONMe_2 + POCl_3 \rightarrow ArCH{=}\overset{+}{N}Me_2\ Cl^- \xrightarrow{H_2O} ArCHO$$

   (h) Houben–Hoesch acylation:

$$ArH + RCN + HCl \xrightarrow[H_2O]{ZnCl_2} Ar{-}CO{-}R$$

4. Group V electrophiles, *e.g.*
   (a) Nitration:

$$ArH + HNO_3 \xrightarrow{H_2SO_4} ArNO_2 + H_2O$$

   (b) Nitrosation:

$$ArH + HNO_2 \xrightarrow{H_2SO_4} ArNO + H_2O$$

   (c) Diazo coupling:

$$Ar^1H + Ar^2N_2^+ \rightarrow Ar^1{-}N{=}N{-}Ar^2 + H^+$$

5. Group VI electrophiles, *e.g.*
   (a) Hydroxylation:

$$ArH + H_2O_2 + HF \rightarrow ArOH + H_2O$$

TABLE 4 (*Contd.*)

(b) Alkoxylation:

$$ArH + Bu^t—O—OH \xrightarrow{AlCl_3} [ArOBu^t] \rightarrow ArOH$$

(c) Sulphonation:

$$ArH + SO_3 \rightarrow ArSO_3H$$

(d) Chlorosulphonation:

$$ArH + 2ClSO_3H \rightarrow ArSO_2Cl + H_2SO_4 + HCl$$

(e) Sulphonylation:

$$ArH + PhSO_2Cl \xrightarrow{AlCl_3} ArSO_2Ph + HCl$$

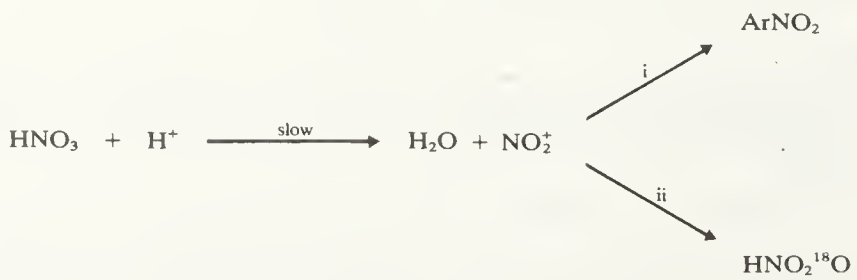
6. Group VII electrophiles — halogenation, *e.g.*

$$ArH + Cl_2 \xrightarrow{Fe} ArCl + HCl$$

$$ArH + Br_2 \longrightarrow ArBr + HBr$$

electrophilic addition-with-elimination reactions are closely related to the σ-complexes. Indeed, some controversy still exists concerning the relative importance of σ-complexes in these reactions.[16] In this section we shall concentrate our attention on the mechanisms of aromatic nitrations because they have recently received much attention.[17] We shall then return to consider other examples of the reactions mentioned in Table 4.

All of the kinetic, spectroscopic, and cryoscopic work reported prior to 1960 supported the view that the nitronium ion (NO_2^+) is the effective electrophile in nitration reactions of arenes. Spectroscopic techniques together with cryoscopic measurements had shown the presence of a low concentration of the nitronium ion in anhydrous nitric acid. The complete conversion of nitric acid into nitronium bisulphate in the presence of a large excess of sulphuric acid was also well established. However, the nitration of aromatic compounds which have reactivities similar to that of benzene still proceeds in the presence of water at levels such that nitronium ions cannot be detected. That these nitrations also involve nitronium is strongly indicated by a comparison of the rate of nitration with the rate of ^{18}O exchange between the medium and the nitric acid. The rate of nitration of certain reactive substrates in partly aqueous media shows zero-order kinetics. This indicates that the nitrating agent is formed from the nitric acid in the slow (rate determining) step prior to attack on the electrophile by the aromatic ring. In the absence of the aromatic substrate, the rate of exchange of ^{18}O between the water and the nitric acid is the same as the zero-order rate of nitration. These results are best interpreted as shown in Scheme 10. The isolation of nitronium salts such as those containing the anions perchlorate, tetrafluoroborate, and hexafluorophosphate, and the fact that these act as efficient nitrating agents, also supports the conclusions reached previously.



i, ArH; ii, $H_2{}^{18}O$.

SCHEME 10

Nitrations have been used to establish the relative reactivities of a large number of aromatic compounds. The statistically corrected positional relative rates, the so-called partial rate factors, for a large number of monosubstituted benzenes were assessed from relative rate data, $k_{C_6H_5R}/k_{C_6H_6}$, obtained either from kinetic studies, or measured in competition reactions, and using the isomer distributions found under the same experimental conditions. Very similar results were obtained when the nitration of equimolar mixtures of benzene and toluene were carried out with nitric acid in nitromethane, acetonitrile, acetic anhydride, or acidic solvents. These results also supported the generality of the nitronium ion mechanism. Representative examples are given in Table 5. It will be seen that, although the isomer distributions for reactions carried out using preformed nitronium salts are similar to those obtained from the earlier results, the relative rates of these latter reactions are much closer to unity, and hence, for example, the partial rate factors for attack at a *meta* position are apparently lower than for an individual position in benzene! The method of calculation is exemplified for the nitration of toluene *versus* benzene in acetic acid at 45 °C, remembering that there are six equivalent positions in benzene, but only one *para* position and two *ortho* and two *meta* positions in toluene:

$$o_f = 24 \times \frac{56.5}{100} \times \frac{6}{2} = 41$$

$$m_f = 24 \times \frac{3.5}{100} \times \frac{6}{2} = 2.5$$

$$p_f = 24 \times \frac{40.0}{100} \times 6 = 58$$

TABLE 5
Orientation, Relative Reactivity, and Partial Rate Factors in the Nitration of Some Representative Molecules

Compound	*Conditions*	*Relative rate*[a]	*Isomer distribution*			*Partial rate factor*		
			ortho	*meta*	*para*	o_f	m_f	p_f
Toluene	HNO_3 in CH_3NO_2, 25 °C	21[b]	61.7	1.9	36.4	38.9	1.3	45.8
Toluene	HNO_3 in AcOH, 45 °C	24[c]	56.5	3.5	40.0	41.0	2.5	58.0
Toluene	NO_2BF_4 in $C_4H_8SO_2$, 25 °C	1.67[d]	65.4	2.8	31.8	3.28	1.4×10^{-1}	3.19
Toluene	NO_2PF_6 in $C_4H_8SO_2$, 25 °C	1.40[d]	67.6	1.4	31.0	2.84	6.0×10^{-2}	2.60
Toluene	NO_2ClO_4 in $C_4H_8SO_2$, 25 °C	1.60[d]	66.2	3.4	30.4	3.18	1.0×10^{-1}	2.92
t-Butylbenzene	HNO_3 in CH_3NO_2, 25 °C	15[b]	12.2	8.2	79.6	5.5	3.7	71.6
Chlorobenzene	HNO_3 in CH_3NO_2, 25 °C	0.031[b]	29.6	0.9	69.5	2.8×10^{-2}	8.4×10^{-4}	1.3×10^{-1}
Chlorobenzene	NO_2BF_4 in $C_4H_8SO_2$, 25 °C	0.14[e]	22.7	0.7	76.6	9.5×10^{-2}	2.9×10^{-3}	6.4×10^{-1}

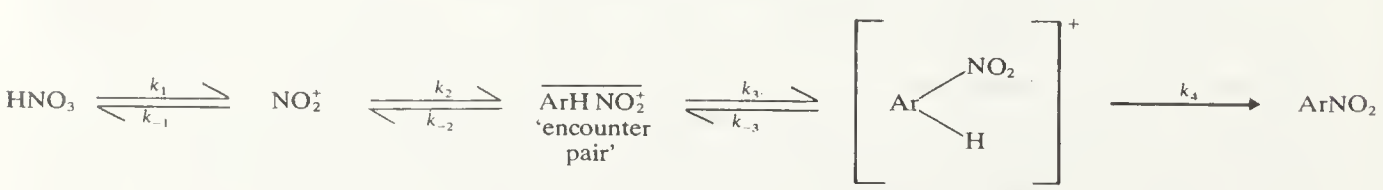
[a] Compared with the rate of nitration of benzene as unity. [b] M. L. Bird and C. K. Ingold. *J. Chem. Soc.*, 1938, 920. [c] H. Cohn, E. D. Hughes, M. H. Jones, and M. G. Peeling, *Nature*, 1952, **169,** 291. [d] G. A. Olah, S. J. Kuhn, and S. H. Flood, *J. Amer. Chem. Soc.*, 1961, **83,** 4571. [e] G. A. Olah, S. J. Kuhn, and S. H. Flood, *J. Amer. Chem. Soc.*, 1961, **83,** 4581.

The results of the studies with benzene–toluene mixtures using preformed nitronium salts (Table 5), and similar experiments using *m*-xylene and mesitylene which indicated relative reactivities compared with benzene of 1.7 and 2.7 respectively, raise a number of queries. The *meta* partial rate factor for toluene has already been alluded to. In addition, it has been pointed out that reactivities obtained from competition experiments can be invalid if significant reaction occurs before the reagents are adequately mixed. Apparently these abnormal reactivity patterns have not been confirmed by determining the rate constants of nitronium salt nitrations using kinetic methods. However, attempts were made to ensure adequate mixing by carrying out reactions at different concentrations of the reagents. These results led to the suggestion that the rates of a number of reactions of arenes with electrophiles — including those involving nitronium salts — are related to the π basicities rather than the σ basicities of the arenes. In other words, π-complex

formation is the rate-determining step. Control over the position of entry of the electrophile would still be determined by the σ basicity, as indicated by the isomer distributions which were obtained.[16a] This view of aromatic nitrations has been re-examined in detail.[16b] It was noted that the relationship between the product ratios for nitrations carried out using nitronium salts and the relative stabilities of the protonated methylbenzenes is not apparently poorer than the correlation with π-complex stability. The product ratios for competitive nitrations of polymethylbenzenes using mixed acids in sulpholan also correlates poorly with π-complex stability.

The question concerning the extent of reaction which occurs during mixing has been examined by studying the nitration of bibenzyl. In this system the reactivity of each ring should be similar to that of toluene and in addition the transmission of substituent effects between the rings should be minimal. Equimolar concentrations of bibenzyl and a nitronium salt, and complete mixing before reaction, should yield mononitrobibenzyl (50%) and dinitrobibenzyl (25%). On the other hand, incomplete mixing before reaction should result in an increase in the amount of unreacted substrate and dinitrobibenzyl, while the amount of mononitrobibenzyl should be reduced. That this is an oversimplification is evident from the results obtained in the nitration of bibenzyl by nitric acid in acetic anhydride. Mixing is unimportant in this system but the amount of dinitrobibenzyl is only about 55% of that expected. When the nitration of bibenzyl in sulpholan was studied with nitronium tetrafluoroborate, using a number of different concentrations and mixing conditions, the amount of disubstituted product always considerably exceeded the calculated values employing the simple method outlined above. Thus the simple competition method is not reliable for defining the relative reactivities of aromatic compounds in nitrations using nitronium salts. Mixing rates evidently do have a major influence.

Kinetic studies[18] of the nitration of arenes which are more reactive than benzene or toluene have also produced interesting results. If we consider the results for nitrations carried out in aqueous sulphuric acid (68.3%), it is seen that, whereas one might expect *p*-xylene, *m*-xylene, and mesitylene to be more reactive than benzene by factors of about 50, 4×10^2, and 1.6×10^4 respectively, in fact a limiting factor of about 40 is reached. In these reactions it was suggested that the rate-determining step involves the formation of an encounter pair between the nitronium ion and the aromatic substrate. What is the difference between this latter suggestion and rate-determining π-complex formation? It has been pointed out previously that the product ratios correlate poorly with π-complex stabilities. The data can be rationalized without requiring attractive interactions in an encounter pair. In that the energy barrier for the separation of an encounter-pair into its constituents may exceed 12 kJ mol^{-1} in the acidic media, there is a sufficient energy range for selectivity in the formation of the σ-complex. Since the rate data fit those expected from diffusion theory, the term 'encounter-pair' is preferred. The discussion above leads us to conclude that Scheme 9 requires modification along the lines indicated in Scheme 11, in which k_4 is only rate determining under very special circumstances. An extension of the treatment is shown in Scheme 11 in which different rate coefficients (k_3) for attack *ortho*, *meta*, or *para* show that isomer distribution is independent of the rate-determining stage, as long as the encounter pair involves the whole arene molecule and not particular carbon atoms within it.



SCHEME 11

The discussion of nitrations can be conveniently summarized in the form of the energy profiles indicated in Figure 1. The experimental data indicate that the formation of the σ-complex is rate determining in the cases of nitrations of benzene and toluene (Figures

1a and 1b, respectively) but the encounter pair formation is rate-determining in the nitration of pseudocumene (1,2,4-trimethylbenzene) (Figure 1c).

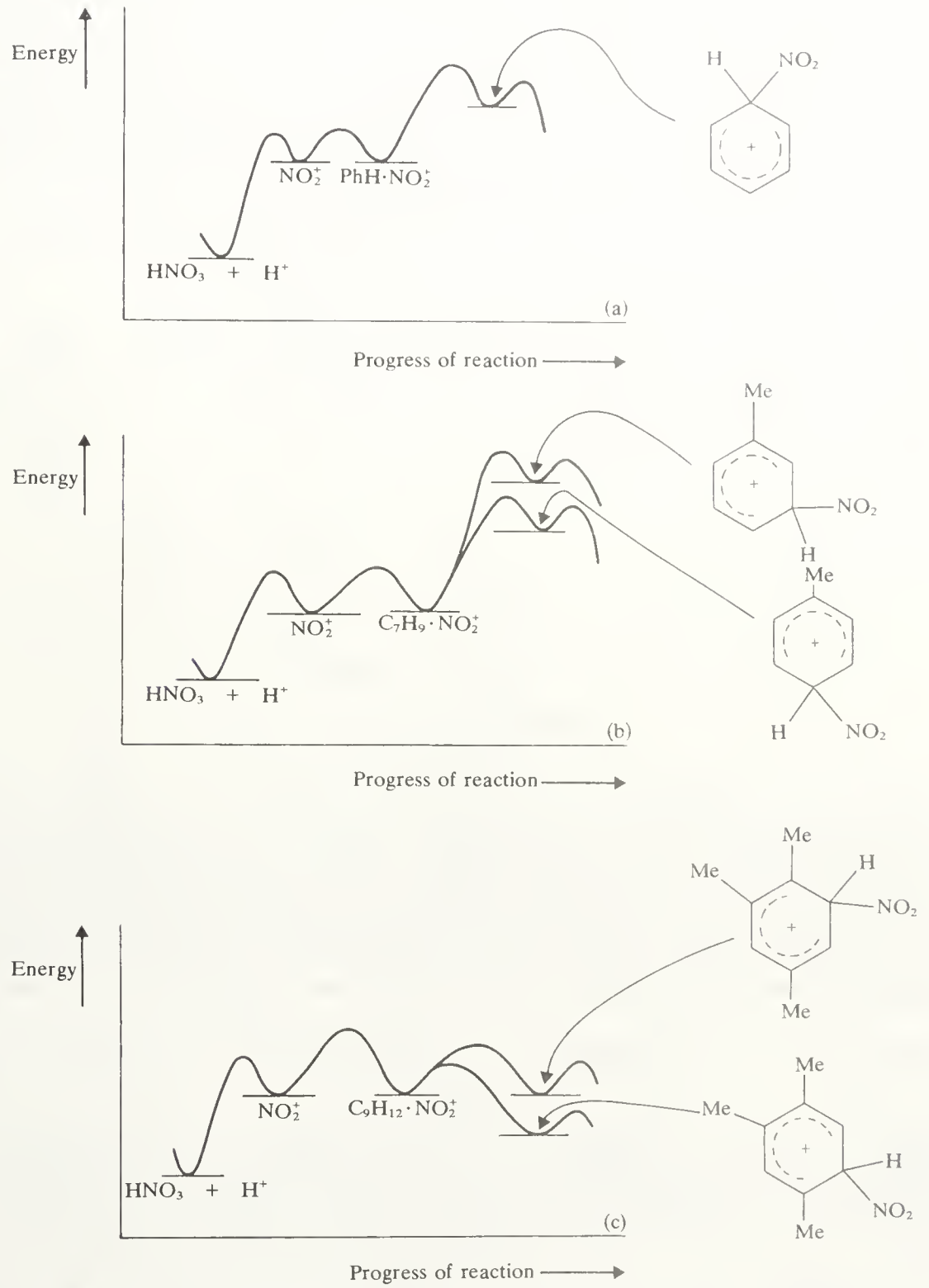
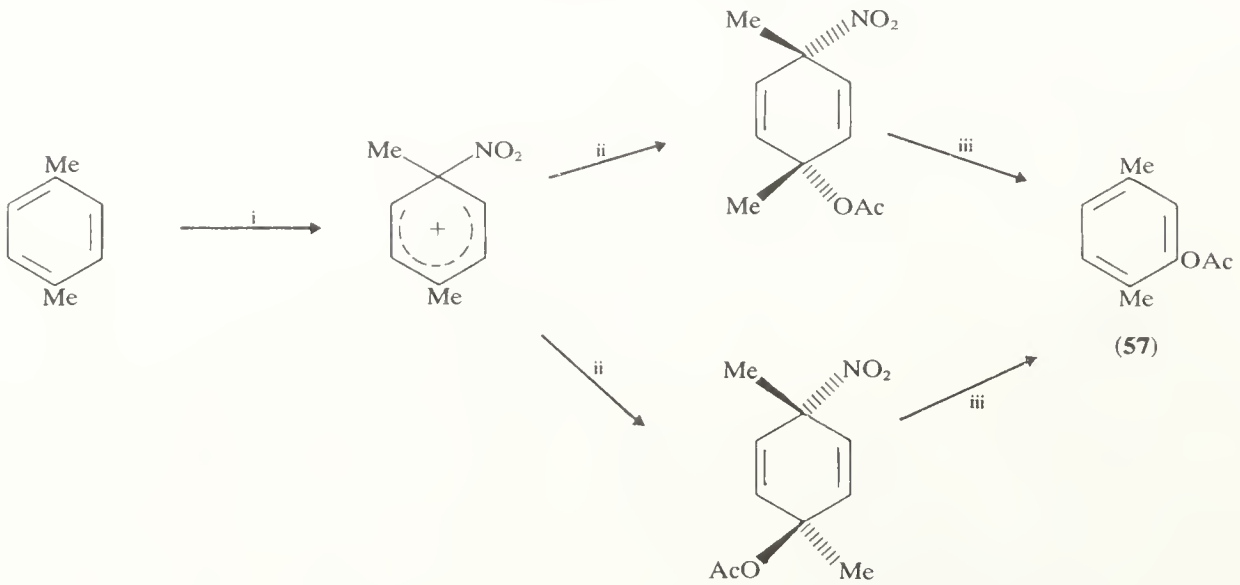


Figure 1 Energy profiles for the nitration of benzene (a) and toluene (b) in which the σ-complexes are produced in the rate-determining steps. (c) Energy profile for the formation of 5- and 6-nitro-1,2,4-trimethylbenzene in which the encounter-pair is formed in the rate-determining step

The isomer distributions which are found in the nitrations of toluene are (Table 5) essentially independent of reaction conditions except for the usual influence of temperature. However, anomalous results obtained in studies using certain polymethylbenzenes

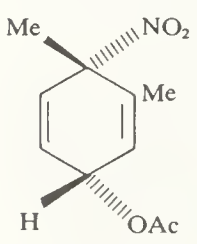
have complicated our understanding of the nitration reactions.[19] In particular, nitrations carried out with nitric acid in acetic anhydride were known to afford acetoxylation products and only served to confuse the issue by suggesting that electrophilic acetoxylation occurred. This is now known not to be the case. Although the nitric acid is mainly present as acetyl nitrate there is still some doubt concerning the precise identity of the electrophile. Thus nitric acid in acetic anhydride reacts with *p*-xylene to afford a mixture of 2,5-dimethylnitrobenzene and 2,5-dimethylphenyl acetate. The isolation of adducts in which the acetyl nitrate has added at positions already substituted (*ipso* attack), and the fact that these adducts decompose by an apparently intramolecular mechanism to give the acetate (**57**), supports the mechanism shown in Scheme 12.



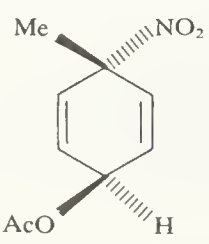
i, $AcONO_2$; ii, AcO^-; iii, $-HNO_2$.

SCHEME 12

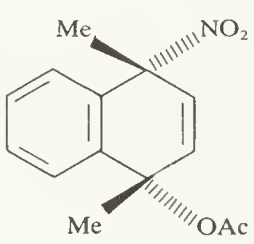
Similar adducts (**58**)–(**64**) have been isolated using other arenes and a number of others have been detected as reaction intermediates. Three adducts were isolated from the reaction of nitric acid in acetic anhydride with *p*-t-butyltoluene at low temperatures. The major product was the 1,2-adduct (**64**), which is presumably formed in greater quantity than the other two isomers because of steric hindrance at the 4-position (*ipso* to t-butyl). Other nucleophiles such as the nitrate ion and water can also capture the *ipso*-substituted σ-complexes. The *ipso*-substituted σ-complexes can also be regenerated by acidolysis.



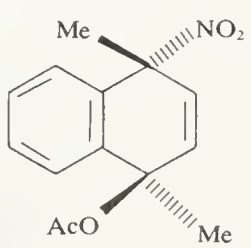
(**58**)



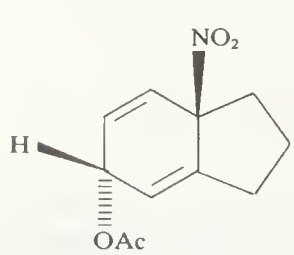
(**59**)



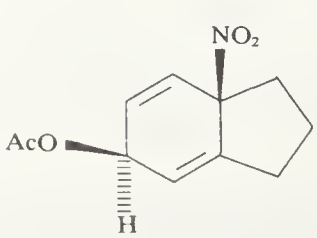
(**60**)



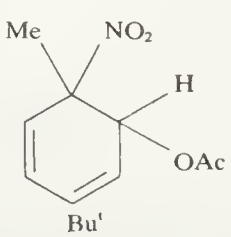
(**61**)



(**62**)

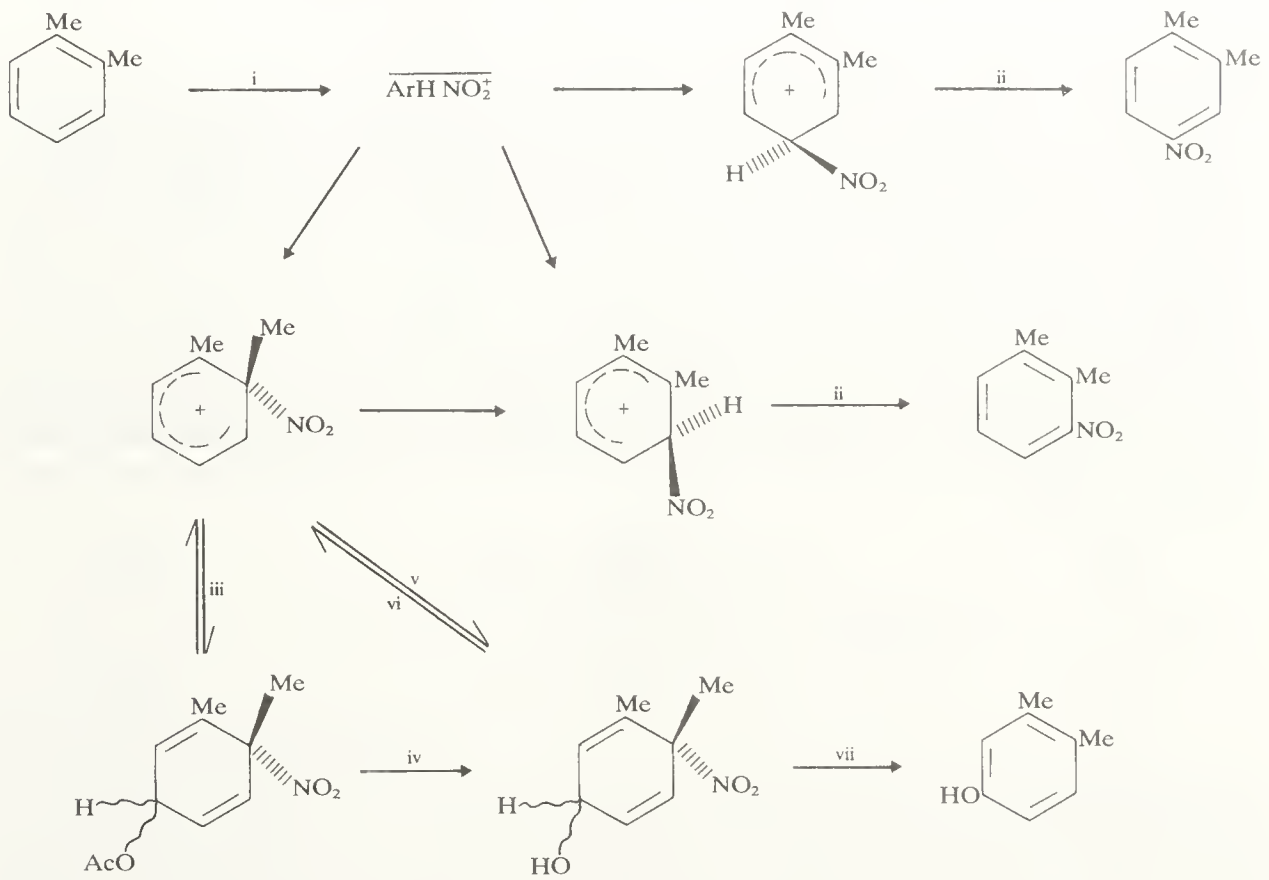


(**63**)



(**64**)

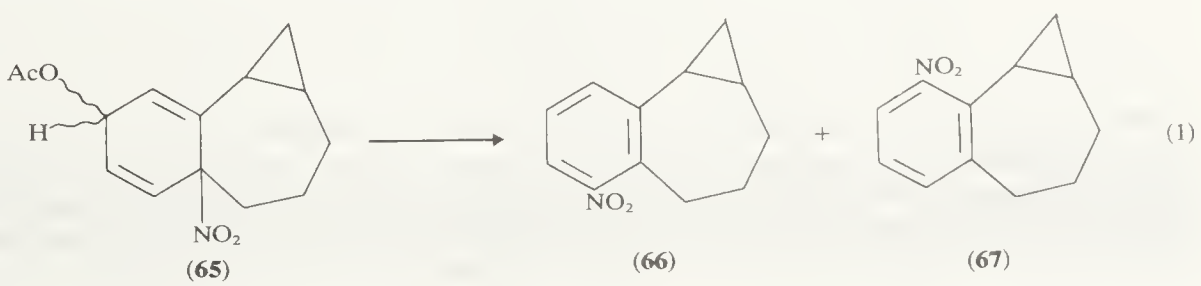
The nitration of *o*-xylene in sulphuric acid gives 2,3-dimethylnitrobenzene and 3,4-dimethylnitrobenzene in yields which depend upon the acidity of the system. At low acidity, nitrodimethylphenols are also isolated. The fact that acidolysis of the esters (**58**) and (**59**) also gives 2,3-dimethylnitrobenzene in yields which increase with acidity lends support to the suggestion that nitration *ortho* to an alkyl group may well frequently involve initial *ipso* attack. The fact that acidolysis of (**58**) and (**59**) does not give rise to 3,4-dimethylnitrobenzene shows that the initial *ipso*-substituted σ-complex does not return to the encounter-pair nor do 1,3- or successive 1,2-shifts of the nitro group occur. These results are summarized in Scheme 13. Similarly, in the nitration of 1,2,4-trimethylbenzene in sulphuric acid, the increase in the yields of 1,2,4-trimethyl-5-and 1,2,4-trimethyl-6-nitrobenzene as the acidity of the system is increased has been attributed to the migration of a nitro group from C-4 to C-5 and from C-1 to C-6, respectively.



i, NO_2^+; ii, $-H^+$; iii, AcO^-; iv, H_2O, AcOH; v, H_2O, H^+; vi, H^+, H_2O; vii, $-HNO_2$.

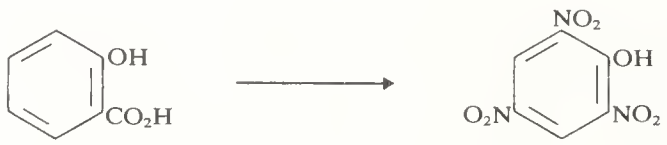
SCHEME 13

No well-authenticated examples of successive intramolecular 1,2-shifts across an unsubstituted position are known at present. Repeated 1,2-shifts from one *ipso* position *via* a second *ipso* position are known. For example, the acidolysis of (**65**) gave the constitutional isomers (**66**) and (**67**), as shown in equation (1).



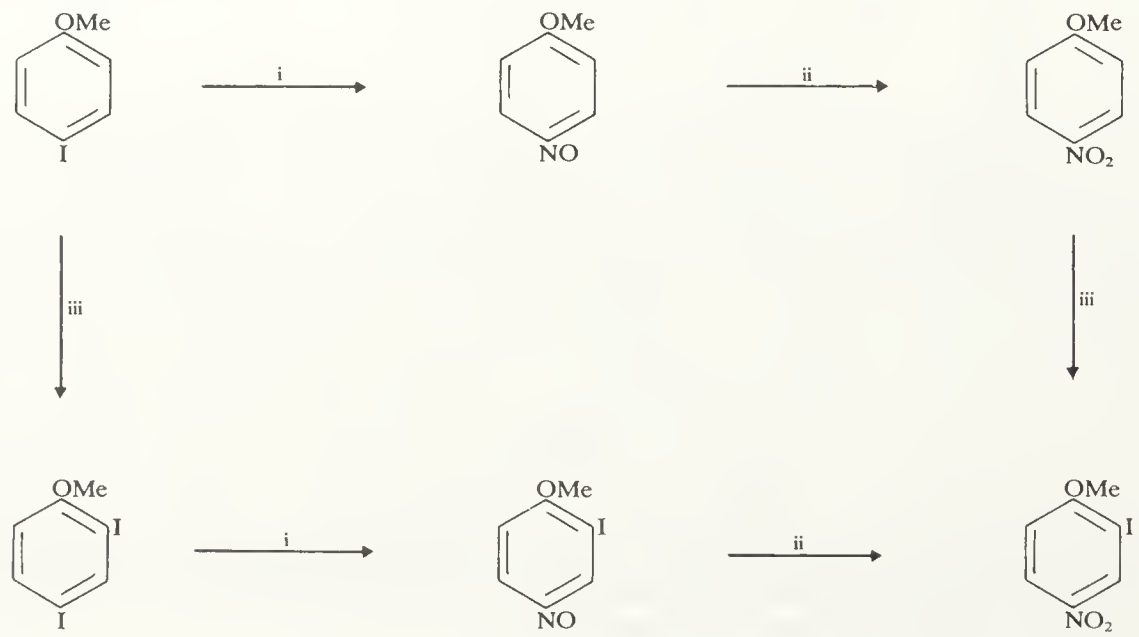
(**65**) (**66**) (**67**) (1)

Loss of the *ipso* substituent, for example proto-desilylation and proto-desulphonation, has been mentioned previously (Table 4). At this point we shall only discuss the replacement of an *ipso* substituent by a nitro group. Many reactions of this type have been known for a long time but little is known about the mechanisms involved in many of them. The reactions include dealkylation, deacylation, desilylation, desulphonation, decarboxylation, dediazoniation, and dehalogenation.[20] Reactions which involve substrates which are strongly activated towards electrophilic attack may involve initial nitrosation followed by subsequent oxidation. This may be the case, for example, in the nitration of salicylic acid (equation 2).



(2)

Nitro-dechlorination has rarely been observed. On the other hand, nitro-debromination is more common, although even in these reactions some may involve initial nitroso-debromination. In the 'absence' of nitrous acid, *i.e.* using nitric acid in acetic anhydride containing urea, *p*-bromoanisole gave *p*-nitroanisole in 31% yield. The nitration of 2,6-dimethyl-4-iodoanisole has been shown to proceed by nitroso-deiodination followed by oxidation; no displacement of iodine occurs in the absence of nitrous acid. The Reverdin rearrangement, in which 4-iodoanisole gives 2-iodo-4-nitroanisole, is a more complex example of the same type (Scheme 14). Once again, no displacement of iodine occurs in the absence of nitrous acid. Nitroso-deiodination only occurs in the presence of the nitrosonium ion or an equivalent species, giving initially *p*-nitroanisole (after oxidation) and 2,4-di-iodoanisole (by iodination of starting material). The former compound is then very slowly iodinated and the latter compound is slowly nitroso-deiodinated and subsequently oxidized.

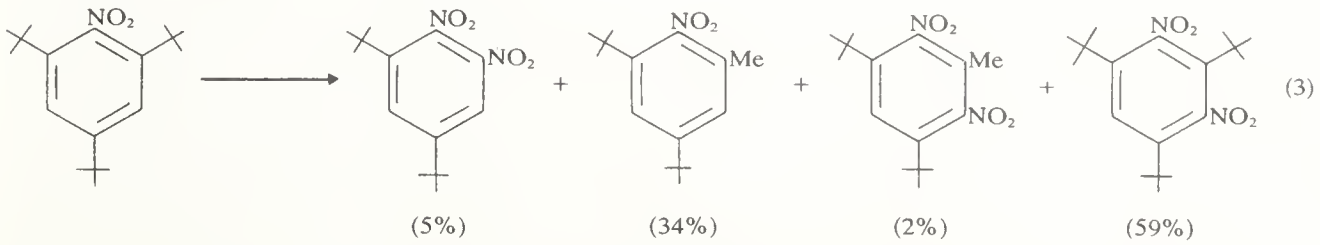


i, 'NO^+'; ii, HNO_3; iii, 'I^+'.

SCHEME 14

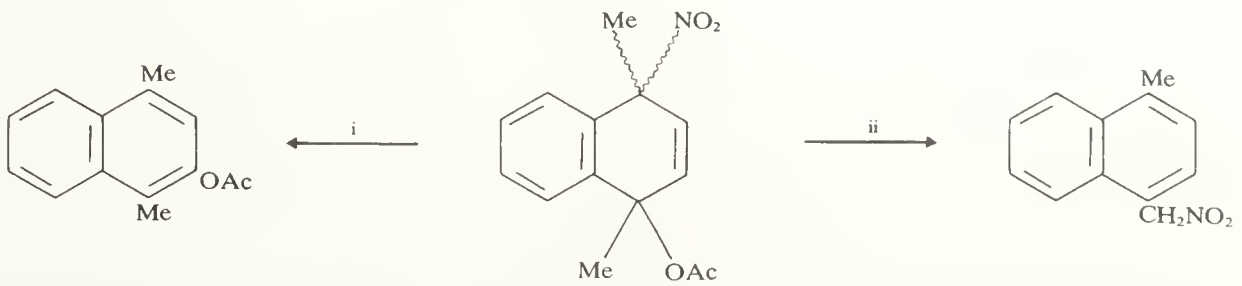
Using less-reactive compounds nitrosation does not obtrude. The nitration of *p*-dibromobenzene in sulphuric acid (69%) gives 2,5-dibromonitrobenzene and 4-bromonitrobenzene in 60% and 34% yield respectively, together with some 1,2,4-tribromobenzene. Some of the 2,5-dibromonitrobenzene may well arise by 1,2-migration from the *ipso* σ-complex as well as by direct nitration of the starting material.

Dealkylation is frequently observed when secondary and tertiary alkyl groups are present, but demethylation is only found with polymethylbenzenes and is then often accompanied by side-chain substitution. For example, the nitration of pentamethylbenzene results in the formation of 1,2-dinitrotetramethylbenzene, while *p*-cymene affords some *p*-nitrotoluene. The nitration of 2,4,6-tri-t-butylnitrobenzene is interesting since this reaction not only results in nitro-de-t-butylation but also leads to the formation of some dinitrodi-t-butyltoluenes (equation 3).



(3)

An example which involves side-chain substitution involves the adducts (**60**) and (**61**). Decomposition of these compounds at 30 °C in acetic acid gives mainly 1,4-dimethyl-2-naphthyl acetate, whereas in acetic anhydride containing nitric acid the main product is 4-methyl-1-naphthylnitromethane (Scheme 15).



i, $MeCO_2H$; ii, $(MeCO)_2O$, HNO_3.

SCHEME 15

2.5.6.2 Kinetic isotope effects[21]

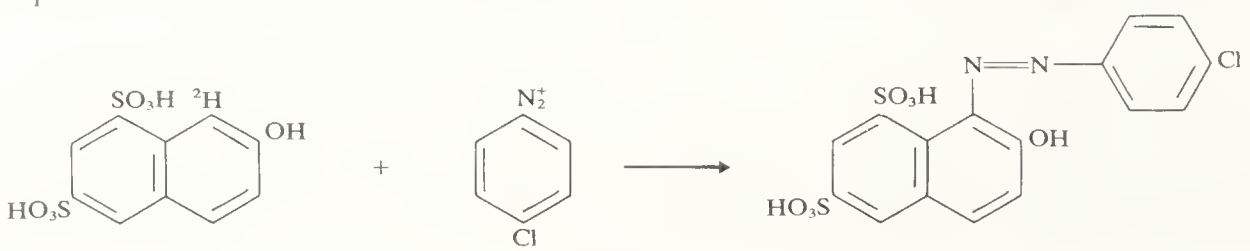
We have mentioned previously that the rate of nitration of hexadeuteriobenzene is identical with the rate of nitration of benzene. This allowed us to conclude that the activation energy for the loss of a proton from the σ-complex (Figure 1a) is less than for the loss of a nitronium ion, *i.e.* that k_4 (Scheme 11) is not rate determining. What are the origins of kinetic isotope effects? There is general agreement that the major factor is the difference in zero-point vibrational energy between bonds to different isotopes. This depends on the mass of the atoms and is lower when the reduced mass is higher. The reduced mass μ of two atoms connected by a covalent bond is:

$$\mu = \frac{m_1 m_2}{m_1 + m_2}$$

Therefore, C—^{2}H, O—^{2}H, and N—^{2}H bonds will have lower energies in the ground state than the corresponding C—H, O—H, and N—H bonds. The complete breaking of a C—^{2}H bond therefore requires more energy than that required to break a C—H bond in the same environment. Thus if such an isotopically substituted bond is broken in the rate determining step in a reaction, then the rate will be lowered by the substitution and is designated as a primary kinetic isotope effect. Conversely, if such an isotopically substituted bond is broken in a non-rate-determining step, no change in rate is observed. In certain cases, secondary isotope effects are observed in reactions where the bond in question is not broken at all. Because the differences in the reduced masses are at their

maximum values when the isotopes are ^1H, ^2H, or ^3H, primary deuterium or tritium kinetic isotope effects are significantly larger than those observed with other elements. Thus $k_{^{12}C}/k_{^{13}C}$ values are typically in the range 1.02–1.10. Deuterium isotope effects usually range from 1 (no isotope effect) to 9 or 10, while tritium isotope effects as high as 30 have been observed.

The absence of a primary kinetic isotope effect in the nitration of benzene has been confirmed by studies using [^3H]benzene and, in the case of toluene, using ring-tritiated toluene. Similarly, no significant ^3H isotope effect was observed in the bromination of benzene and toluene. On the other hand, sulphonation does show a small isotope effect and hence step 2 (Scheme 9) is at least partially rate-determining in sulphonation ($k_{^1H}/k_{^2H} \approx 2$). Another example is the iodination of [2,4,6-$^2H_3$]phenol in an acetate buffer, which shows an isotope effect $k_{^1H}k_{^2H} = 4$. The diazo coupling reaction between the *p*-chlorobenzenediazonium ion and β-[1-^2H]naphthol-6,8-disulphonic acid provides an interesting example (Scheme 16). Whereas $k_{^1H}/k_{^2H}$ can be as high as 6.5 for this base-catalysed reaction and step 2 (Scheme 9) then controls the rate, the $k_{^1H}/k_{^2H}$ does vary considerably with the reaction conditions. Evidently the approach of base, which removes the proton from the σ-complex, is severely hindered by the substituents at positions 2 and 8, particularly by the *peri* substituent. The reversion to the starting materials does not require a base.



SCHEME 16

If we consider that part of the energy profile (Figure 1a) around the σ-complex, we must assume that the increase in the activation energy corresponding to the loss of a proton still does not exceed the activation energy for loss of a nitronium ion when deuterium replaces protium. This may be represented qualitatively as in Figure 2(a). Similar qualitative diagrams for the sulphonation of benzene and the reaction of Scheme 16 are shown in Figures 2(b) and 2(c), respectively.

2.5.6.3 Reactions involving *ipso* protonation

These reactions may be divided into two types: those which are hydrogen exchange reactions and those in which a substituent other than hydrogen is displaced.

Much kinetic work has been reported in connection with acid-catalysed hydrogen exchange reactions of arenes.[18] This work has aimed both at a determination of the mechanism of the reaction and also at the evaluation of substituent effects. This type of reaction can be used to deuteriate and tritiate aromatic rings selectively. The general mechanism outlined previously (Scheme 9) has been confirmed. Indeed, the isolation of σ-complexes has been reported.[22] Thus at low temperatures mesitylene reacts with hydrogen fluoride in the presence of boron trifluoride to afford the yellow σ-complex which reverts to starting materials at higher temperatures (−15 °C) (equation 4). Using the less nucleophilic hexafluoroantimonate as the counter-ion, the mesitylene salt does not decompose until 51 °C. The ^1H n.m.r. spectrum of this latter salt showed resonances at δ 2.7 (*o*-CH_3), 2.8 (*p*-CH_3), 4.5 (CH_2), and 7.6 (CH).

Protonated benzene has been prepared by adding a solution of benzene in SO_2ClF to a rapidly stirred mixture of HF–SbF_5 (1:1 molar ratio) in SO_2ClF at −78 °C. At −80 °C this mixture showed a sharp singlet in the ^1H n.m.r. spectrum at δ 8.09, with strong ^{13}C–H satellites (3.3%) [$J(^{13}C–H) = 26$ Hz]. This chemical shift results from time averaging the

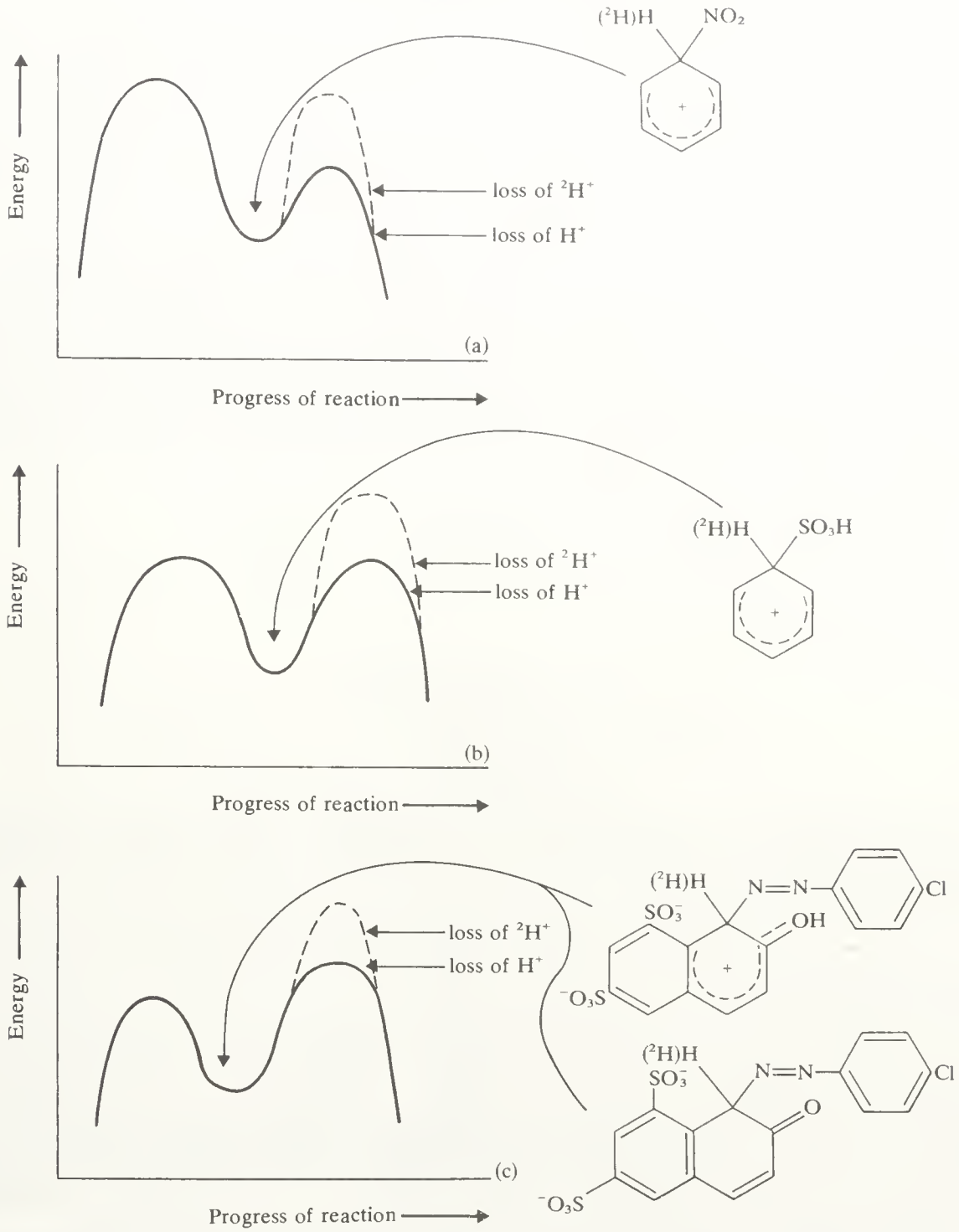
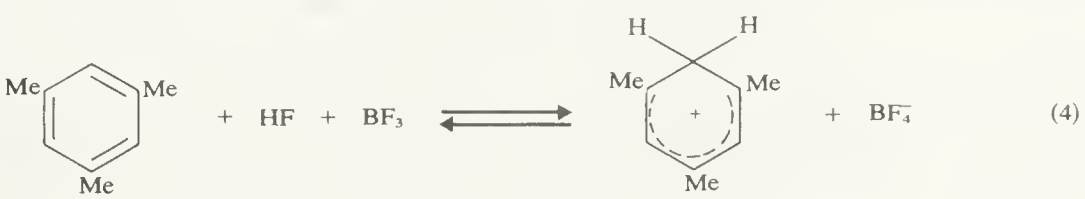


Figure 2 Energy profiles to exemplify the absence or presence of primary kinetic ^2H isotope effects

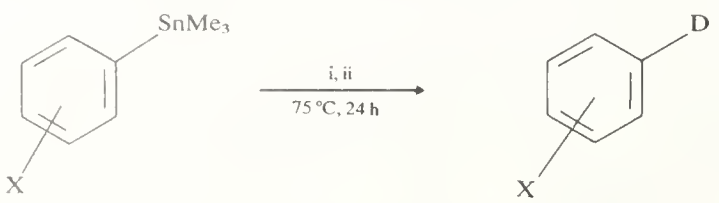
degenerate set of ions and was confirmed by ^{13}C n.m.r. spectroscopy, which gave δ (^{13}C) at 144.8. By changing the solvent, the ^1H n.m.r. spectrum was recorded at $-134\,°C$ and then showed resonances at δ 5.69 (CH_2), 8.22 (*m*-H's), 9.42 (*p*-H), and 9.58 (*o*-H's).



(4)

The reversibility of sulphonation and Friedel–Crafts alkylations will be discussed in more detail at a later stage. At this point we will concentrate our attention on proto-demetallations. Proto-desilylation has been studied in considerable detail,[23a] as have reactions involving germanium, tin, and lead analogues. The rate of cleavage of $ArMEt_3$ compounds by aqueous methanolic perchloric acid increases in the series (M =) Si < Ge ≪ Sn ≪ Pb. Primary kinetic isotope effects in the range $k_{1H}/k_{2H} = 1.55$–3.05 are observed using deuterium chloride in deuterium oxide. This confirms the operation of the mechanism involving a σ-complex (Scheme 9).[24b]

Proto-desilylation finds use in synthesis, *e.g.* in the formation of the steroid (**56**), where the final step involves removal of two trimethylsilyl residues by means of trifluoroacetic acid (Scheme 8). The preparation of specifically deuteriated compounds can be achieved similarly, as in the examples given in Scheme 17. This method appears to be preferable to the hydrolysis of Grignard or organolithium reagents if high isotopic purity (>98%) is required. It also has the potential advantage of being usable in cases where Grignard reagents cannot be prepared, *e.g.* in the presence of carbonyl, nitro, and cyano groups.



X = H, *o*-Me, *m*-Cl, *p*-OMe
m-CF_3, *p*-F, or *p*-Br

i, $MeCO_2D$; ii, D_2O.

SCHEME 17

Protodeauration, a relatively new electrophilic substitution, occurs when phenylauritriphenylphosphine is allowed to react with hydrogen chloride in ethanolic solution (equation 5).

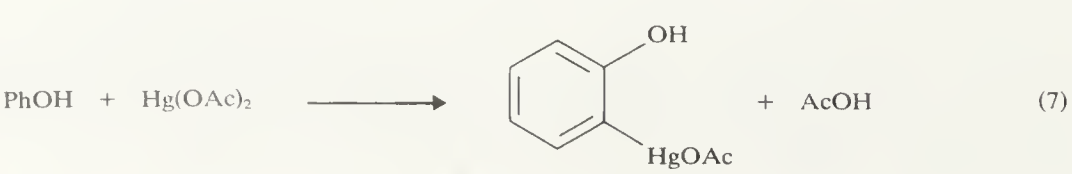
$$PhAuPPh_3 + HCl \longrightarrow PhH + Ph_3PAuCl \quad (5)$$

2.5.6.4 Metallations

Electrophilic metallations involving aromatic substrates are observed using, for example, mercury, thallium, and lead salts. These reactions should not be confused with metallations involving, for example, organolithium compounds such as n-butyl-lithium. In these latter reactions it is the most acidic hydrogen in the aromatic substrate which is removed, formally by the n-butyl anion. Thus fluorobenzene is metallated *ortho* to the halogen and 2-fluoronaphthalene affords 54% of 1- and 46% of 3-lithio-2-fluoronaphthalene.

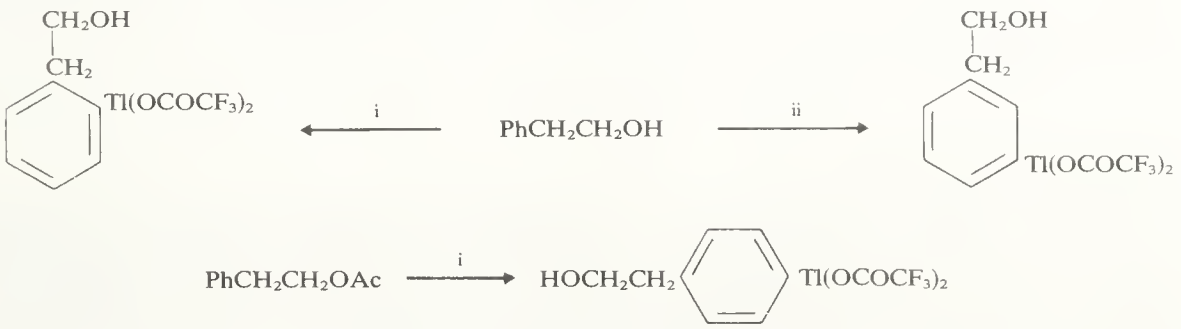
Salts of divalent mercury effect electrophilic mercuriation of aromatic compounds. For example, mercury(II) nitrate, in the presence of mercury(II) oxide (to remove the nitric acid) and in the absence of air, reacts with benzene (equation 6); and mercury(II) acetate reacts with phenol (equation 7). Lead tetra-acetate plumbylates *m*-dimethoxybenzene more rapidly than the other two isomers and hence provides evidence in favour of the electrophilic nature of this reaction.

$$PhH + Hg(NO_3)_2 \rightleftharpoons PhHgNO_3 + HNO_3 \quad (6)$$



The direct thalliation of many aromatic compounds is rapid at room temperature using thallium(III) trifluoroacetate.[24a] Using thallium(III) salts in trifluoroacetic acid–acetic acid mixtures, toluene has been found to be seven times as reactive as benzene and results in predominantly *para* substitution (87%). Even aromatic substrates containing electron-withdrawing substituents, such as benzoic acid and benzotrichloride, undergo substitution with thallium(III) trifluoroacetate in trifluoroacetic acid when heated under reflux.

Like aromatic mercuriation, the corresponding thalliations constitute rare examples of freely reversible electrophilic substitutions. Thus the reaction of 2-phenylethanol with thallium(III) trifluoroacetate at room temperature proceeds under kinetic control to yield the *ortho*-substitution product, possibly by intramolecular delivery of the electrophilic thalliating species. On the other hand, reaction at 73 °C gives predominantly *meta* substitution (thermodynamic control). The possible intervention of a Lewis acid–Lewis base complex between the side-chain hydroxyl group and the thallium(III) trifluoroacetate is indicated by the reaction of 2-phenylethyl acetate, which results in predominantly *para* substitution at room temperature (kinetic control). These results are summarized in Scheme 18.



i, $Tl(OCOCF_3)_3$, 25 °C; ii, $Tl(OCOCF_3)_3$, 73 °C.

SCHEME 18

The reactions of aromatic compounds with thallium salts would probably be of little general interest were it not for the fact that a large number of very useful synthetic transformations can be effected using the aryl-thallium salts as intermediates. For example, *p*-nitrotoluene can be prepared in good yield, almost free of the other two isomers, by the reaction of *p*-tolylbis(trifluoroacetyl)thallium with nitrogen dioxide.[24b] A number of other typical reactions are illustrated in equations (8)–(11).[24a]

$$ArTl(OCOCF_3)_2 + KI(aq) \longrightarrow ArI \quad (8)$$

$$ArTl(OCOCF_3)_2 + Pb(OAc)_4 \longrightarrow ArOH \quad (9)$$

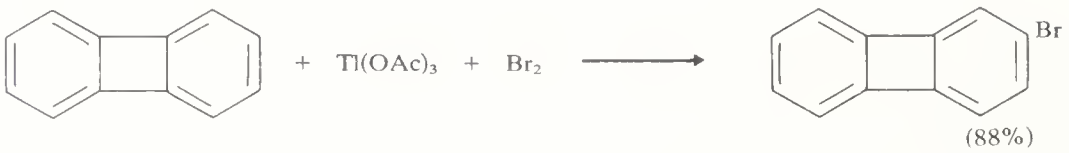
$$ArTl(OCOCF_3)_2 + KCN(aq) \xrightarrow{h\nu} ArCN \quad (10)$$

$$ArTl(OCOCF_3)_2 + LiAl^2H_4 \longrightarrow Ar^2H \quad (11)$$

It is not always necessary to isolate the arylthallium reagent. This is illustrated by the remarkably specific brominations which have been observed using bromine in the presence of thallium(II) acetate (equations 12 and 13).

$$RPh + Tl(OAc)_3 + Br_2 \longrightarrow \text{R-C}_6\text{H}_4\text{-Br} \quad (12)$$

R = OMe, 91%
R = F, 70%
R = Ph, 93%



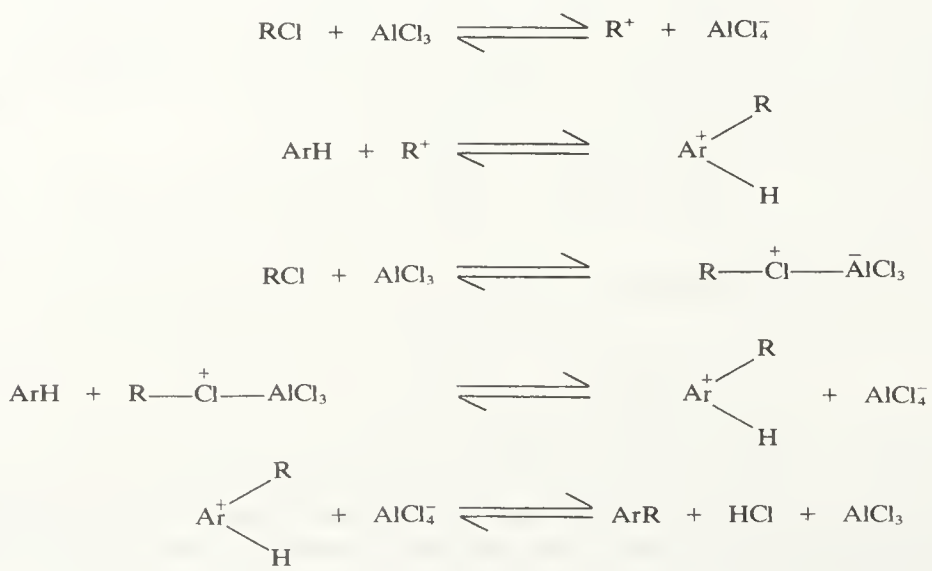
(13)

2.5.6.5 Group IV electrophiles

In this section we shall be concerned mainly with Friedel–Crafts alkylations and acylations.[25a] The other related reactions which are listed in Table 4, heading 3, will be considered more briefly. All of these reactions involve the formation of a new carbon–carbon bond. As with the other examples of electrophilic addition-with-elimination reactions, the aromatic species acts as a nucleophile and hence the other species, which is initially electrically neutral, undergoes nucleophilic substitution. In the majority of the reactions to be considered in this section, the electrophilic component would not be sufficiently reactive to undergo reaction with the weakly nucleophilic aromatic component except in the presence of a suitable catalyst. The catalyst increases the electrophilicity of the non-aromatic component.

(*i*) *Friedel–Crafts alkylation*

We shall consider alkylation first. Lewis acids are normally employed to catalyse alkylations using alkyl halides, alcohols, and esters (Scheme 19). Where the electrophile is generated from an olefin, a proton acid is usually required. Other alkylating agents can be used and these include thiols, ethers, sulphides, sulphates, and even, in special circumstances, alkanes.[25b] It is noteworthy that ethylene oxide is useful in adding a two-carbon fragment and cyclopropane a three-carbon fragment. As with normal nucleophilic substitution reactions (Chapter 3), two extreme mechanisms should be considered.



SCHEME 19

Aluminium chloride is the most frequently used catalyst in Friedel–Crafts alkylations. It is probable that no single order of reactivity of the catalysts can be drawn up since arene, electrophile, and reaction conditions may well interact to change a given sequence for one reaction when compared with another. A sequence which has been suggested[26] is Al(III) > Ga(III) > Fe(III) > Sb(V) > Zr(IV) > Sn(IV) > B(III) > Sb(III).

Alkyl halides are frequently the electrophiles of choice, and with particularly nucleophilic aromatic substrates and reactive alkyl halides, zinc(II) chloride, a mild catalyst, may be used with advantage. The order of reactivity with respect to the halogen is F > Cl > Br > I. Thus 1-chloro-3-fluoropropane reacts with benzene in the presence of boron trichloride to afford 1-chloro-3-phenylpropane. With all alkylating agents the reactivity order is allyl ≡ benzyl > tertiary alkyl > secondary alkyl > primary alkyl.

Friedel–Crafts alkylations are among the most complex of all of the electrophilic addition-with-elimination reactions. Not only is there no single mechanism (Scheme 19) which is appropriate to all examples, but also other complications arise. The entering alkyl group is, of course, electron releasing and hence the product of the reaction is more susceptible to reaction with an electrophile than was the original substrate. Di- and poly-alkylation is frequently observed. However, by using the arene as the solvent, and by using high-speed stirring, it is frequently possible to obtain good yields of monoalkylated products. These two factors are of considerable importance. Simple alkylbenzenes show relative rates of Friedel–Crafts alkylations in the range 1.5–3 times as fast as benzene. Efficient stirring minimizes the effect of the preferential solubility of the alkylbenzenes in the catalyst layer where the reaction takes place.

In most cases the presence of strong electron-withdrawing groups on the arene ring reduces the nucleophilicity of the arene to the extent that Friedel–Crafts alkylation is not possible under normal circumstances. Thus nitrobenzene is frequently used as a solvent in Friedel–Crafts reactions as an alternative to carbon disulphide. Reactions carried out using substrates containing amino, hydroxy, and alkoxy groups present difficulties. These groups, because of their relatively high basicities, coordinate with the Lewis acid catalysts and hence the catalyst is effectively removed from the system. Thus arylamines are only alkylated easily by olefins using aluminium anilides as catalysts.

The duality in the mechanism of Friedel–Crafts alkylation results in an important synthetic limitation. Rearrangement of the alkyl residue is frequently observed.[27] If the alkylation proceeds by a mechanism which can be formally regarded as analogous to an S_N2 displacement, then rearrangement does not present a problem. Straight-chain alcohols usually do not rearrange using aluminium chloride as the catalyst although they do in the presence of boron trifluoride or sulphuric acid. The precise reaction conditions frequently influence the result. For example, although benzene reacts with n-propyl chloride in the presence of aluminium chloride at room temperature to afford mostly n-propylbenzene, at higher temperatures considerable amounts of cumene are formed (equation 14).

$$\mathrm{PhH} + \mathrm{CH_3CH_2CH_2Cl} \xrightarrow{\mathrm{AlCl_3}} \underset{(35\%)}{\mathrm{PhCH_2CH_2CH_3}} + \underset{(65\%)}{\mathrm{PhCH(CH_3)_2}} \qquad (14)$$

The rearrangement usually occurs in the order primary to secondary to tertiary and usually proceeds by hydride ion migration. Migration of an anionic fragment can occur. Examples of these types of rearrangements are given in equations (15) and (16).

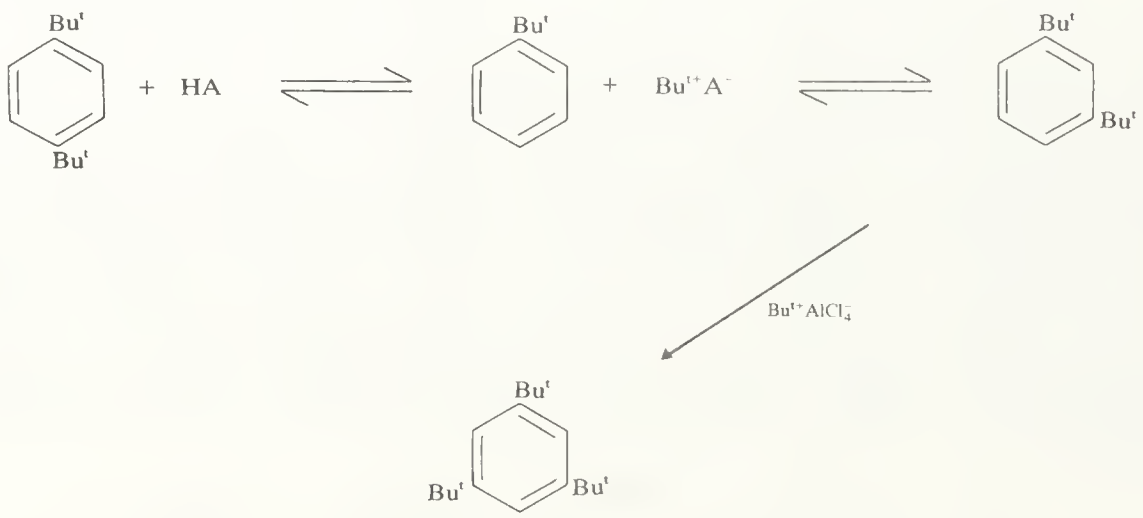
$$\mathrm{PhH} + \mathrm{Me_2CHCH_2Cl} \xrightarrow{\mathrm{AlCl_3}} \mathrm{PhCMe_3} \qquad (15)$$

$$\mathrm{PhH} + \mathrm{Me_3CCH_2OH} \xrightarrow{\mathrm{BF_3}} \mathrm{Ph{-}\overset{\mathrm{Me}}{\overset{|}{\underset{\mathrm{Me}}{\underset{|}{C}}}}{-}CH_2Me} \qquad (16)$$

The boron trifluoride catalysed reaction of benzene with [2-^{14}C]ethyl fluoride results in scrambling of the label in the ethylbenzene when the reaction is carried out in non-polar solvents. No scrambling was observed when the reaction was carried out in nitromethane. These results were taken to indicate the intermediacy of carbenium ions under the former conditions.[28] In contrast, only minor scrambling was observed in the reaction of 1-chloro[1,1-$^2H_2$]propane with benzene.[29] Scrambling in this latter reaction would require either two hydride shifts or one methyl shift in order to isomerize an n-propyl carbenium

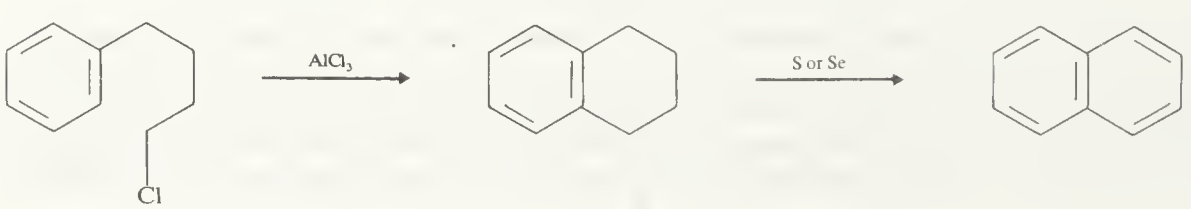
ion to another n-propyl carbenium ion. The order of thermodynamic stability of alkylbenzenes is tertiary < secondary < primary and thus some reactions which appear to proceed without rearrangement may in fact proceed under thermodynamic control in which the initially formed secondary product (kinetic control) undergoes a second rearrangement to the primary alkyl product. This is only possible because of the reversibility of the Friedel–Crafts alkylation (Scheme 19). Because of these difficulties, primary alkylarenes are often prepared by means of Friedel–Crafts acylation followed by reduction of the carbonyl function by the Clemmensen or Wolff–Kishner procedures.

The problems associated with rearrangements of the alkyl residue are not the sole reasons for using this alternative approach. Transalkylation of the product formed under kinetic control can lead eventually to the most thermodynamically stable product. The *meta*-alkyl derivative is thermodynamically the most stable. As an example it was found that the reaction of toluene with ethyl bromide in the presence of gallium(III) bromide gave *o*-ethyltoluene (38.4%), *m*-ethyltoluene (21%), and *p*-ethyltoluene (40.6%). If we compare this product distribution with that observed in the nitration of toluene, the percentage of the *m*-isomer is evidently high. The principle may be applied in a useful way. Thus the reaction of t-butylbenzene with t-butyl chloride in the presence of aluminium chloride (initially at −40 °C) affords 1,3,5-tri-t-butylbenzene in about 80% yield.[30] The same product is also obtained by the t-butylation of 1,4-dibutylbenzene. [^{3}H]-Labelling studies indicated predominant, if not complete, intermolecular transfer of t-butyl groups. The results are in accord with the mechanism given in Scheme 20.

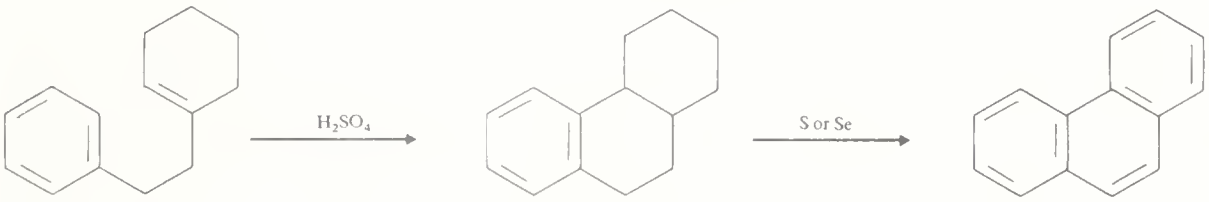


SCHEME 20

One of the most important synthetic applications of Friedel–Crafts alkylations is in ring-closure reactions. The most frequently used method involves the reaction between aluminium chloride and an aromatic substrate with a side chain having a halogen, hydroxyl, or an olefinic residue in an appropriate position. The reactions shown in equations (17), (18), and (19) can be used in the synthesis of tetrahydronaphthalene, octahydrophenanthrene, and indan derivatives. Dehydrogenation in the first two cases affords the naphthalenes and phenanthrenes. In the last example (equation 19) a sulphonic acid ion-exchange resin (Amberlist-15) was found to be more satisfactory[31] than Bradsher's reagent,[32] sulphuric acid, or formic acid.



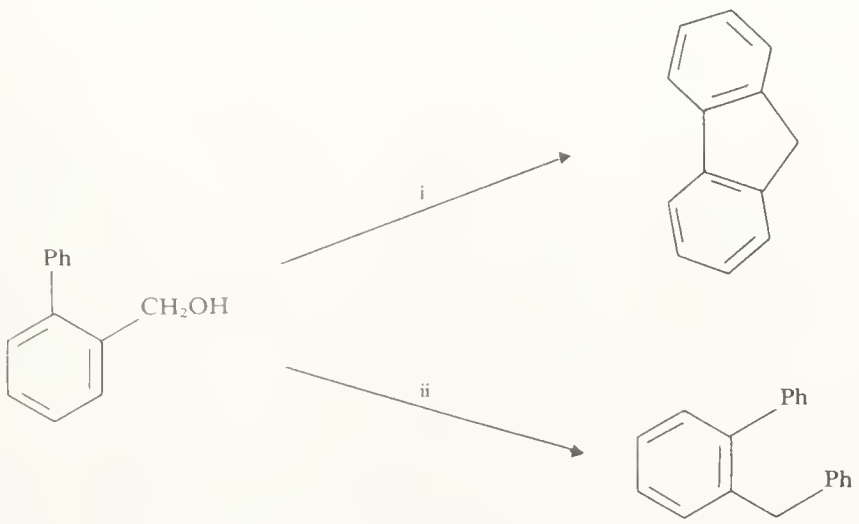
(17)



(18)

(19)

Fluorene derivatives may be prepared by the cyclodehydration of 2-arylbenzyl alcohols using Amberlist-15.[33] However, the reaction must be carried out in a non-aromatic solvent such as cyclohexane since the intermediate 'hot' cation attacks benzene and nitrobenzene (Scheme 21). Aromatic cyclodehydration of the type exemplified in equation (20) is evidently related to those reactions shown above, as also are the reactions shown in equations (21) and (22).

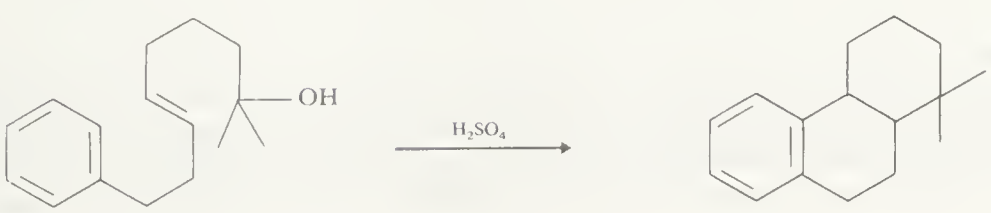


i, Amberlist-15 in cyclohexane; ii, Amberlist-15 in benzene.

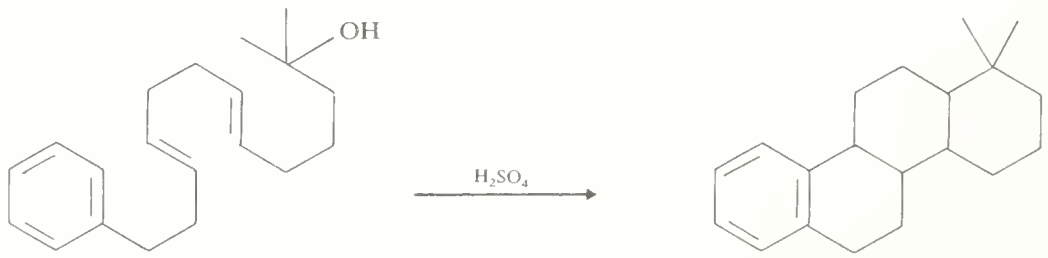
SCHEME 21

(93%)

(20)



(21)



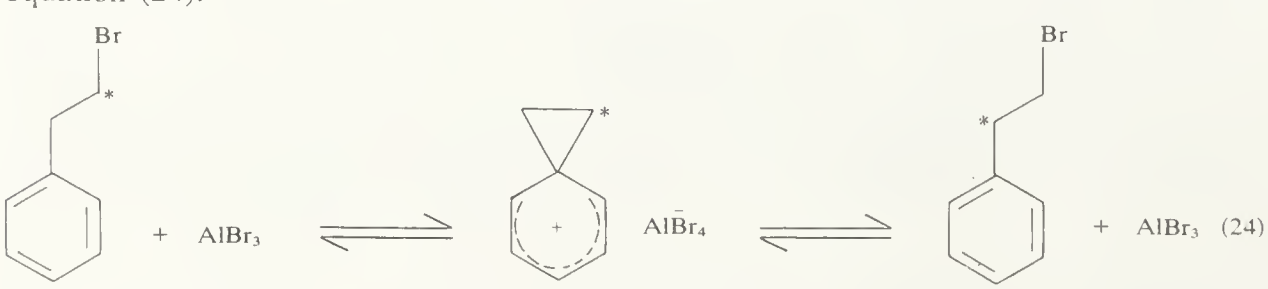
(22)

From the discussion above, it is clear that carbenium ions are involved in the majority of Friedel–Crafts alkylations.[18] With certain reagents, the formation of the carbenium ion is particularly easy because of the stability of the cation. Indeed, in special cases the alkylation of particularly nucleophilic aromatic residues, *e.g.* phenols and arylamines, proceeds in the absence of a catalyst. This is the case with triphenylmethyl chloride[34] and 1-chloroadamantane.[35] The tropylium ion does not attack benzene but does alkylate anisole (equation 23).[36]

(23)

In the case of alkylations involving primary reagents, it is likely that entirely free carbenium ions are not involved. The ion may then exist as a dipolar complex (as formulated in Scheme 19) or alternatively as a tight ion pair. In some reactions, kinetic studies have shown reactions to be third order, *i.e.* first order in each of the electrophilic reagent, the aromatic substrate, and the catalyst. Since it is known that free carbenium ions attack arenes rapidly, the aromatic substrate would not appear in the rate expression if the slow step in the reaction just involved the slow formation of a carbenium ion. Another possibility involves an S_N2 reaction with respect to the electrophile. Such a possibility is excluded in many reactions by virtue of the almost complete racemization which is observed using appropriate chiral electrophiles. One notable exception involves the apparently complete inversion using optically active methyloxiran.[37]

Rearrangement is possible even in the absence of free carbenium ions, since products arising from hydride-ion shifts have been observed in other circumstances which are known to involve tight ion-pairs. As well as the possibility of rearrangement occurring before attack by the arene, the reversibility of Friedel–Crafts alkylations does not preclude rearrangement after the formation of the initial alkylarene. It is appropriate to note at this point that isotope scrambling occurs when [1-^{14}C]ethyl bromide reacts with aluminium bromide in the absence of an arene, and that with 2-phenyl[1-^{14}C]ethyl bromide, scrambling is so rapid that it can only be followed kinetically at temperatures below −70 °C. This is, of course, a special case and presumably involves the sequence shown in equation (24).

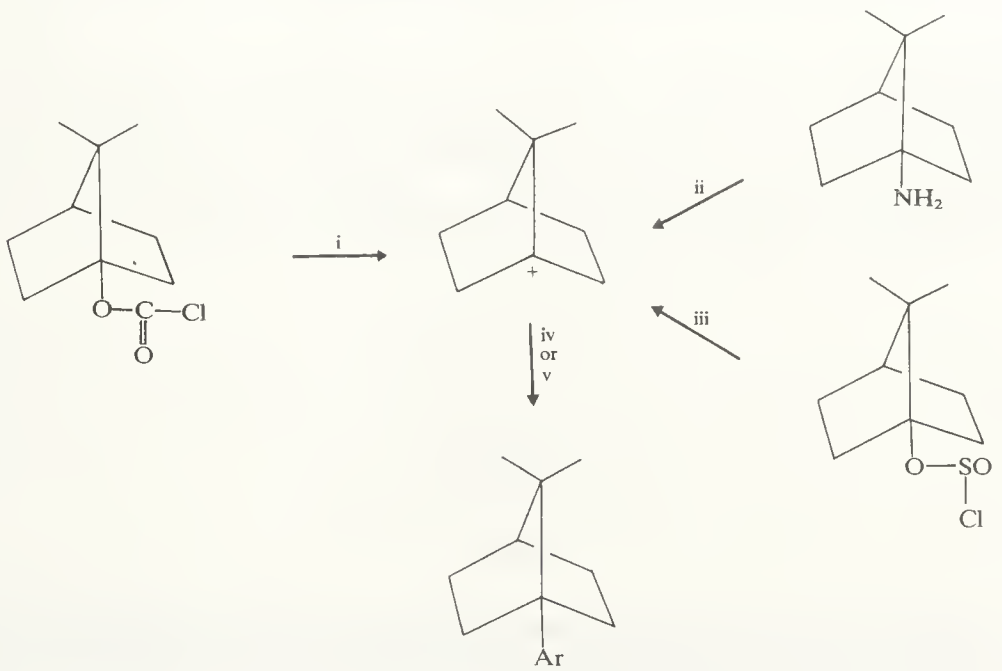


(24)

We have not made any mention so far of the reactions of carbenium ions generated by diazotization of primary amines. This method is known to produce 'hot' or 'unencumbered' carbenium ions. A correspondence has been observed between amine deaminations and chloroformate dechlorodecarboxylations. This is undoubtedly due to the presence of excellent leaving groups in the respective intermediates [diazonium ions (RN_2^+)

and carboxylium ions (R—O—$\overset{+}{C}$O)]. We shall concentrate our attention on the reactions of carbenium ions generated from chloroformates with the assistance of silver(I) ions,[38] since the recent results in this area do have a general bearing on a number of important aspects of electrophilic addition-with-elimination reactions.

The inertness of the bridgehead position in bicyclo[2,2,1]heptanes to many attempts to generate a cation is well known.[39] Thus 1-aminoapocamphane reacts with nitrosyl chloride in chlorobenzene to afford a mixture of 1-chlorophenylapocamphanes in 9% yield. The reaction of 1-chloroformylapocamphane with silver hexafluoroantimonate in chlorobenzene at room temperature is much cleaner and gave 1-chloroapocamphane (17%) and a mixture of 1-chlorophenylapocamphanes (81%). The ratio of *ortho* : *meta* : *para* isomers was found to be identical to that formed in the deamination reaction (*i.e.* 39:35:26). It is also important to note that 1-chloroapocamphane is unreactive towards silver(I) ions. That these reactions proceed *via* the bridgehead cation is established by the fact that an analogous reaction of the chloroformate carried out in nitrobenzene gave 1-(*m*-nitrophenyl)apocamphane as the only substitution product, in 24% yield. The possibility that these reactions (Scheme 22) proceed *via* a bridgehead radical is excluded by the *ortho* : *meta* : *para* ratio. The 1-apocamphyl radical, generated by thermolysis of the diacyl peroxide in chlorobenzene, gives an *ortho* : *meta* : *para* ratio of 13:60:27. The formation of 1-(*m*-nitrophenyl)adamantane has also been reported from the reaction of 1-adamantyl chloroformate with silver(I) hexafluoroantimonate in nitrobenzene.[40]



i, $AgSbF_6$; ii, NOCl; iii, $AgBF_4$; iv, C_6H_5Cl; v, $C_6H_5NO_2$.

SCHEME 22

Competition data are available[41] for reactions of 1-chloroformylapocamphane with silver(I) hexafluoroantimonate in aromatic solvent mixtures such as chlorobenzene–benzene, chlorobenzene–toluene, benzene–toluene, and chlorobenzene–nitrobenzene. The most striking feature is that benzene is more reactive than toluene, $k_B/k_T = 1.28 \pm 0.24$. A more usual value would be $k_B/k_T = 0.61$ for the isopropylation of toluene–benzene mixtures.[18] The analysis of all of the data suggests that the reactions proceed *via* rate limiting σ-complex formation even though it is an extremely reactive electrophile.

One final point of general interest in connection with aromatic electrophilic addition-with-elimination reactions emerges from the study of silver(I) ion reactions with chloroformates. This is concerned with the reaction using methyl chloroformate in anisole.

The reaction of [$^2H_3$]methyl chloroformate showed that the reaction proceeds predominantly by initial attack on oxygen. Further, the dimethylphenyloxonium salt does not rearrange to *o*-methylanisole intramolecularly. These results suggest that initial interactions involving electrophiles and non-bonded electrons could be of more importance than has been thought previously.

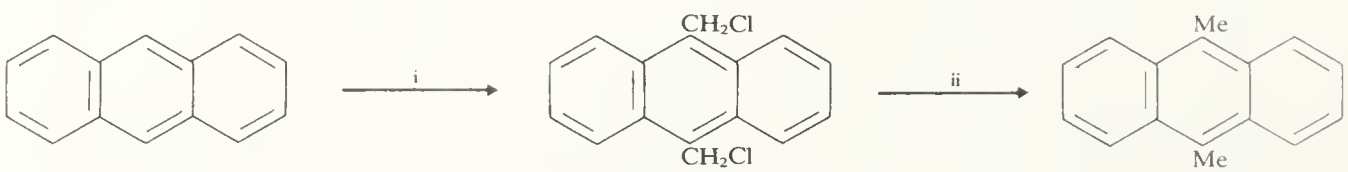
(*ii*) *Chloromethylation*

The introduction of a chloromethyl group into aromatic compounds occurs when the arene is treated with formaldehyde and hydrogen chloride, usually in the presence of a Lewis acid.[25] For example, benzyl chloride can be prepared in good yield by passing dry hydrogen chloride into a suspension of zinc(II) chloride and paraformaldehyde in benzene (equation 25).

$$PhH + CH_2O + HCl \xrightarrow{ZnCl_2} PhCH_2Cl + H_2O \qquad (25)$$

Fluoromethylation, bromomethylation, and iodomethylation may be effected using the appropriate halogen acid. Other aldehydes may also be used to haloalkylate aromatic substrates. The reaction is successful in the presence of certain electron-releasing substituents (*e.g.* alkyl and alkoxy) and electron-withdrawing groups (*e.g.* nitro). Although nitrobenzene can be chloromethylated, *m*-dinitrobenzene is inert. Amines and phenols are too reactive — unless other electron-withdrawing groups are present — and polymers are formed.

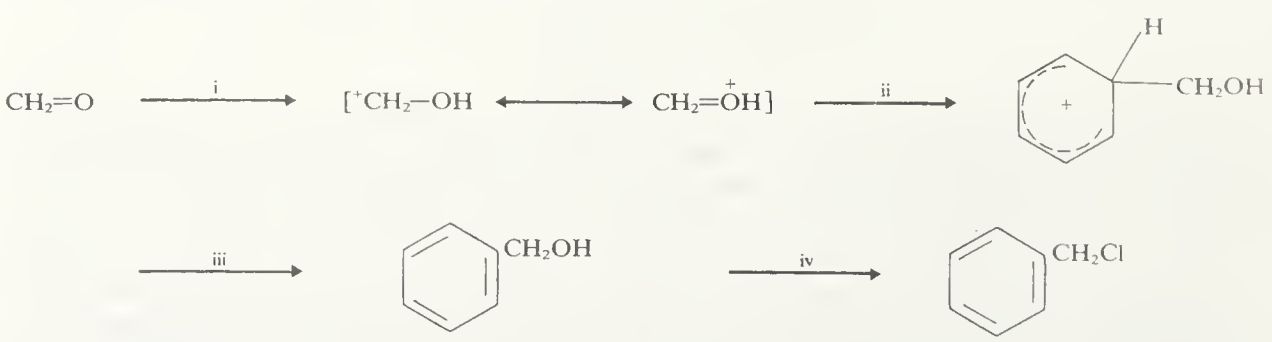
Chloromethylation of polycyclic arenes is also successful. Thus naphthalene is chloromethylated predominantly in the α-position. The chloromethylation of anthracene is difficult to stop at the monochloromethyl stage but does afford 9,10-di(chloromethyl)anthracene in good yield.[42] Reductive dechlorination to 9,10-dimethylanthracene, a useful Diels–Alder diene which is otherwise difficult to obtain, is achieved[43] using lithium tetrahydroaluminate in THF (Scheme 23).



i, CH_2O, HCl, $ZnCl_2$; ii, $LiAlH_4$.

SCHEME 23

Studies of the mechanism of the chloromethylation indicate that the benzylic alcohol is formed initially and this is then converted into the final product. The attacking electrophile is the hydroxymethyl cation (Scheme 24).



i, H^+; ii, C_6H_6; iii, $-H^+$; iv, HCl, $ZnCl_2$.

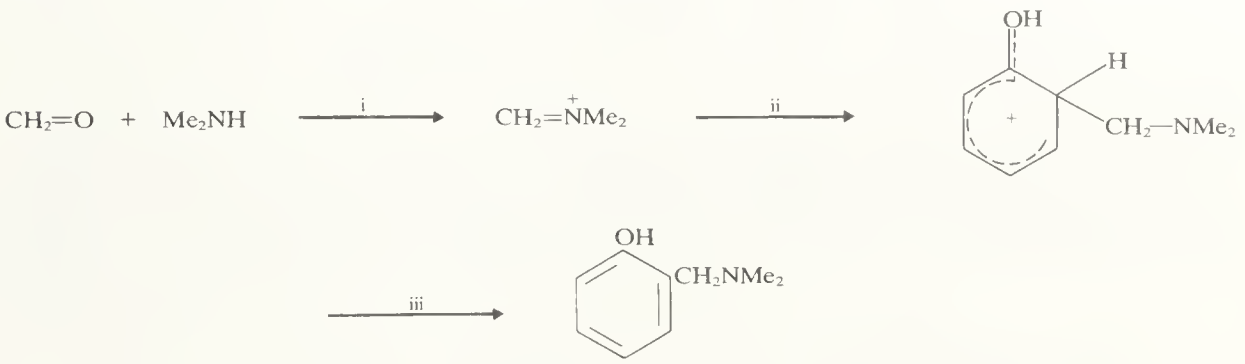
SCHEME 24

There are two complications which can arise with chloromethylation. Both of these have been alluded to already. The chloromethyl group is electron-releasing, though less so than the methyl group. It is therefore usually difficult to avoid some further chloromethylation. This is not such a major problem as in the case of Friedel–Crafts alkylations. The second problem is concerned with the fact that the product is a benzylic halide which, in the presence of a Lewis acid, can Friedel–Crafts alkylate a second molecule of the initial substrate (equation 26). This secondary reaction is particularly important when electron-releasing substituents are present and leads to polymer formation with reactions of phenols and arylamines.

$$PhCH_2Cl + PhH + ZnCl_2 \longrightarrow Ph_2CH_2 \qquad (26)$$

(*iii*) *Aminomethylation*

The introduction of an aminomethyl group into an aromatic residue is evidently related to chloromethylation. It is a special case of the Mannich reaction. The electrophile involved is not very reactive and therefore reaction only occurs with particularly nucleophilic arenes. Although the reaction is useful with compounds such as pyrrole and indole, aminoalkylation of carbocyclic systems is restricted at present to phenols (Scheme 25) and secondary and tertiary arylamines.[44] It is possible that the use of pre-formed electrophiles such as dimethyl(methylene)ammonium trifluoroacetate[45] will lead to improvements.



i, H^+, $-H_2O$; ii, C_6H_5OH; iii, $-H^+$.

SCHEME 25

(*iv*) *Friedel–Crafts acylation*

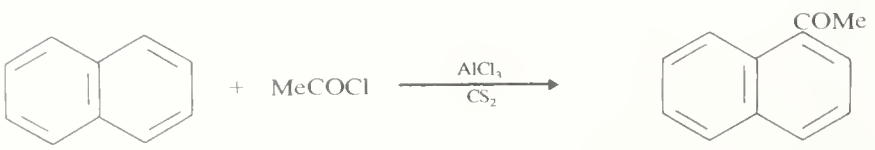
The most important general method for the preparation of aryl ketones involves reactions of acyl halides or carboxylic anhydrides with arenes, in the presence of a Lewis acid; also, reactions of carboxylic acids with arenes, in the presence of a protic acid.[25] Mixed carboxylic-sulphonic anhydrides,[46] especially those derived from trifluoromethanesulphonic acid, are particularly reactive acylating agents and can smoothly acylate benzene in the absence of a catalyst. The mixed anhydrides can also be formed *in situ* by the reaction of acyl halides with trifluoromethanesulphonic acid. The trifluoromethanesulphonic acid can be recovered as the barium salt in an almost quantitative yield. Typical examples of the range of Friedel–Crafts acylations are given in equations (27)–(39).

$$PhH + MeCOCl \xrightarrow{AlCl_3} PhCOMe \quad (97\%) \qquad (27)$$

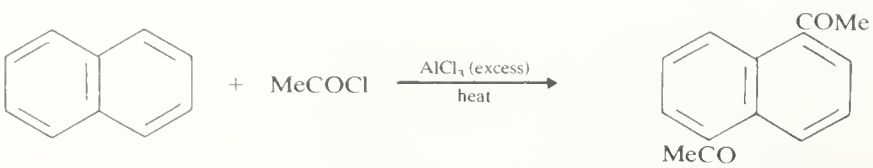
$$PhMe + (MeCO)_2O \xrightarrow{AlCl_3} Me\text{-}C_6H_4\text{-}COMe \quad (80\%) \qquad (28)$$

(80%) (29)

PhPh + MeCOCl $\xrightarrow{AlCl_3}$ Ph, COMe (90%) (30)



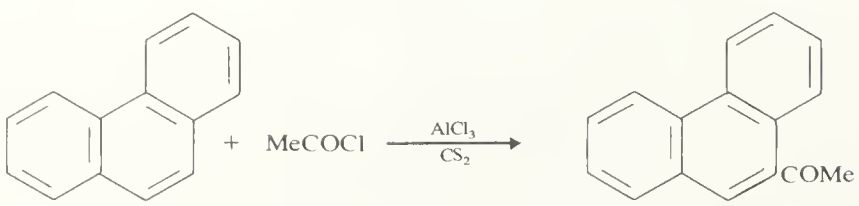
(92%) (31)



(33%) (32)

(60%) (33)

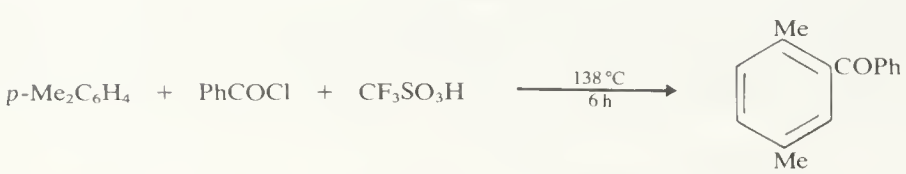
(71%) (34)



(65%) (35)

PhH + CF_3SO_3COPh $\xrightarrow{60\,^\circ C}$ Ph_2CO (90%) (36)

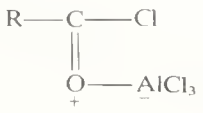
(84%) (37)



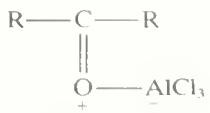
(82%) (38)

(54%) (39)

In reactions using acyl halides, the chlorides are normally used. The other halides can be used and the reactivity order is usually I > Br > Cl > F. The normal catalysts for Friedel–Crafts alkylations can be used but aluminium chloride is usually used. The major difference from the situation in the alkylation reactions is that slightly in excess of one mole of catalyst is required using an acyl halide, and employing a carboxylic anhydride slightly in excess of two moles of catalyst is required. One mole of catalyst is removed from the system by coordination with each carbonyl group present. The 1 : 1 complexes formed between acyl chlorides and aluminium chloride (**68**) is sometimes generated before the aromatic substrate is added. The product is similarly coordinated to aluminium chloride (**69**).



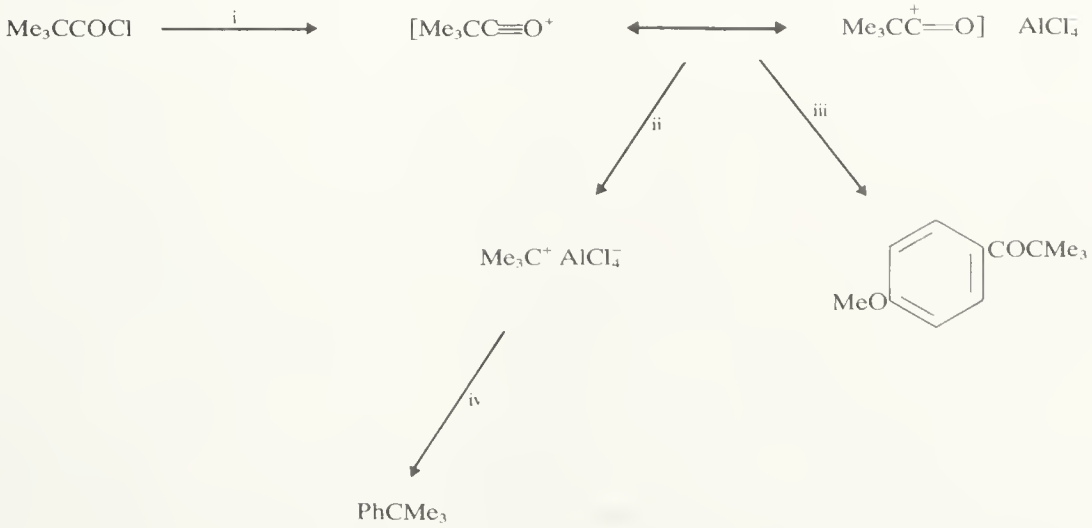
(**68**)



(**69**)

The acylation of di- and poly-alkylbenzenes sometimes produces difficulties. Thus although the acetylation of *p*-xylene in carbon disulphide proceeds normally to afford 2,5-dimethylacetophenone, the reaction carried out using the arene as solvent yields 2,4-dimethylacetophenone. Evidently transalkylation occurs during acetylation, and evidence for *ipso* attack should be looked for in Friedel–Crafts reactions. In general, however, Friedel–Crafts acylation is more straightforward than the alkylation. The electron-withdrawing effect of the carbonyl group results in the product of an acylation being less nucleophilic than the starting materials and hence less reactive.

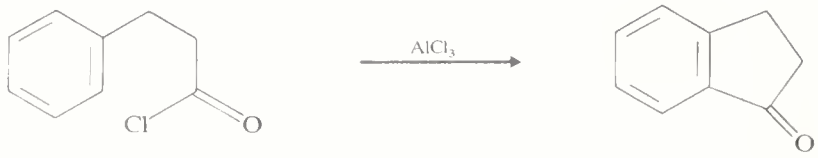
A further advantage of acylation compared with alkylation is that rearrangement of the alkyl residue in the acylating reagent does not occur. Furthermore, disproportionation reactions are rare. An exception to this general statement concerns pivaloylation. Thus the reaction of benzene with pivaloyl chloride in the presence of aluminium chloride gives mainly t-butylbenzene. Anisole, on the other hand, gives mainly *p*-methoxypivalophenone (Scheme 26). Evidently carbon monoxide is lost in the former reaction because of the relatively high stability of the t-butyl cation.



i, $AlCl_3$; ii, −CO; iii, PhOMe; iv, PhH.

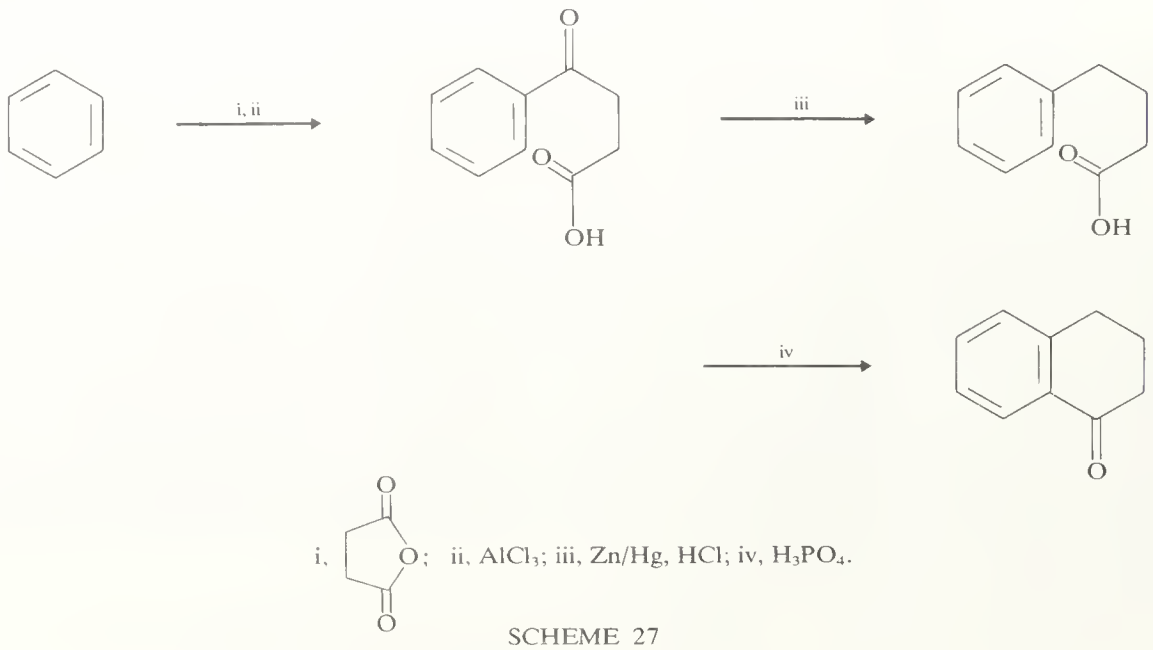
SCHEME 26

Intramolecular Friedel–Crafts acylations are of considerable value in the synthesis of di- and poly-cyclic ring systems. Thus, for example, 1-indanone can be prepared by the cyclization of β-phenylpropionyl chloride (equation 40). Similarly, 3,4-dihydronaphthalen-1-(2*H*)-one (α-tetralone) can be prepared from γ-phenylbutyric acid. The required acid can be made in two steps from benzene (Scheme 27). γ-Lactones such



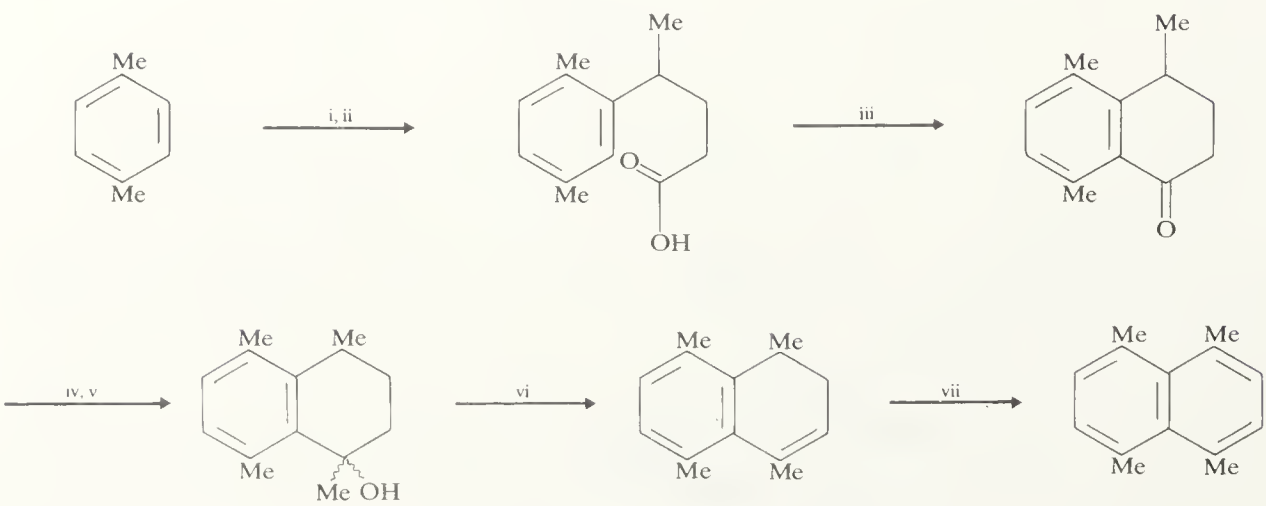
(40)

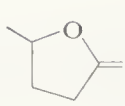
as γ-butyrolactone alkylate arenes in the presence of aluminium chloride and hence afford the γ-phenylbutyric acid in one step. The synthesis of 1,4,5,8-tetramethylnaphthalene exemplifies this procedure (Scheme 28). There are many changes which can be rung on this theme. Starting with naphthalene one can prepare phenanthrene derivatives, and by using phthalic anhydride, in place of succinic anhydride or a γ-butyrolactone, one can prepare anthracene derivatives starting with benzene or 1,2-benzanthracene (Scheme 29) starting with naphthalene.



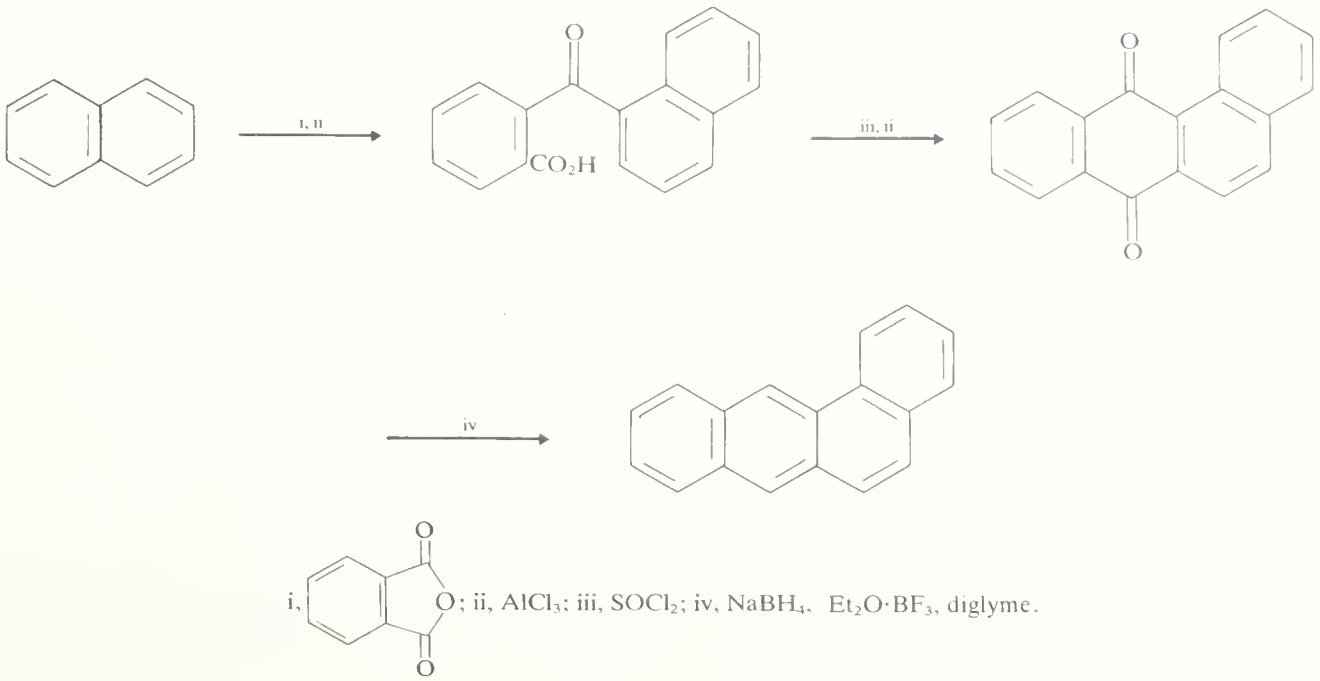
i, ; ii, $AlCl_3$; iii, Zn/Hg, HCl; iv, H_3PO_4.

SCHEME 27



i,  ; ii, $AlCl_3$; iii, H_3PO_4; iv, MeMgI; v, H_3O^+; vi, HCO_2H; vii, S or Se.

SCHEME 28

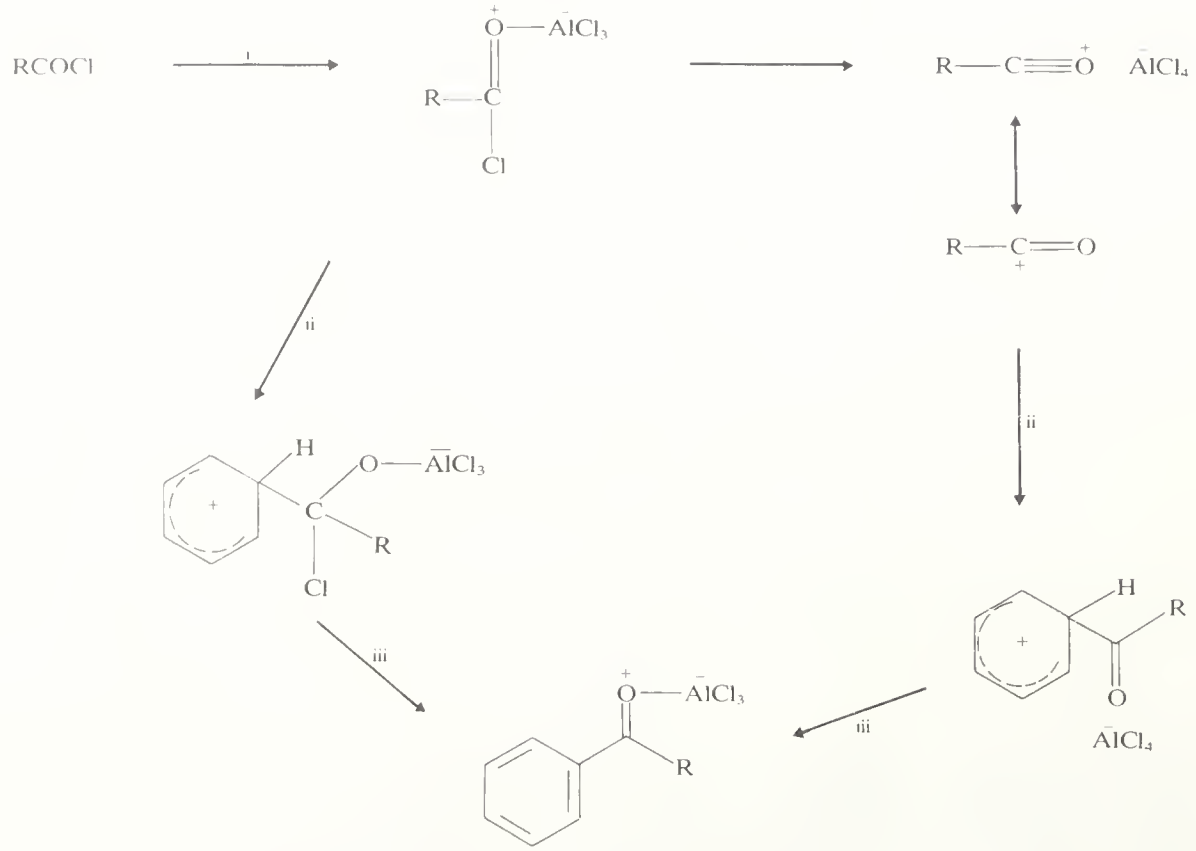


SCHEME 29

The Friedel–Crafts acylations, like the alkylations, exhibit a duality of mechanism. At one extreme a free acylium ion is involved while at the other end of the spectrum the arene attacks the 1 : 1 complex (**68**) directly. In between a tight ion pair must be considered (see Scheme 30). Precisely which mechanism operates will depend on a number of factors, including the nucleophilicity of the arene, the structure of the acylating agent, the catalyst, and the solvent system used. Thus the acetylium ion has been detected by i.r. spectroscopy in the liquid complex formed between acetyl chloride and aluminium chloride, and in polar solvents such as nitrobenzene. On the other hand, only the complex (**68**), and not the acetylium ion, has been detected in chloroform. Much recent work[18] has been carried out and allows some rationalization of the situation. The steric hindrance to acetylation of toluene compared with nitration, for example (Table 5), is noteworthy. Thus *p*-methylacetophenone is formed in very high yield using acetyl chloride and aluminium chloride (a 97% yield has been reported), whereas *o*-nitrotoluene is the major isomer produced on nitration (see, however, the discussion on *ipso* attack). When acetylation is carried out in carbon disulphide, less steric hindrance is noted compared with reactions performed in nitrobenzene. Naphthalene gives 1-acetylnaphthalene in carbon disulphide but mainly 2-acetylnaphthalene when nitrobenzene is used as the solvent. Interestingly, benzoylation is less sterically demanding than acetylation. The anomalous reactivity sequence in the acylation of benzene and mesitylene is probably due to a change in the mechanism of the reactions.[47] Similarly, the lower reactivity of chloroacetyl chloride compared with acetyl and benzoyl chloride reactions with highly nucleophilic arenes[48] may be due to changes in the precise mechanistic detail. In a reaction involving a free acylium ion ($RC{\equiv}O^+$), the rate of reaction will be reduced by electron release from the group R. The converse would be the case for reactions involving the acyl halide–catalyst complex (**53**). We should note at this point that acylium hexafluoroantimonates have been obtained and used successfully in Friedel–Crafts acylations.[49]

(*v*) *Formylations*[25]

We shall include in this section the reactions 3(a)–(g) from Table 4 and, in addition, formylations involving formyl fluoride, dichloromethyl ether, and the Reimer–Tiemann reaction.



i, $AlCl_3$; ii, PhH; iii, −HCl.

SCHEME 30

Formylation of benzene and simple alkylbenzenes can be achieved in good yield using carbon monoxide, hydrogen chloride, and aluminium chloride at high pressure ($1–2.5 \times 10^7$ N m^{-2}). The reactions can be carried out at atmospheric pressure in the presence of copper(I) chloride, which apparently provides a high local concentration of carbon monoxide by coordination. This is known as the Gattermann–Koch reaction. The reaction functions as if formyl chloride ionizes to give the formylium ion and this is the presumed electrophile. However, the high yields of 4-formyl-alkylbenzenes argues for a bulkier electrophile. The reagent mixture is conveniently generated by the action of chlorosulphuric acid on formic acid (equation 41). The reaction of hydrogen chloride with *N*-formylimidazole generates formyl chloride in methylene chloride at −65 °C (equation 42).

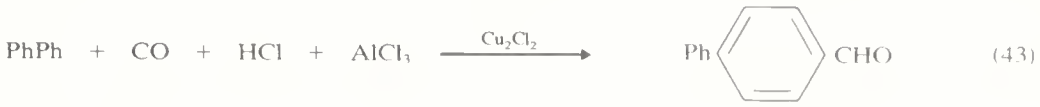
$$HSO_3Cl + HCOOH \longrightarrow HCl + CO + H_2SO_4 \qquad (41)$$

(42)

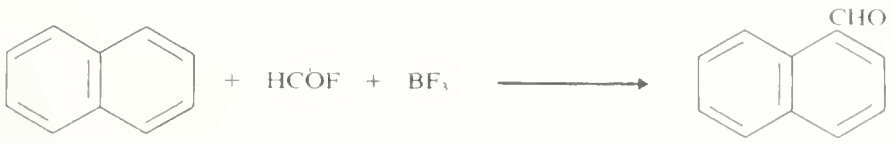
Benzene and toluene afford benzaldehyde and *p*-tolualdehyde in 90% and 85% yield respectively using the atmospheric pressure procedure, and biphenyl has been converted into 4-formylbiphenyl (equation 43) in yields as high as 73%. However, with certain alkylbenzenes there is a tendency for transalkylation or dealkylation to occur during the reaction. Thus *p*-xylene gives 2,4-dimethylbenzaldehyde and tri-isopropylbenzene gives only di-isopropylbenzaldehyde(s). Naphthalene appears not to give a naphthaldehyde.

A useful modification of this reaction involves the use of formyl fluoride,[50] which is prepared by the reaction of the mixed anhydride of formic and acetic acids with

anhydrous hydrogen fluoride. The formyl fluoride (b.p. −29 °C) is continuously removed as it is formed. Naphthalene does form 1-naphthaldehyde in 73% yield using this method (equation 44).

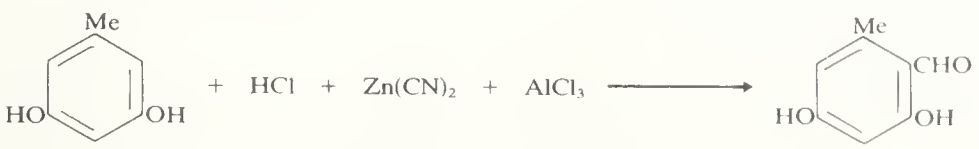


(43)

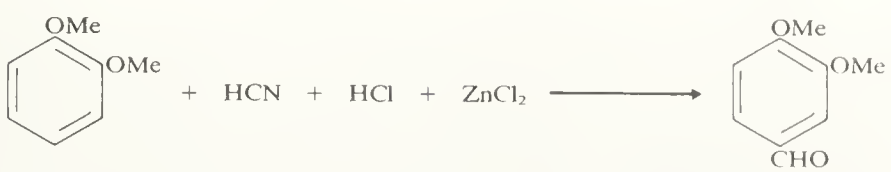


(44)

Formylation with zinc(II) cyanide and hydrogen chloride is known as the Gattermann reaction. Whereas the Gattermann–Koch method is unsuccessful with phenols and aryl ethers, this method does give good yields. The reaction originally used hydrogen cyanide, hydrogen chloride, and a Lewis acid catalyst such as zinc(II)chloride. The reactions shown in equations (45) and (46) exemplify the Gattermann reaction. The mechanism of the Gattermann reaction is obscure. However, aldimine salts are the initial products which undergo hydrolysis to the aldehyde. The electrophile may well be a formimidium complex with the Lewis acid catalyst.



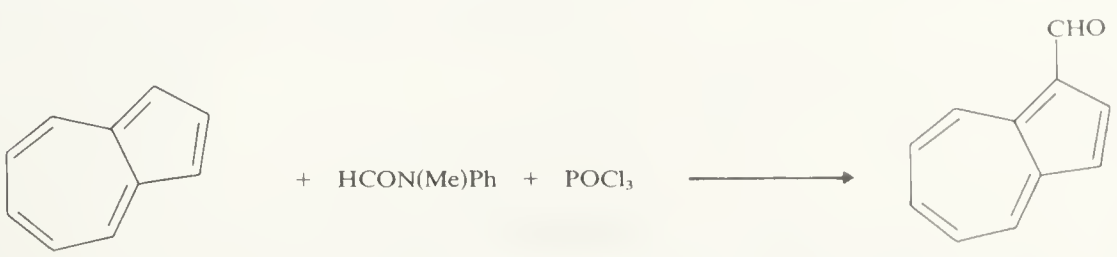
(96%) (45)



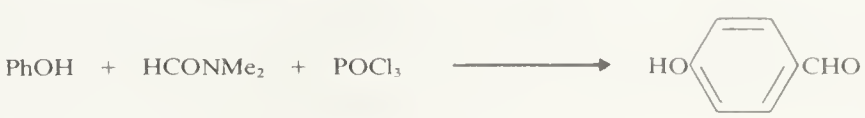
(68%) (46)

The Vilsmeier reaction, in which formylation is achieved using a disubstituted formamide and phosphoryl chloride or phosgene, represents a particularly useful method. It is, however, only usable with particularly nucleophilic aromatic compounds. *N*-Methylformanilide and *N*,*N*-dimethylformamide are the two most frequently used formamide derivatives. The Vilsmeier reaction fails to give aldehydes in attempted reactions using benzene, alkylbenzenes, and naphthalene. The reactions also fail, or at best only give low yields, using aryl ethers with the *para* position already occupied.

Azulene is formulated (equation 47) in the 1-position in 85% yield, and anthracene at position-9 and acenaphthene at position-3 in 85% and 92% yields, respectively. Phenol gives *p*-hydroxybenzaldehyde (equation 48) and *N*,*N*-dimethylaniline affords *p*-*N*,*N*-dimethylaminobenzaldehyde (equation 49) in 85% and 50% yields respectively.



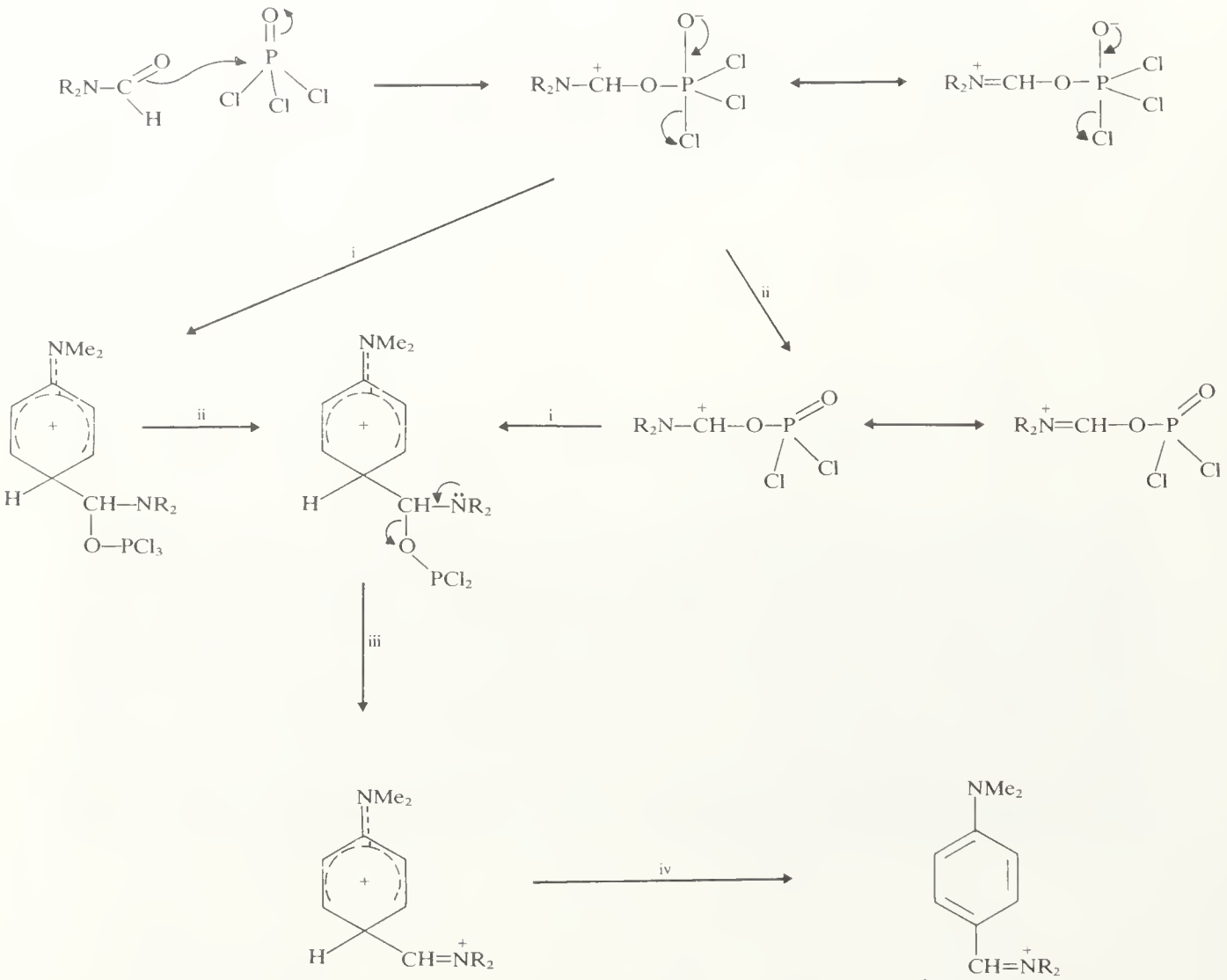
(47)



(48)

$$PhNMe_2 + HCON(Me)Ph + POCl_3 \longrightarrow Me_2N\text{-}C_6H_4\text{-}CHO \qquad (49)$$

The precise structure of the electrophile involved in Vilsmeier formylations has been the subject of a number of studies. Early results[51] showed that, with the exception of *N,N*-disubstituted formamides, the Vilsmeier reaction only proceeds using phosphoryl chloride, and not using phosgene or thionyl chloride. When benzanilide is used, a ketone is only obtained if the amide, phosphoryl chloride, and the nucleophilic aromatic substrate are simultaneously present. More recent work[52] using *N,N*-dimethylthioformamide shows markedly different reactivities — as judged by the yields of the products obtained — when compared with formylations using *N,N*-dimethylformamide. These results lead one to the conclusion that the electrophile is not a phosphorus-free reagent and are in accord with Scheme 31.

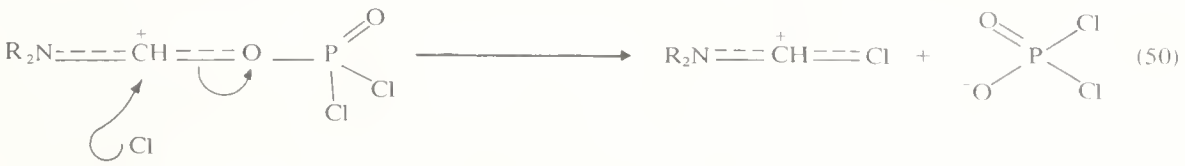


i, $PhNMe_2$; ii, $-Cl^-$; iii, $-O\bar{P}(O)Cl_2$; iv, $-H^+$.

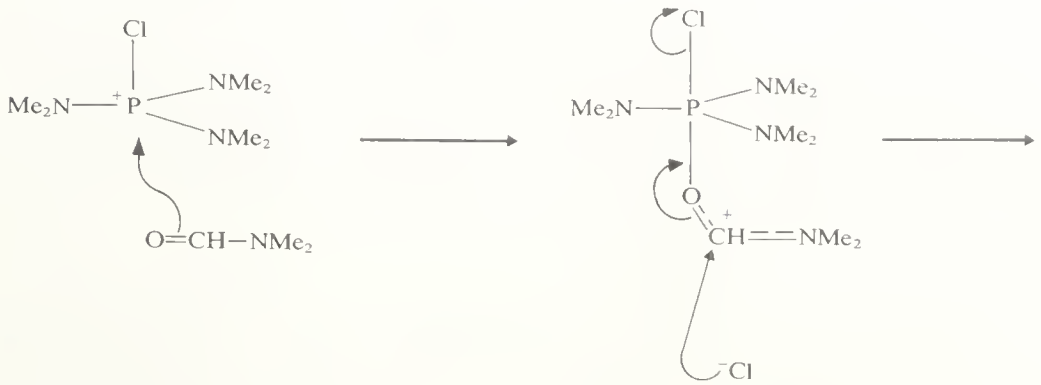
SCHEME 31

On the other hand, abundant evidence is available[53] which shows that phosphoryl chloride reacts with *N,N*-dimethylformamide to give a phosphorus-free electrophile and an anionic phosphorous residue (equation 50). The absence of spin–spin coupling between the low-field proton and ^{31}P in the ^1H and ^{31}P n.m.r. spectra is in accord with this (equation 50). It is not surprising that such a final cation is formed, but, in the writer's

opinion, this does not prove that this is the electrophile involved in Vilsmeier formylations, since the aromatic substrate was not included in the reaction mixtures. It is noteworthy that chloro(trisdimethylamino)phosphonium hexafluorophosphate gave a quantitative yield of *N*-formyl-*N*-methylaniline with *N*-methylaniline in *N*,*N*-dimethylformamide. On the other hand, this reagent, which could easily fragment to the supposed Vilsmeier formylating agent (equation 51), gave no *C*-formylation with *N*,*N*-dimethylaniline.[54]



(50)



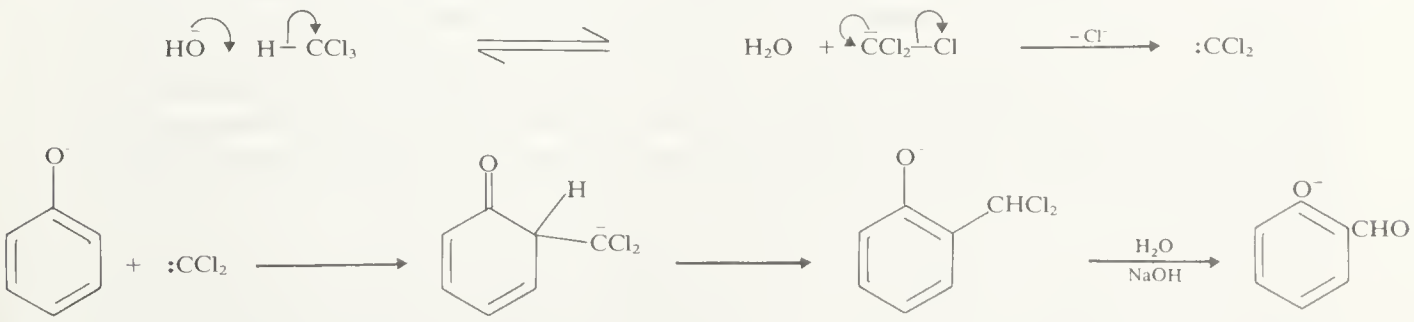
$$Me_2N{=}{=}\overset{+}{C}H{=}{=}Cl \quad + \quad (Me_2N)_3P{=}{=}O \qquad (51)$$

Arenes such as benzene, biphenyl, naphthalene, *etc.*, are formylated using dichloromethyl alkyl ethers in the presence of a Lewis acid catalyst. These ethers are carcinogenic and hence this type of reaction is normally avoided. However, the dichloromethyl alkyl ethers are easily prepared by the reaction of phosphorus pentachloride with alkyl formates. The most frequently used catalysts are titanium(IV) chloride and tin(IV) chloride. The reaction probably proceeds as shown in Scheme 32.

i, $AlCl_3$; ii, ArH; iii, $-H^+$; iv, $-MeCl$.

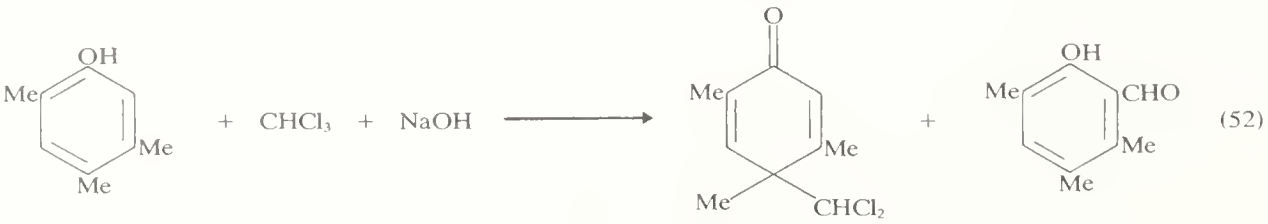
SCHEME 32

The Reimer–Tiemann reaction, which is only useful for the formylation of phenols — and certain nucleophilic heterocyclic systems such as pyrrole and indole — seldom gives yields above 50%.[55] The reaction is carried out in alkaline solution and the electrophile is the neutral dichlorocarbene (Scheme 33).

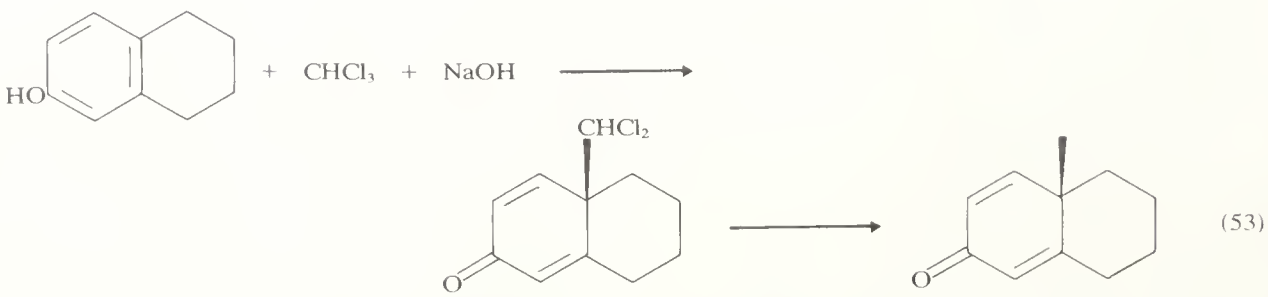


SCHEME 33

Phenols which carry a substituent in the *para* position give, in addition to the salicylaldehyde derivative, 4,4-disubstituted cyclohexa-2,5-dienones. The two chlorine atoms are retained since they are neopentyl in type and hence sterically hindered towards hydrolysis by an S_N2 mechanism (equation 52). This type of reaction has been made use of in the introduction of an angular methyl group into decalin derivatives. The two chlorine atoms may be removed by hydrogenolysis (equation 53).

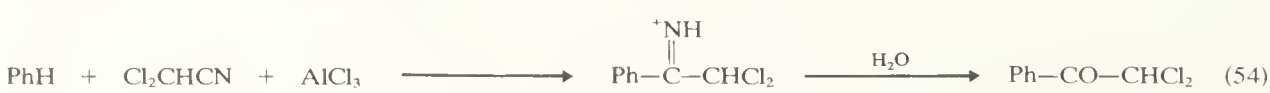


(52)



(53)

The acylation of arenes can be achieved by a modification of the Gattermann reaction in which an alkyl or an aryl cyanide replaces hydrogen cyanide.[25] This reaction is usually known as the Houben–Hoesch reaction. In most cases a Lewis acid catalyst is required; zinc(II) chloride is the most frequently used. The reaction is only useful with arenes using activated nitriles such as dichloroacetonitrile which with benzene and aluminium(III) chloride affords, after hydrolysis of the initial ketiminium salt, ω,ω-dichloroacetophenone (equation 54). In this reaction the electrophile may be the protonated nitrile.



(54)

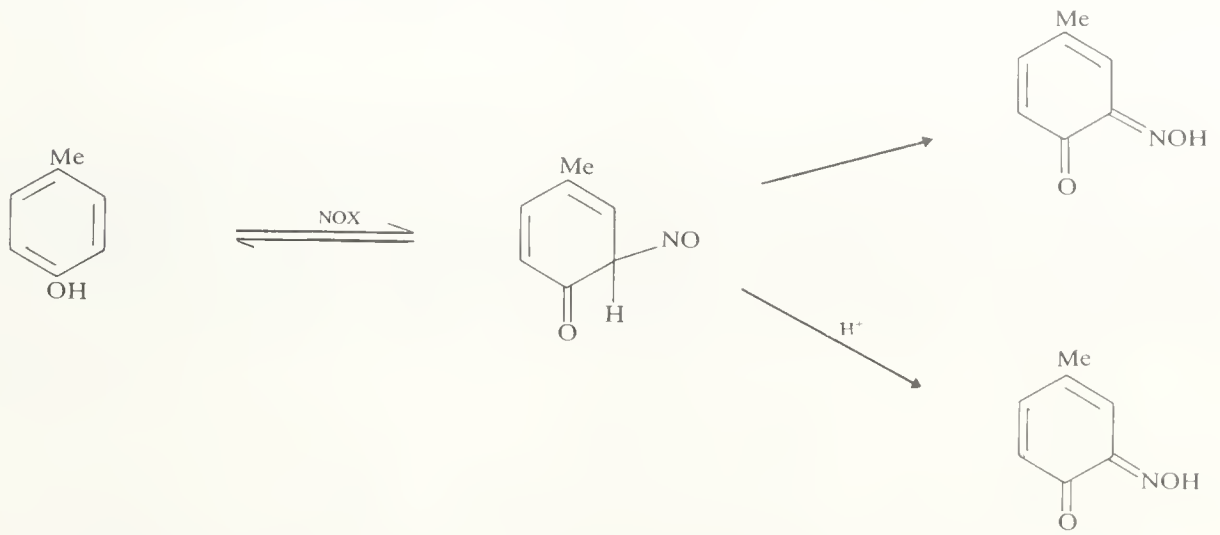
2.5.6.6 Group V electrophiles

We have already discussed the nitration reactions of arenes on p. 254. In this section we will consider nitrosation and diazo coupling reactions of aromatic compounds.

The *C*-nitrosation of aromatic systems is normally only effective with nucleophilic substrates such as phenols and tertiary amines[56] — primary amines form diazonium salts and secondary amines *N*-nitroso compounds. The *N*-nitroso compounds can be isomerized to the *C*-nitroso compounds by the Fischer–Hepp rearrangement (see Chapter 7). Certain primary and secondary arylamines can be *C*-nitrosated directly using nitrosyl-sulphuric acid in concentrated sulphuric acid. The nitroso groups can be introduced into an arene which is normally too unreactive for nitrosation by a nitroso-destannylation reaction (equation 55). This device takes advantage of the better leaving group ability of, for example, the trimethylstannyl residue compared with a proton.[57]

(55)

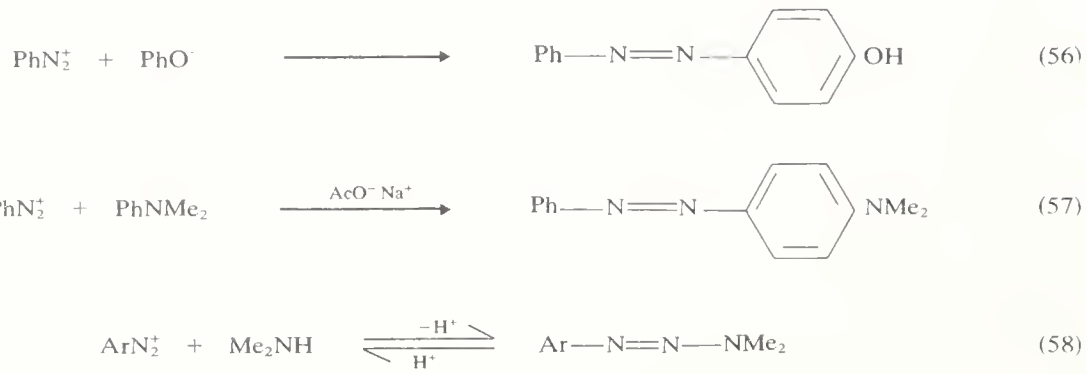
In the nitrosation of phenols it is much more difficult to establish the precise nature of the electrophile than is the case in nitrations. Nitrosation normally requires particularly nucleophilic aromatic substrates because the nitrosonium ion is much more stable than the nitronium ion and hence much less reactive. Kinetic studies[58] showed that the nitrosonium ion is at least 10^{14} times less reactive than the nitronium ion. Nitrosation almost certainly does involve the nitrosonium ion in concentrated perchloric acid (>5M). Nitrosation of benzene and toluene does occur in 10.4M perchloric acid, but since the nitrosonium ion and perchloric acid are oxidizing agents, much nitro compound is in fact isolated. A consequence of the high stability of the nitrosonium ion is that the reverse of step 1 (Scheme 9) is particularly easy and so k_{-1}/k_2 is large. Significant primary kinetic isotope effects are observed. For reactions with phenol and [4-^{2}H]phenol, $k_{1H}/k_{2H} = 3.8 \pm 0.5$, and for anisole, $k_{1H}/k_{2H} = 2.7 \pm 0.3$. [$^2H_6$]Benzene in deuteriosulphuric acid reacts about 8.5 times more slowly than ordinary benzene in sulphuric acid. Thus rate-limiting decomposition of the σ-complex seems to be characteristic of aromatic nitrosations with substrates of widely different nucleophilicities. The nitrosation of *p*-cresol is thought to proceed by two pathways (Scheme 34), both of which involve the rapid and reversible formation of a dienone intermediate, which then slowly transforms into the product either spontaneously or by an acid-catalysed process.



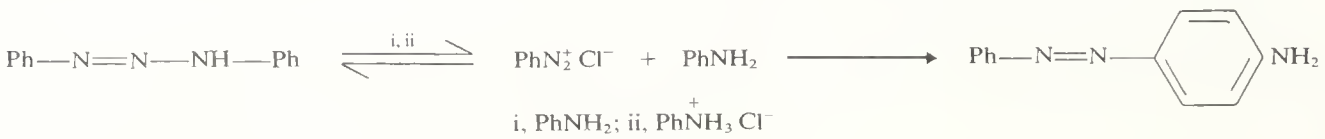
SCHEME 34

Aromatic diazonium ions, because they are normally only weakly electrophilic, usually only couple to form azo compounds with particularly nucleophilic aromatic compounds. The majority of the examples involve reactions of amines and phenols.[59] Substitution usually occurs *para* to the electron-releasing substituent, unless that position is already substituted, in which case *ortho* substitution occurs. The acidity of the solution is important in coupling reactions of both phenols and amines. With phenols, reaction only occurs rapidly in slightly alkaline solution (equation 56), presumably because the unionized form is not normally sufficiently reactive. The pH of the solution of the phenolate ion must not be too high or the reaction fails because the arenediazonium ion is diverted to the corresponding aryl radical *via* the diazo hydroxide. The reactions of arenediazonium salts with amines are normally carried out in neutral or weakly basic media (equation 57). The fact that coupling occurs in the *para* position, even in acidic media, shows that reaction occurs with the unprotonated amine. Primary and secondary amines frequently couple at nitrogen, particularly if strongly acidic conditions are avoided, to give triazenes. This is particularly useful in some instances, since the diazonium species can be regenerated under acidic conditions and hence the triazenes, which are relatively stable, can be regarded as protected diazonium salts (equation 58).

The coupling of the benzenediazonium ion with aniline affords the yellow triazene (diazoaminobenzene). When diazoaminobenzene is warmed with aniline and anilinium

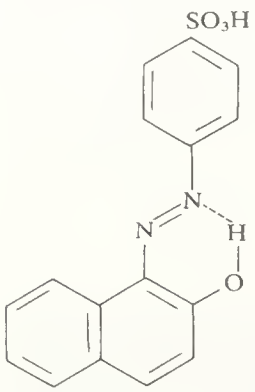


chloride for some time it rearranges intermolecularly to *p*-aminoazobenzene. This rearrangement involves the formation of the unstable, but kinetically favoured, product which then disproportionates and recombines slowly to the thermodynamically more stable product (Scheme 35).

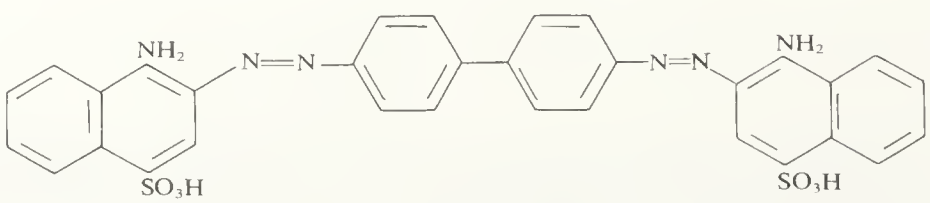


SCHEME 35

The formation of azo compounds for use as dyestuffs has been practised for over 100 years. Sulphonic acid groups are usually present in order to impart water solubility. The simple azobenzene derivatives are all yellow or orange. Deeper shades of colour, as well as fastness to light and washing, are obtained by increasing the extent of conjugation of the chromophore. Typical azo dyes include Orange II (**70**) and Congo Red (**71**).



(**70**)

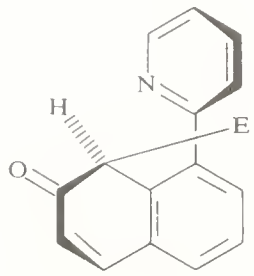


(**71**)

Acylated amines, aryl ethers, and phenolic esters are not normally nucleophilic enough to form azo derivatives with arenediazonium salts unless strong electron-withdrawing groups are present to increase the electrophilicity of the diazonium function. The 2,4,6-trinitrobenzenediazonium ion does couple with mesitylene, 1,2,3,5-tetramethylbenzene, and pentamethylbenzene, but, surprisingly, it does not attack durene (1,2,4,5-tetramethylbenzene).

We have mentioned previously (p. 264) the observation of kinetic isotope effects in the coupling reactions of an arenediazonium salt. Evidence has been produced[60] which shows that the removal of the proton by base from the σ-complex (Scheme 9) does not necessarily require a linear transition state involving the sp^2-carbon, hydrogen, and base. The diazo coupling of 8-phenyl-2-naphthol exhibits a primary kinetic isotope effect ($k_{1H}/k_{2H} = 2.7$) which has a steric origin. On the other hand, diazo coupling reactions of 8-(2′-pyridyl)-2-naphthol show no isotope effects. Since the steric requirements of both 8-substituents must be approximately equal, the absence of an isotope effect in the second

reactions is due to intramolecular base catalysis. The attack of the base on the leaving proton takes place before the electrophilic group becomes coplanar with the naphthalene nucleus (see **72**).

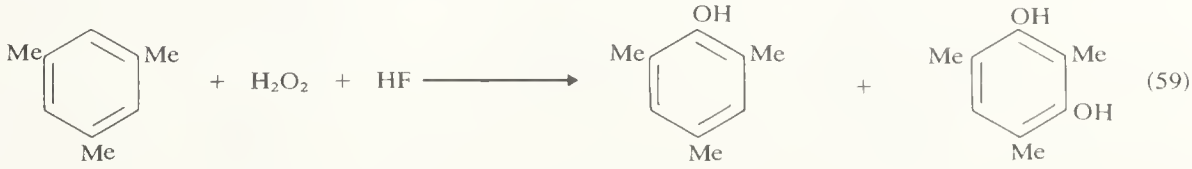


(**72**)

2.5.6.7 Group VI electrophiles[18,56]

In this section we shall consider in more detail those reactions shown in Table 4 (heading 5). Although there is no completely unambiguous evidence that monovalent oxygen electrophiles attack arenes,[61] there are two main reactions which we should consider.

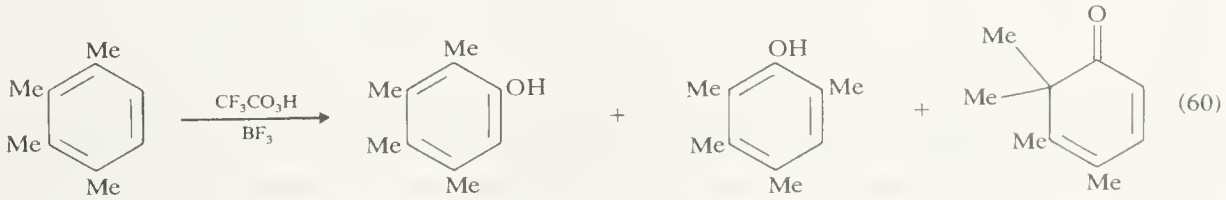
The hydroxyl cation has been suggested as the electrophilic species involved in reactions of benzene and simple alkylbenzenes with hydrogen peroxide which are catalysed by liquid hydrogen fluoride.[62] In the reaction with mesitylene (equation 59), 2,4,6-trimethylphenol (mesitol) and 2,4,6-trimethylresorcinol were obtained in 74 and 25 mol % respectively. Although the reaction with benzene was found to be unsuccessful using these conditions, a reaction of benzene in the presence of carbon dioxide, under pressure, gave 37 mol% of phenol, together with catechol (16 mol %) and 1,4-dihydroxybenzene (37 mol %). The high $o:p$ ratios obtained with toluene, for example, may reflect radical involvement.[63]



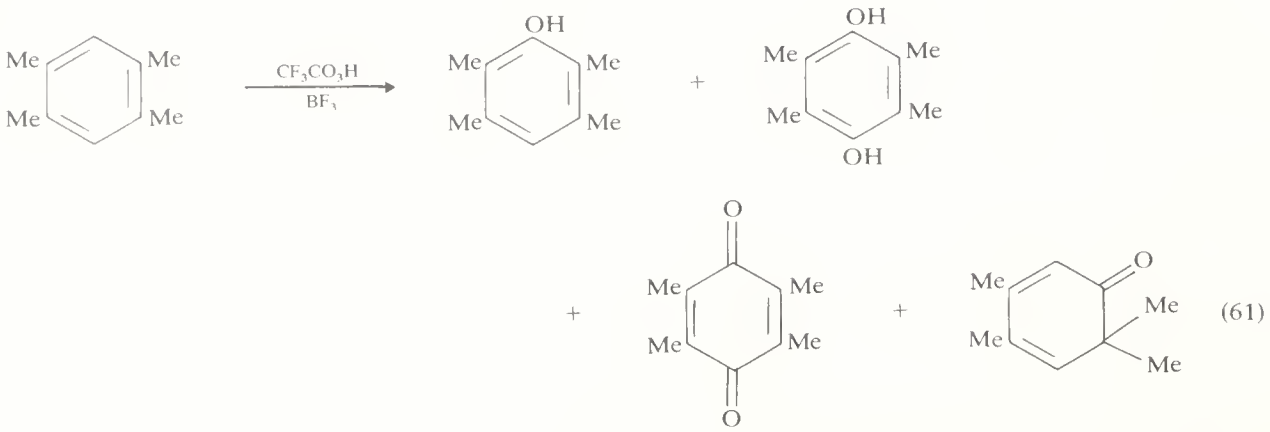
(59)

The use of aluminium chloride has also been advocated as a catalyst in the hydroxylation of arenes with hydrogen peroxide.[64] For example, cresols ($o:m:p = 60:8:32$) and methoxyphenols ($o:m:p = 44:1:55$) were obtained in 40 and 70% yields, respectively, from toluene and anisole.

The hydroxylation of certain substituted arenes may also be achieved using trifluoroperacetic acid in the presence of boron trifluoride.[65] The successful use of this reagent is undoubtedly due to the presence of the excellent leaving group trifluoracetate. Thus reaction with mesitylene is exothermic at $-40\,°C$ and gives mesitol in essentially quantitative yield. 1,2,3,5-Tetramethylbenzene also gives an excellent yield of the expected phenol. Interestingly, 1,2,3,4-tetramethylbenzene gives, in addition to the expected phenol, two products where 1,2-methyl shifts have occurred (equation 60). Durene also gives a rearrangement product (equation 61).

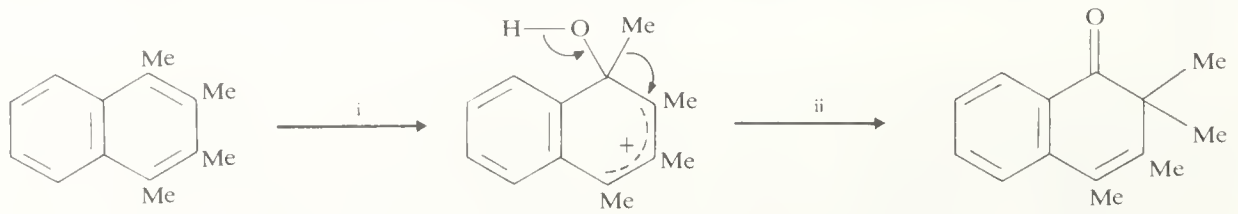


(60)



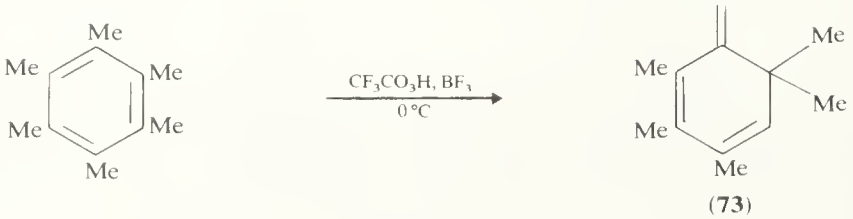
(61)

Advantage has been taken of these reactions, where *ipso* attack is followed by an alkyl shift (Scheme 36), to prepare cyclohexa-2,4-dienones which would otherwise be difficult to obtain. Thus hexamethylbenzene affords the dienone (**73**) and tetramethylbenzocyclobutene the dienone (**74**) in 95% and 34% yields, respectively (equations 62 and 63). Hydride shifts, the analogues of the NIH shift, have been detected.



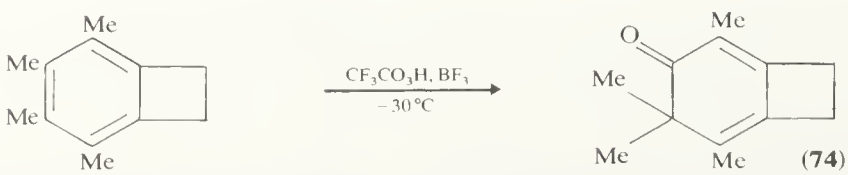
i, CF_3CO_3H, BF_3, −16 °C; ii, $-H^+$.

SCHEME 36



(62)

(**73**)



(63)

(**74**)

Reactions of simple arenes with t-butyl hydroperoxide in the presence of aluminium chloride have been studied.[66] The phenols which are finally isolated were thought to arise by cleavage of t-butyl aryl ethers and hence the electrophile was suspected of being the t-butoxy cation. Once again a high *ortho* : *para* ratio was obtained in the reaction with toluene.

The reactions of aromatic substrates with sulphur electrophiles have been much studied over a very long period of time. Many reviews exist.[18,25,56,67] The scope of the sulphonation reaction is wide and is applied, by varying the precise conditions, to compounds containing either electron-withdrawing or electron-releasing groups. Early observations of relative reactivities and orientations showed that the reaction (equation 64) involved an electrophilic reagent, but the exact nature of the species has been difficult to establish with certainty because of the complex variations which are possible. Kinetic studies are made difficult by the fact that the reaction is reversible, that the mechanism may change

according to the strength of the sulphuric acid, and that the reaction products (which can isomerize) are difficult to isolate and purify. In addition, since water is produced during the reaction with sulphuric acid, rate coefficients decrease during an experiment unless a large excess of acid is used.

$$ArH + H_2SO_4 \rightleftharpoons ArSO_3H + H_2O \quad (64)$$

The electrophile undoubtedly varies with the reagent used, although in all cases sulphur trioxide is involved either in a free form or combined with a carrier such as sulphuric acid or the hydroxonium ion. At concentrations of aqueous sulphuric acid below about 80% the equilibrium is thought to involve that shown in equation (65), while at higher concentrations the equilibrium in equation (66) is implicated. Other potential sulphonating species are shown in equations (67)–(69).

$$2H_2SO_4 \rightleftharpoons H_3SO_4^+ + HSO_4^- \quad (65)$$

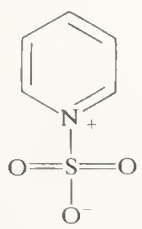
$$H_2SO_4 + SO_3 \rightleftharpoons H_2S_2O_7 \quad (66)$$

$$2H_2SO_4 \rightleftharpoons SO_3 + H_3O^+ + HSO_4^- \quad (67)$$

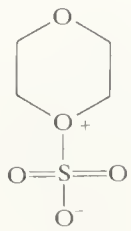
$$3H_2SO_4 \rightleftharpoons HSO_3^+ + H_3O^+ + 2HSO_4^- \quad (68)$$

$$4H_2SO_4 \rightleftharpoons S_2O_6 + 2H_3O^+ + 2HSO_4^- \quad (69)$$

In fuming sulphuric acid the reagent is thought to be $H_3S_2O_7^+$ at concentrations up to about 104% sulphuric acid; at higher concentrations (*i.e.* more sulphur trioxide) it is $H_2S_4O_{13}$.[68] Sulphur trioxide can also be 'carried' by pyridine (**75**) or dioxan (**76**), both of which are sulphonating agents.



(**75**)



(**76**)

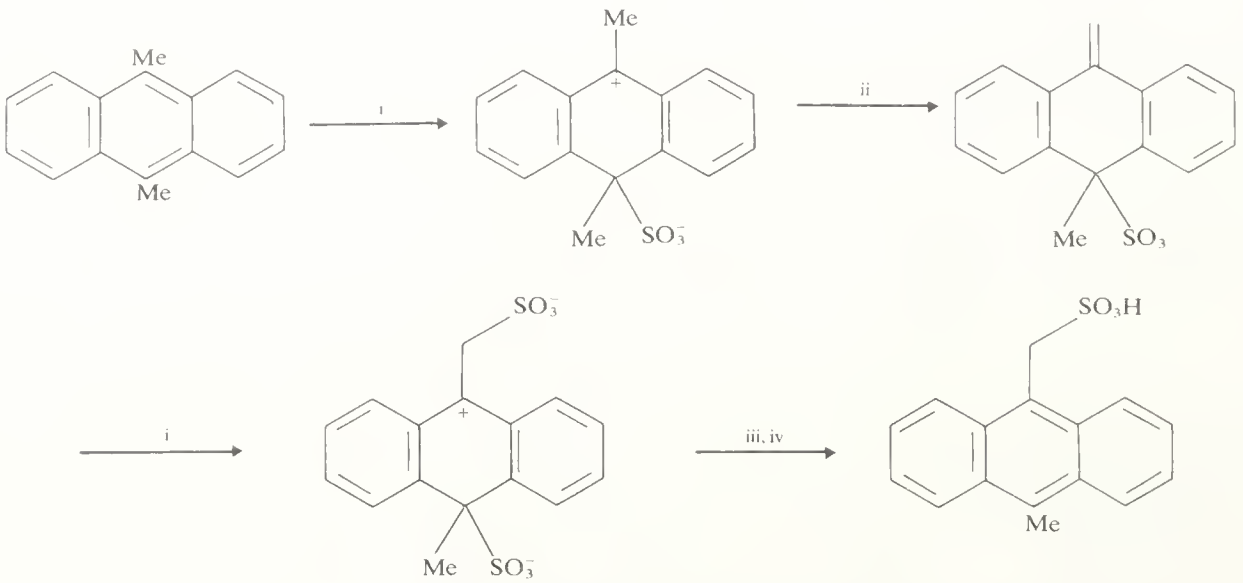
The mechanism of sulphonation is essentially that outlined in Scheme 9. However, unlike most of the other reactions discussed, sulphonation is reversible. Proto-desulphonation usually is effected by heating the sulphonic acid with dilute sulphuric acid.

Benzene is normally sulphonated with oleum containing 5–20% sulphur trioxide. For more reactive compounds such as the alkylbenzenes, sulphuric acid (95%) is effective, *e.g.* equation (70). Toluene, using these conditions, affords a mixture of toluenesulphonic acids ($o : m : p \approx 10 : 1 : 20$).

(70)

Primary kinetic isotope effects have been observed in the sulphonation of [1,3,5-$^2H_3$]benzene.[69] Using sulphur trioxide in fluorotrichloromethane at −35 °C, a value

$k_{1H}/k_{2H} = 1.23$ was obtained [see Figure 2(b)]. The sulphonation of anthracene at the 9-position with the dioxan–sulphur trioxide complex (**76**) at 40 °C in dioxan proceeds with a maximal substrate kinetic isotope effect ($k_{1H}/k_{2H} = 6.8$).[70] The fact that in protic media anthracene yields only anthracene-1- and anthracene-2-sulphonic acids is undoubtedly a thermodynamic effect. It is of interest to note that the sulphonation of 9,10-dimethylanthracene with the complex (**76**) in dioxan at 40 °C leads to side-chain sulphonation, in high yield, probably *via* initial *ipso* attack on sulphur trioxide, as shown in Scheme 37.[71]



i, SO_3; ii, $-H^+$; iii, $+H^+$; iv, $-SO_3$.

SCHEME 37

The relatively easy reversal of the sulphonation reaction with arenes has established classic examples of kinetic and thermodynamic control in electrophilic addition-with-elimination reactions. Thus although the sulphonation of toluene at low temperatures gives the isomer distribution mentioned earlier, when the reaction is carried out at about 160 °C the more stable toluene-*m*-sulphonic acid is the major product. The sulphonation of naphthalene by sulphuric acid at 80 °C gives naphthalene-1-sulphonic acid in 96% yield, whereas at 165 °C an 85% yield of naphthalene-2-sulphonic acid is obtained. Naphthalene-1- rearranges to naphthalene-2-sulphonic acid in sulphuric acid at 165 °C. Evidently the 1-sulphonic acid is formed the faster of the two but the 2-sulphonic acid is thermodynamically the more stable. The relative instability of naphthalene-1-sulphonic acid is due in part to repulsive *peri* interactions, while its more rapid formation relates to the lower energy of the transition state leading to the 1-substituted σ-complex (Figure 3).

Since the proto-desulphonation is so easily achieved, the sulphonic acid group can be used as a protecting group, as is indicated (Scheme 38) by the synthesis of *o*-nitroaniline from acetanilide.

Aromatic sulphonyl chlorides[67] can be prepared by the direct interaction of aromatic compounds with chlorosulphuric acid (equation 71). Arenesulphonic acids may also be prepared using the same reagent, and this suggests that the initial product is the arenesulphonic acid which is converted into the final product by the excess of chlorosulphuric acid which is present. In a typical reaction, benzene, at about 25 °C, gives benzenesulphonyl chloride in 75% yield.

Sulphonylation is effected by a Friedel–Crafts type reaction by the reaction of an arene with a sulphonyl chloride in the presence of a Lewis acid such as aluminium(III) chloride. Mechanistically, the reactions resemble Friedel–Crafts reactions in that, with benzene and less nucleophilic aromatic compounds, third-order kinetics are followed: for example, with chlorobenzene and phenyl sulphonyl chloride the rate shown in equation (72) is followed.

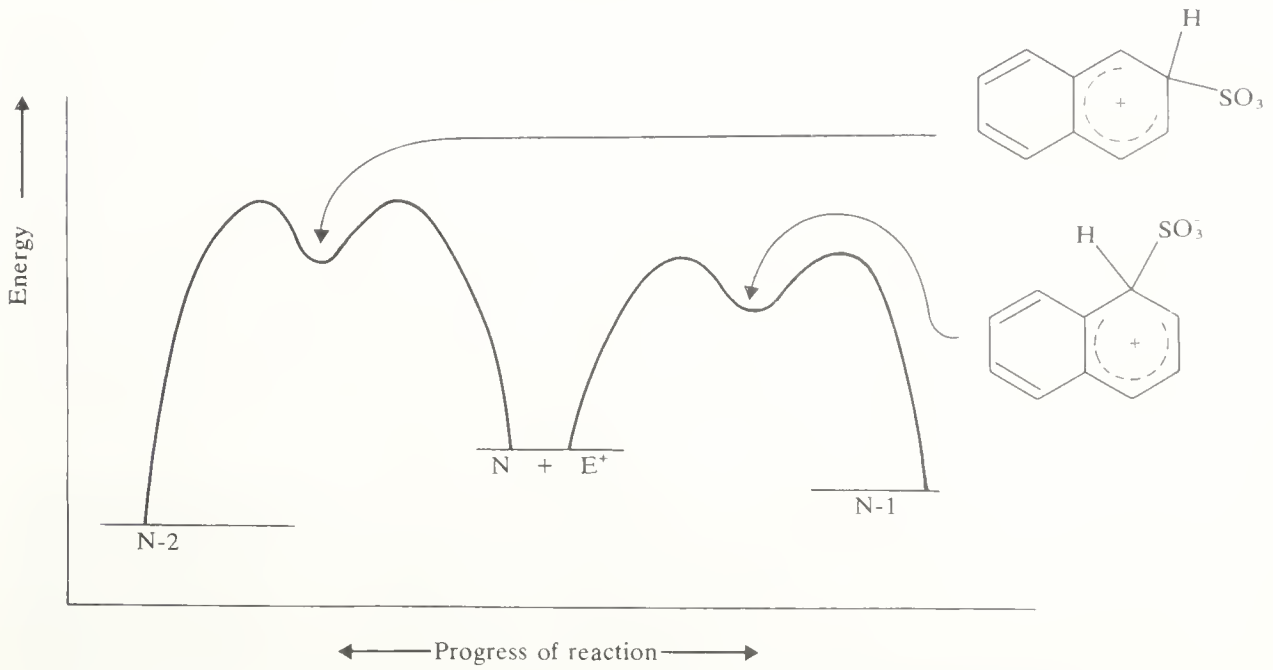
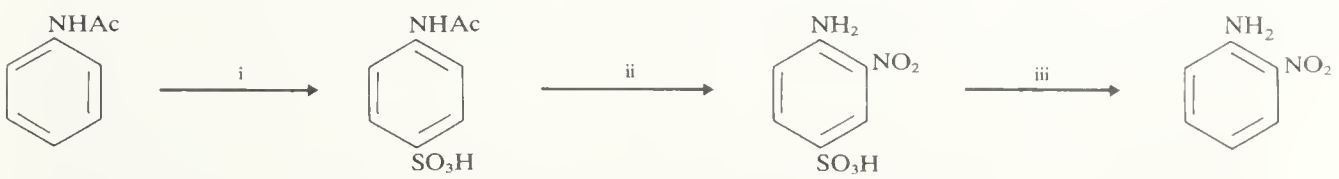


Figure 3 Energy profile for the sulphonation of naphthalene (N = naphthalene; $E^+ = SO_3$; N-1 = naphthalene-1-sulphonic acid; N-2 = naphthalene-2-sulphonic acid).



i, H_2SO_4; ii, HNO_3; iii, H_2SO_4, H_2O.

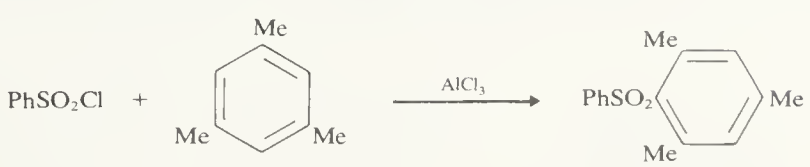
SCHEME 38

$$ArH + ClSO_3H \longrightarrow ArSO_2Cl + H_2O \quad (71)$$

The slow step in the reaction involves attack of the arene on the electrophile. With more nucleophilic substrates, *e.g.* mesitylene, the slow step involves the formation of the electrophile and hence equation (73) is followed. The products of these reactions are sulphones (equation 74).

$$\text{rate} = k[AlCl_3][PhSO_2Cl][PhCl] \quad (72)$$

$$\text{rate} = k[AlCl_3][PhSO_2Cl] \quad (73)$$



(74)

2.5.6.8 Group VII electrophiles[18,25a,56]

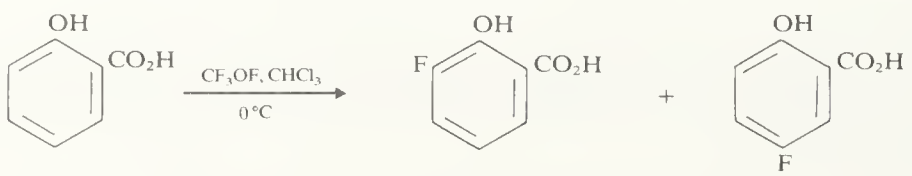
Three general procedures are available for the introduction of halogen into an aromatic compound by means of an electrophilic reagent. In order of increasing reactivity these are (i) molecular halogen, (ii) molecular halogen in the presence of a catalyst such as the

halides of iodine, tin(IV), iron(III), antimony(V), and aluminium, and (iii) positive halogen, usually associated with a carrier, *e.g.* the hypochlorous acidium ion. Which of these is the method of choice depends on the nucleophilicity of the aromatic substrate. Thus, for example, although chlorine or bromine react with benzene in solvents that are polar or acidic, these reactions are very slow. The reactions between chlorine and benzene takes several days before they are complete. On the other hand, the reaction of bromine with aniline is so rapid that it may be carried out in dilute aqueous solution at ambient temperature. Even then it is not possible to stop the reaction before 2,4,6-tribromoaniline is formed. This is essentially due to the fact that the intermediate bromoanilines are successively weaker bases than their precursors and are therefore less likely to be protonated. It is convenient to separate the following discussion into three divisions which will be concerned with fluorination, chlorination and bromination, and iodination reactions.

Fluorination of aromatic compounds with molecular fluorine at room temperature is uncontrolled. By carrying out reactions with fluorine in acetonitrile at temperatures in the range −15 to −75 °C, controlled fluorination of benzene and a number of its derivatives has been effected.[72] Electron-withdrawing substituents retarded the reactions, and hence these fluorinations were carried out at the upper end of the indicated temperature range. The orientation of the substitutions was that expected for reactions involving electrophilic fluorine. For example, the reaction with toluene gave values for $o:m:p = 5:1:4$, while for nitrobenzene $o:m:p = 1.3:7.9:0.8$. The fluorination of benzene and fluorobenzene has been reported using xenon difluoride in carbon tetrachloride containing a trace of hydrogen chloride.[73] A radical-cation mechanism was proposed.

The use of fluoroxytrifluoromethane at low temperatures (usually in the range −75 to −20 °C) in halogenated solvents allows the direct introduction of fluorine into suitably activated aromatic rings.[74] Benzene only gives a 17% yield of fluorobenzene, which is increased to 65% when the reaction mixture is photolysed.[75] A radical mechanism is presumably involved in this latter reaction.

Salicylic acid reacts with fluoroxytrifluoromethane in chloroform at 0 °C to afford the 3- and 5-fluoro derivatives in a 1:4 ratio respectively (equation 75), and with *N*-acetyl-2-naphthylamine, *N*-acetyl-1-fluoro-2-naphthylamine was obtained. In both of these reactions the orientation is that expected for an electrophilic fluorination.



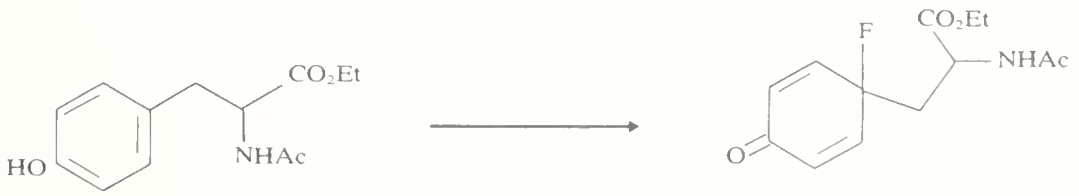
(75)

Reactions of *p*-substituted phenols gave dienones as a result of *ipso* attack. Thus oestrone methyl ether (**77**) and oestrone acetate (**78**) both gave 10β-fluoro-19-norandrosta-1,4-diene-3,17-dione (**79**) (equation 76). Similarly (equation 77), ethyl *N*-acetyltyrosinate gave a dienone. 2,6-Dimethylphenol also gave a product derived from initial *ipso* attack. In this case (equation 78) the dienone dimerized.

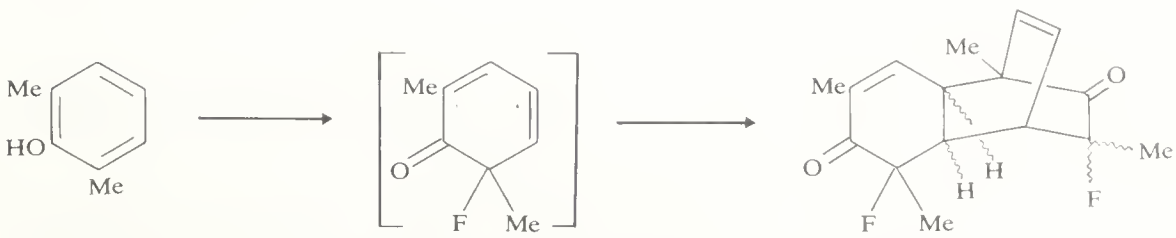
(**77**) R = Me
(**78**) R = Ac

(**79**)

(76)



(77)



(78)

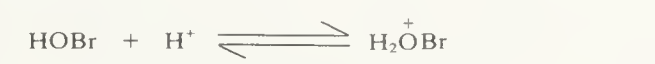
Considerable research effort has been devoted to the development of systems whereby controlled chlorination and bromination of aromatic compounds can be achieved. Positively charged chlorinating and brominating species have been particularly important targets. The relevant evidence and some of the points of controversy have been reviewed.[76] The rates of bromination of aromatic compounds by hypobromous acid in aqueous solution is of the following form:

$$\text{rate} = k[\text{ArH}][\text{HOBr}][\text{H}^+]$$

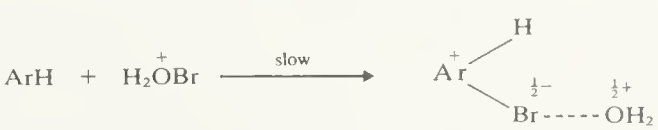
but this does not establish whether water is involved in the transition state or not. Whereas molecular bromine reacts very slowly with benzene, hypobromous acid can, at sufficiently high acidity, brominate compounds of low nucleophilicity such as nitrobenzene.

Bromination by molecular bromine, like nitration, shows a marked steric effect, but reactions involving 'positive bromine' do not. Thus while the molecular bromination of t-butylbenzene results in little substitution *ortho* to the t-butyl group, a significant amount of *o*-bromo-t-butylbenzene is formed using 'positive bromine.' Benzene and [$^2H_6$]benzene are brominated at almost identical rates. There is evidence that, for certain reactive substrates at low acidities, the transition state can be reached by protonation of a preformed complex.[77] The solvent isotope effect on the bromination of benzene in perchloric acid (0.16M) gives $k_{H_2O}/k_{H_2O} = 2.2$. This does leave a question. Why is this type of reaction pathway available for bromination but not nitration? Presumably the answer to this question is related to the fact that the nitric acidium ion is not the effective electrophile in nitration reactions. Equations (79)–(84) summarize the present position.

Bromination using bromine and an appropriate silver(I) salt in an acid evidently makes use of a positively charged species since aromatic compounds which are normally unreactive are attacked. Bromine together with silver(I) nitrate in nitric acid or with silver(I) sulphate in sulphuric acid are useful systems. It is not known whether Br^+ or some coordinated species, such as $AgBr_2^+$ or Br^+SO_3, is involved.



(79)



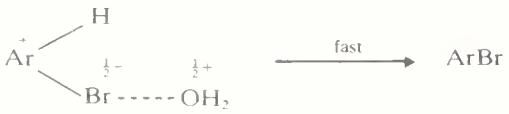
(80)

or

(81)

(82)

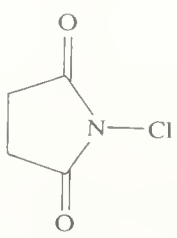
(83)



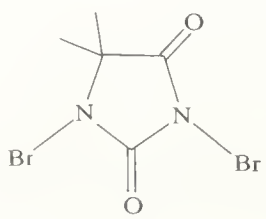
(84)

Reactions involving 'positive chlorine' are similar to those involving 'positive bromine', but 'positive chlorine' is less favoured thermodynamically than 'positive bromine'. The steric requirements of 'positive chlorine' are relatively small.[78]

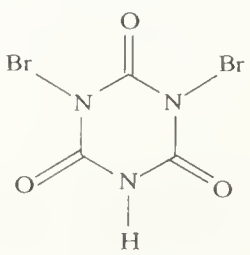
Other reagents have been used including *N*-chloro- and *N*-bromo-amides in the presence of acids. These include *N*-chlorosuccinimide (**80**), 1,3-dibromo-5,5-dimethylhydantoin (**81**), and dibromoisocyanuric acid (**82**).[79] The last of these reagents is a very powerful brominating agent;[80] thus nitrobenzene is rapidly converted into pentabromonitrobenzene by (**82**) in oleum at room temperature.



(**80**)

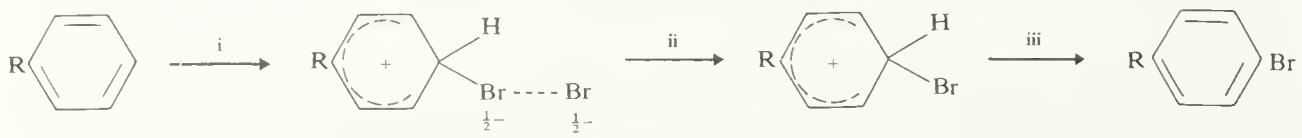


(**81**)



(**82**)

The halogenation of particularly nucleophilic aromatic compounds by the molecular halogens chlorine and bromine is well known. Proton loss, as judged by the absence of primary kinetic isotope effects, is still not part of the rate-determining stage. The current view of the mechanism is summarized in Scheme 39, exemplified for bromination.



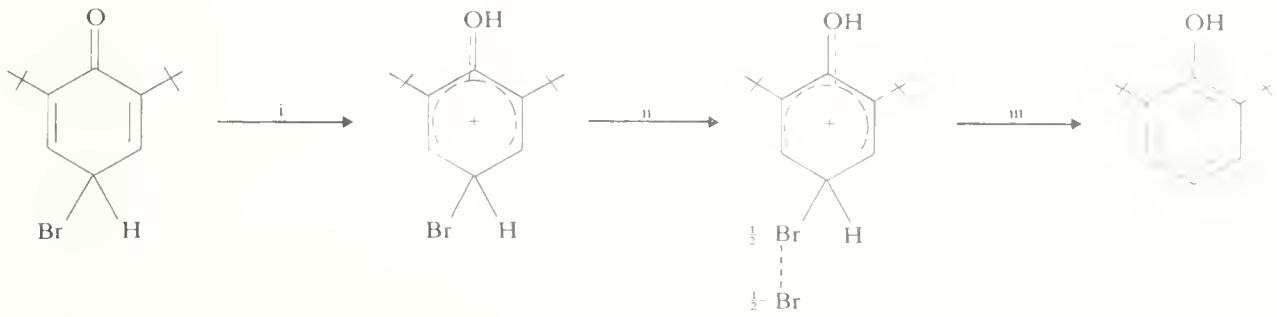
i, Br_2; ii, $-Br^-$; iii, $-H^+$.

SCHEME 39

This interpretation has received support from what is effectively the reverse of all but the final step of Scheme 40. The acid-catalysed prototropic rearrangement of 4-bromo-2,6-di-t-butylcyclohexa-2,5-dienone to 4-bromo-2,6-t-butylphenol has been studied in the presence of added anions.[81] In the presence of lithium bromide, debromination competes with prototropic rearrangement (Scheme 40). The existence of a reverse solvent deuterium isotope effect shows that a proton pre-equilibrium is involved and hence the transition state must be as shown. Invoking the principle of microscopic reversibility allows us to conclude that the bromination of 2,6-di-t-butylphenol involves a transition state of the same composition.

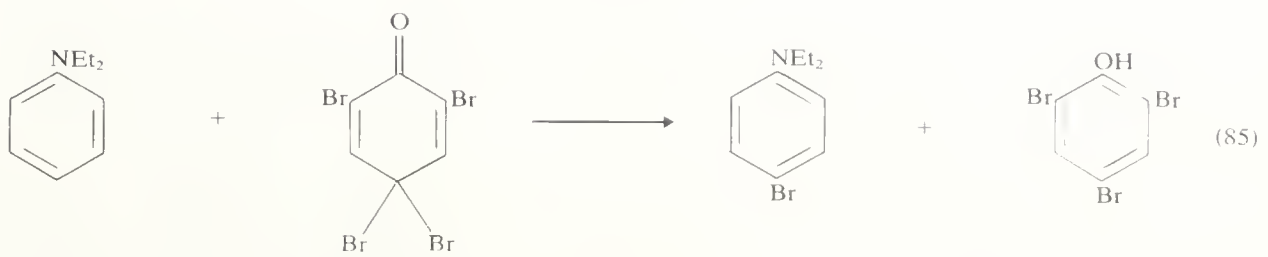
Although not strictly relevant to the immediate discussion, it is noteworthy that 2,4,4,6-tetrabromocyclohexa-2,5-dienone is a mild and selective brominating agent for aromatic amines.[82] Thus, for example, aniline in dichloromethane at $-20\,°C$ is converted into *o*- and *p*-bromoanilines in 87% yield (*o*:*p* ratio = 9.6:0.4). *N*,*N*-Diethylaniline affords *p*-bromo-*N*,*N*-diethylaniline in 96% yield (equation 85). The role of cyclohexadienes in the halogenations of arenes has been recently summarized.[83]

We have stressed the importance of *ipso* attack in a number of reactions which have been discussed previously. This type of reaction is also met in, for example, chlorinations.



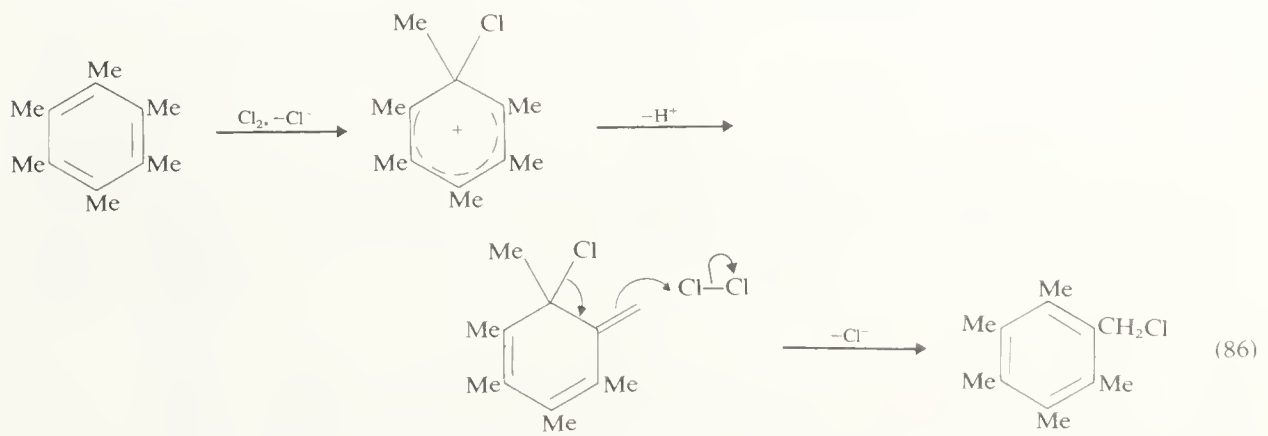
i, H^+; ii, Br^-; iii, $-Br_2$.

SCHEME 40



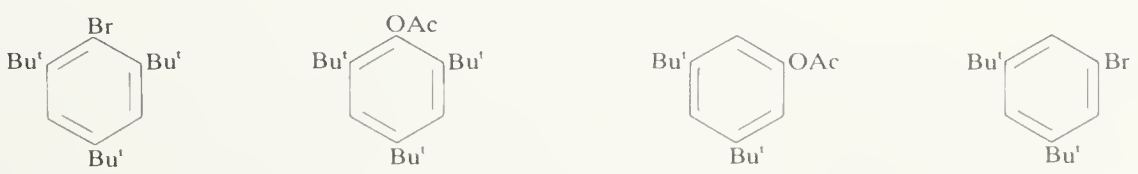
(85)

Reaction of hexamethylbenzene must proceed in such a way, and in this case leads to side-chain substitution, probably as shown in equation (86).[84]

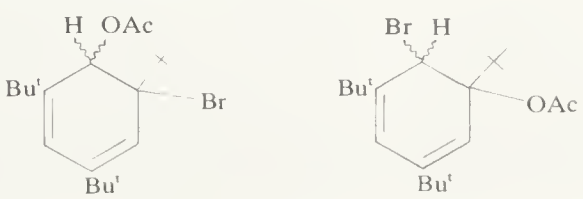


(86)

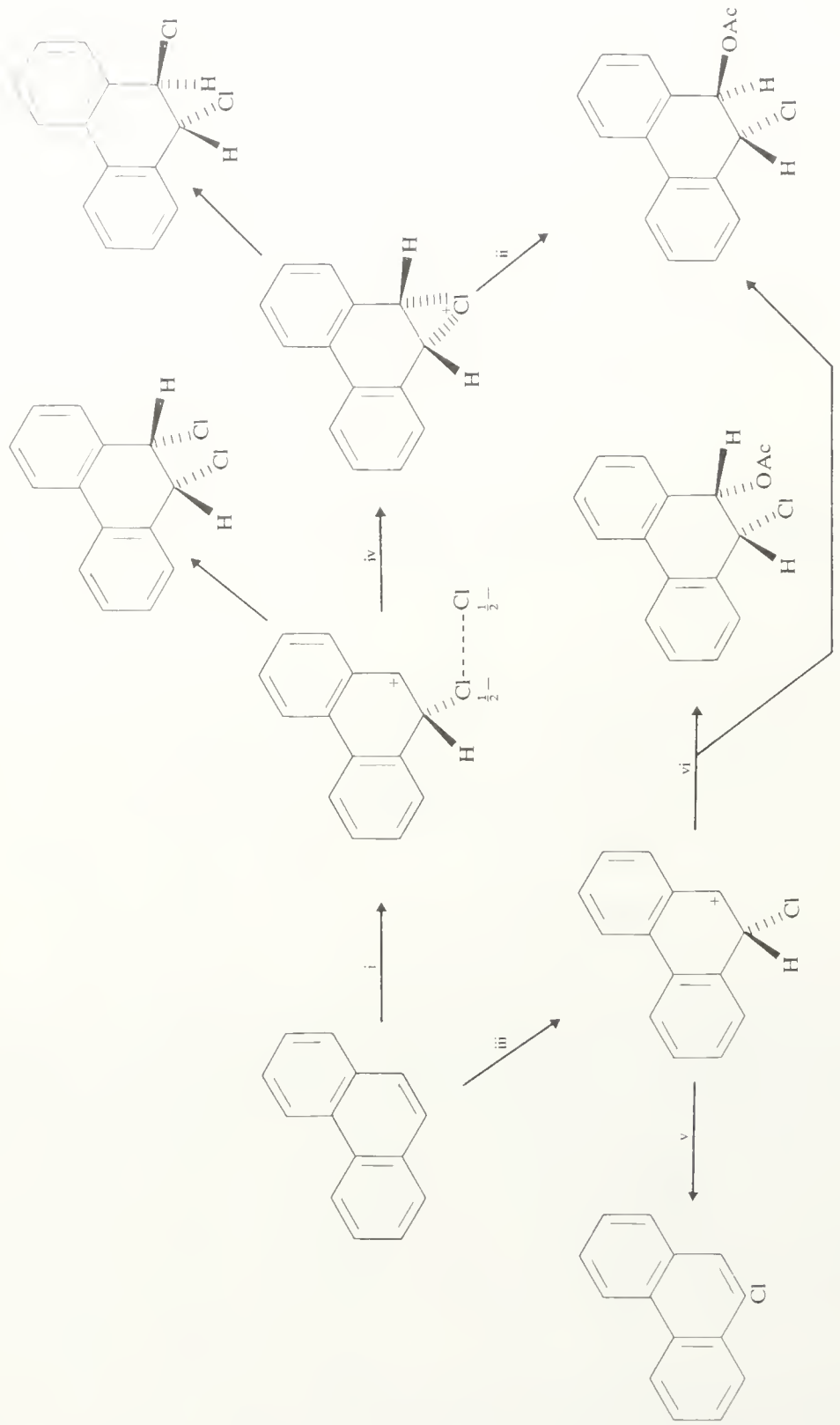
The chlorination of 4-t-butylbiphenyl leads to a number of products, including *ca.* 6% 4-chlorobiphenyl. This product may arise from attack at the *ipso* position but it may also be envisaged as arising *via* an addition–elimination sequence. Thus the reaction of bromine and silver(I) salts with 1,3,5-tri-t-butylbenzene in acetic acid affords the products (**83**)–(**86**) and addition–elimination sequences involving (**87**) and (**88**) are clearly implicated.[85]



(**83**) (**84**) (**85**) (**86**)



(**87**) (**88**)

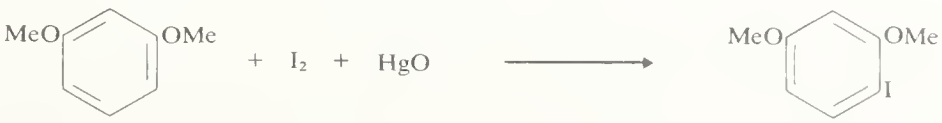


i, Cl_2; ii, AcOH, $-HCl$; iii, AcOCl, $-AcO^-$; iv, $-Cl^-$; v, $-H^+$; vi, AcO^-.

SCHEME 41

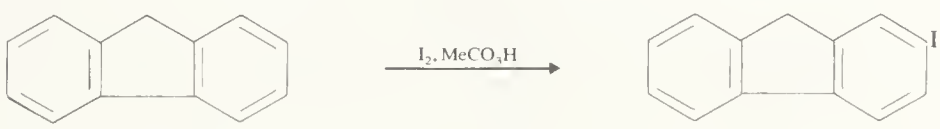
Cyclohexa-1,3-diene intermediates have been trapped on a number of occasions. Thus the chlorination of biphenyl leads to a not insignificant amount of 1-phenyl-3,4,5,6-tetrachlorocyclohexene. Similarly, the chlorination of naphthalene by molecular chlorine in acetic acid leads to a number of products. 1-Chloronaphthalene is the major product (66%) but other products include naphthalene tetrachlorides and acetoxynaphthalene trichlorides. The chlorination of phenanthrene using chlorine in acetic acid also leads to a complex mixture of products, all of which are stable under the reaction conditions. A simplified rationalization of the results is given in Scheme 41.[86]

It is only with particularly nucleophilic aromatic compounds that iodinations can be achieved using elemental iodine. The direct substitution of benzenes can be accomplished if the reaction is carried out using iodine and an oxidizing agent. Benzene and iodine in the presence of nitric acid give iodobenzene in 86% yield. A wide range of oxidizing agents have been used in order to increase the electrophilicity of iodine and these include, in addition to nitric acid, hydrogen peroxide, iodic acid, sulphur trioxide, yellow mercury(II) oxide, and peracetic acid. Thus 1,3-dimethoxybenzene gives the 4-iodo derivative (equation 87) in excellent yield using iodine and yellow mercury(II) oxide.



(87)

The exact nature of the electrophile is not known with any degree of certainty in the majority of cases. It has been suggested that, using hydrogen peroxide, the electrophile is the hypoiodous acidium ion. Using peracetic acid the evidence points to acetyl hypoiodite or its protonated form. This last system promises to be useful as a preparative method since not only is it faster than the traditional methods, but also an increase in the steric requirements should allow greater selectivity. This method even gives good yields in the presence of compounds which are susceptible to oxidation as long as the quantity of peracetic acid is carefully controlled.[87] Thus the iodination of acenaphthene gave 5-iodoacenaphthene, and fluorene (equation 88) gave 2-iodofluorene in 40% and 65% yields, respectively.



(88)

There is no evidence that protodeiodination is a rapid reaction other than in those cases, such as the iodophenols, where the aromatic compound is rendered very nucleophilic by the presence of strong electron-releasing substitutents. Even nitrodehalogenation in *p*-haloanisoles, where the attacking electrophile is stronger than a proton, proceeds more slowly than nitrodeprotonation (nitration). Thus the relative rates using nitric acid in acetic anhydride were found to be 0.18 (I), 0.079 (Br), 0.061 (Cl), and 1.0 (H).[88] It is then not surprising that reduction of *p*-iodotoluene using hydrogen iodide is a very slow reaction and was observed to be only 85% complete after eight days at room temperature.[89] The frequently expressed opinion, that an oxidizing agent is added to the iodine in order to oxidize the hydrogen iodide and hence preclude the reverse reaction, is evidently incorrect.[90] The oxidizing agent is added in order to generate an electrophile which is more potent than molecular iodine. Iodine in oleum is a particularly reactive system and can be used to introduce a number of iodine atoms into systems containing strong electron-withdrawing groups. For example, tetraiodophthalic anhydride can be prepared from phthalic anhydride in 80% yield (equation 89) using 60% oleum at a temperature of 175 °C. Lower temperatures and a lower concentration of free sulphur trioxide results in greater control over the number of iodine atoms which are introduced. At room temperature and using 20% oleum, nitrobenzene affords 3-iodonitrobenzene as

the only product, while using the same system at 100 °C, 3,4,5-tri-iodonitrobenzene was obtained.[91]

(89)

2.5.7 DIRECTIVE EFFECTS IN ELECTROPHILIC ADDITION-WITH-ELIMINATION REACTIONS

The non-equivalence of the hydrogen atoms in a monosubstituted benzene is evident. If reactions with electrophiles proceeded at each position with equal facility, the three disubstituted products would be formed in the ratio $o:m:p = 2:2:1$. That is not the case is clear from the discussion in Section 2.5.6. Qualitative[92] and quantitative[92,93] treatments of this topic are available and therefore a detailed treatment will not be given here. Substituents not only exert a directive effect with respect to the positions of entry of a second substituent, but they also have a marked effect on the rate of the reaction. Isomer distributions obtained from a large number of electrophilic addition-with-elimination reactions of aromatic compounds, together with relative partial rate data, allow substituents to be classified under three headings, some of which are shown in Table 6.

TABLE 6
Classification of Directive Effects

$\frac{k_{C_6H_5X}}{k_{C_6H_6}} < 1$	*e.g.* X = CO_2H	*meta*-Products
	= NO_2	
	= $\overset{+}{N}Me_3$	
	= CF_3	
$\frac{k_{C_6H_5X}}{k_{C_6H_6}} < 1$	*e.g.* X = F	*ortho, para*-Products
	= Cl	
	= Br	
	= CH_2Cl	
$\frac{k_{C_6H_5X}}{k_{C_6H_6}} > 1$	*e.g.* X = Me	*ortho, para*-Products
	= Ph	
	= NMe_2	
	= NHCOMe	
	= OH	
	= OMe	

As we discussed in Section 2.5.6, the rate of formation of the σ-complex is rate determining in a very large number of electrophilic addition-with-elimination reactions. In these cases it is assumed that the transition states for the formation of the individual σ-complexes are like the σ-complexes, that the free energies of activation involved reflect the thermodynamic stabilities of the σ-complexes, and that the thermodynamic stabilities of the σ-complexes, in turn, depend on the polar, mesomeric, and steric effects of the substituents.

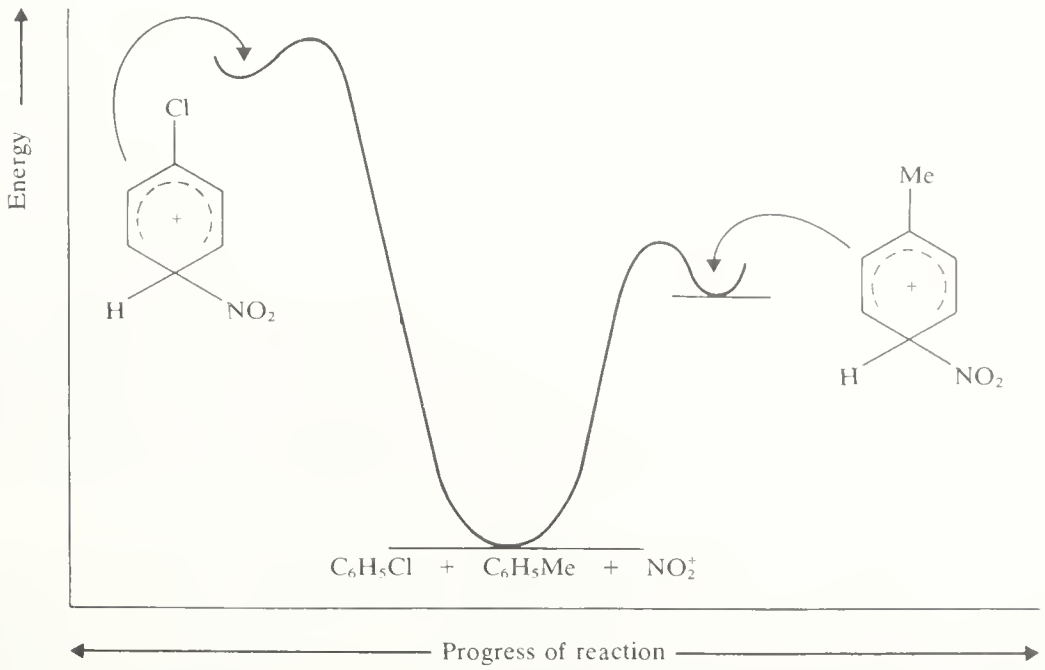


Figure 4 Comparison of the reactions of toluene and chlorobenzene with the nitronium ion

Any group which withdraws electron density from the aromatic ring system will result in a lowering of the rate of reaction with an electrophile, and *vice versa* (Figure 4). Similarly, a group which can disperse the positive charge from the ring in the σ-complex will result in a lowering of the free energy of activation for the formation of that σ-complex, and *vice versa* (Figure 5). Thus although the chlorine atom in chlorobenzene exerts a polar effect which reduces the electron density in the ring, and hence reduces the rate of reaction, compared with benzene, the positive charge can be delocalized efficiently if the electrophile attacks at an *ortho* or *para* position [resonance contributors (**89**) and (**90**)]. Delocalization of the positive charge for attack at a *meta* position would require us to invoke a high-energy structure (**91**) which contributes little to its stability.

Steric effects are well documented. Thus the chlorination of toluene by molecular chlorine in the absence of a catalyst gives the following partial rate factors: $o_f^{CH_3} = 620$,

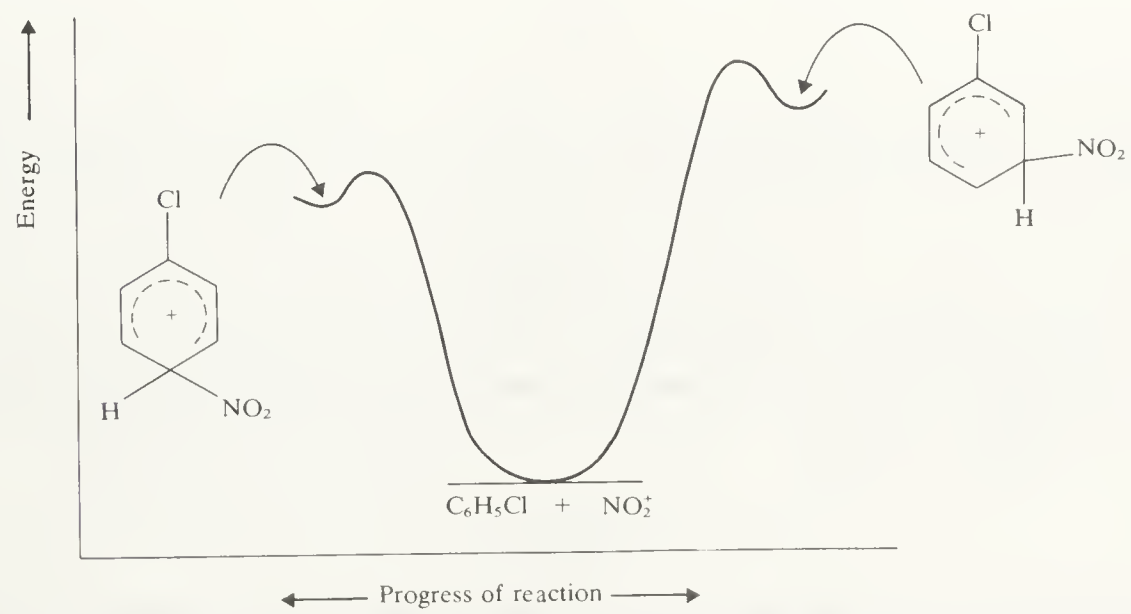
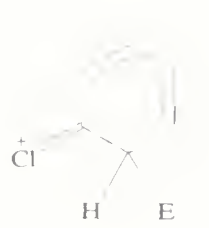
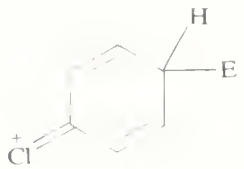


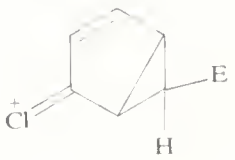
Figure 5 Comparison of the reactions of chlorobenzene with the nitronium ion at the *meta* and *para* positions.



(89)



(90)

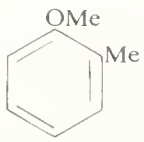


(91)

$m_f^{CH_3} = 5$, and $p_f^{CH_3} = 820$. The related data for t-butylbenzene are $o_f^{Bu^t} = 57$, $m_f^{Bu^t} = 6$, and $p_f^{Bu^t} = 400$. The relative rate data for the *para* bromination of anisole, 2-methylanisole, and 2,6-dimethylanisole illustrate the steric inhibition of mesomeric electron release [structures (**92**)–(**94**)], as also do the data for *para* chlorination of acetanilide ($p_f = 2.5 \times 10^6$), 2-methylacetanilide ($p_f = 6.2 \times 10^5$), and 2,6-dimethylacetanilide ($p_f = 1.2 \times 10^3$).

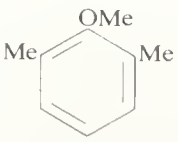
$p_f = 10^{10}$

(92)



$p_f = 6 \times 10^{10}$

(93)



$p_f = 4 \times 10^9$

(94)

Once we know the partial rate factors we can make predictions concerning the proportion of the isomers which will be produced when two or more substituents are present on a ring. This assumes that the effect of substituents is additive, and that the reaction under consideration proceeds under kinetic control. In many cases agreement is quite good, but there are many examples where a marked deviation from additivity is observed. The nitration of the 3-methoxy-*N*,*N*,*N*-trimethylanilinium ion is just one example.[94] The major problem associated with the development of a satisfactory theoretical treatment of the quantitative aspects of substituent effects is due to the complex way in which polar, mesomeric, and steric effects interact to produce the resultant substituent effect. A theoretical treatment of why additivity sometimes fails has been presented.[95]

An empirical treatment based on the Hammett equation:

$$\log \frac{k}{k_H} = \rho\sigma$$

is normally used.[93] The two parameters are σ, the substituent constant, and ρ, the reaction constant. Rate and equilibrium constants, for example, for the hydrolysis of *m*- and *p*-substituted ethyl benzoates are thus correlated. No attempt is made to include the results for *ortho* substituents because of the variable nature of steric interactions between the *ortho* substituent and the substituent undergoing reaction. The Hammett substituent constant, σ values, do not correlate the partial rate factors for electrophilic addition-with-elimination reactions. The main reason for this failure is associated with the differences in the charge distribution in, for example, a benzoate anion and the cation (σ-complex) involved in the reaction of an aromatic compound with an electrophile. The Hammett parameters must be replaced by a new set of constants, σ^+, the substituent constant, and ρ^+, the reaction constant:

$$\log \frac{k}{k_H} = \rho^+\sigma^+$$

designated with $^+$ in order to distinguish them from the Hammett values and also to indicate their use in reactions in which positive charge is introduced into the aromatic system. Again, only the relative rates for *meta* and *para* substitution are treated for a

benzene containing a substituent Y:

$$\log \frac{k_{m\text{-Y}}}{k_{\text{H}}} = \log m_{\text{f}}^{\text{Y}} = \rho^{+}\sigma_{m\text{-Y}}^{+}$$

$$\log \frac{k_{p\text{-Y}}}{k_{\text{H}}} = \log p_{\text{f}}^{\text{Y}} = \rho^{+}\sigma_{p\text{-Y}}^{+}$$

As we have already indicated (in Section 2.5.6), not all electrophiles are equally powerful. Thus the nitronium ion is reactive enough to cause substitution in rings which already have strong electron-withdrawing groups present. On the other hand, arenediazonium salts only couple with aromatic systems which have strong electron-releasing substituents present. The ρ^{+} values are defined by the slopes of the correlation:

$$\frac{\Delta \log (k/k_{\text{H}})}{\Delta \sigma^{+}} = \rho^{+}$$

lines for reactions involving a particular electrophile, using a particular set of reaction conditions.

Substituents (Y) with negative values of σ_m^+ or σ_p^+ are activating for that position and substituents with positive values are deactivating. The ρ^{+} values correspond to the reactivity of the electrophile as well as to the way the reaction is stabilized or destabilized by the group Y. Electrophilic reactions have negative ρ^{+} values. Thus a *p*-methyl group has a small influence on the rate of the Friedel–Crafts isopropylation ($p_{\text{f}}^{\text{Me}} = 5.0$; $\rho^{+} = -2.3$) but a large influence on the non-catalytic bromination reaction ($p_{\text{f}}^{\text{Me}} = 2420$; $\rho^{+} = -12.1$). A large negative value for ρ^{+} results with electrophiles of relatively low reactivity. As the reactivity of the electrophile decreases, so its selectivity increases. A good measure of the selectivity (S_{f}) of an electrophile is given by the ratio of the *para* and *meta* partial rate factors using toluene as the substrate:

$$S_{\text{f}} = \log \frac{p_{\text{f}}^{\text{Me}}}{m_{\text{f}}^{\text{Me}}}$$

S_{f} is related to ρ^{+} by:

$$S_{\text{f}} = \rho^{+}(\sigma_p^{+} - \sigma_m^{+})$$

The highly reactive electrophiles do not require much assistance from the aromatic π-electron system in order to achieve the transition state for formation of the σ-complex. That is, the transition state is early on the reaction coordinate, and the carbon to electrophile distance is relatively large with little charge developed in the aromatic nucleus. The converse is the case with the stable, and highly selective, electrophiles, and in these cases the transition states more nearly resemble the σ-complexes. Typical examples of reactions of toluene with electrophiles are given in Table 7.

TABLE 7

Typical Reactions of Toluene with Electrophiles[a]

Reaction, conditions	S_{f}	ρ^{+}	m_{f}^{Me}	p_{f}^{Me}
1. Bromination, Br_2, AcOH–H_2O, 25 °C	2.644	−12.1	5.5	2420
2. Bromination, HOBr, $HClO_4$–50% dioxan, 25 °C	1.373	−6.2	2.5	59
3. Nitration, HNO_3, AcOH–H_2O, 45 °C	1.366	−6.04	2.5	58
4. Mercuration, $Hg(OAc)_2$, AcOH, 25 °C	1.014	−4.0	2.23	23

[a] See Ref. 93, p. 50.

As we have already seen (Section 2.5.6), polynuclear hydrocarbons undergo electrophilic addition-with-elimination reactions. They also undergo electrophilic additions more easily than is the case with benzene derivatives. The prediction of the relative rates

and isomer distributions for kinetically controlled reactions in polynuclear hydrocarbons is possible in a semi-quantitative way using molecular orbital theory. The rate differences are presumed to be related to the change in the π-electron energy in the conversion of the arene into the arenonium ion (σ-complex) in the rate-determining step. The energy of an electron in a p-orbital of an isolated sp^2 carbon atom is designated α and the energy of an electron in the vicinity of two sp^2 carbon atoms which are within bonding distance is designated β. Thus for the hypothetical cyclohexatriene, $E_\pi = 6\alpha + 6\beta$, and for benzene, $E_\pi = 6\alpha + 8\beta$. From the resonance energy of benzene ($\beta = 76.6$ kJ mol^{-1}) the change in π-electron energy on protonation of benzene is

$$E_\pi^{C_6H_6} - E_\pi^{C_6H_7^+} = 2\alpha + 2.54\beta$$

where the energy change associated with the formation of a new σ-bond is not considered. The term 2α occurs in all calculated π-electron energy changes which arise when polynuclear arenes react with electrophiles. It is convenient to define the cation localization energy (L^+) for reaction with an electrophile (X^+):

$$L^+ = E_\pi^{ArH} - E_\pi^{ArHX^+} - 2\alpha$$

so that for the protonation of benzene

$$L^+ = 2.54\beta = 194.6 \text{ kJ mol}^{-1}$$

Table 8 gives the localization energies for different positions in a number of polycyclic hydrocarbons.

TABLE 8

Cation Localization Energies for Polycyclic Hydrocarbons

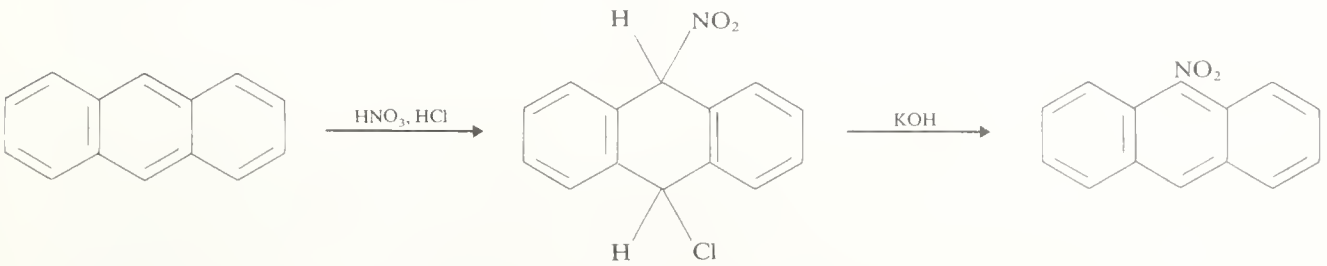
Compound	*Position*	L^+ (kJ mol^{-1})
Biphenyl	2	183.8
	3	194.6
	4	187.7
Naphthalene	1	176.2
	2	190.0
Anthracene	1	172.3
	2	183.8
	9	154.0
Phenanthrene	1	177.7
	2	191.5
	3	187.7
	9	176.2

This approach suggests that, for biphenyl, substitution should occur at positions-2 and -4 more easily than is the case for benzene. The 3-position should give partial rate data which are identical to those for benzene. The observed values are slightly smaller. The localization approximation ignores the small polar influence of the phenyl substituent, which is destabilizing. The results for naphthalene suggest that attack of an electrophile should occur predominantly at position-1. This is observed.

The reactions of electrophiles with anthracene and phenanthrene, as we have seen in Section 2.5.6, often result in overall addition to the 9- and 10-positions. This is entirely reasonable. Thus the L^+ values predict that the 9-substituted ion should be strongly favoured under kinetic control, and that it should be formed much more rapidly than is the related σ-complex with benzene. Addition-with-elimination reactions of benzene predominate because this process restores the aromatic delocalization energy (153.2 kJ mol^{-1}). On the other hand, although the stabilization energy of anthracene is

351.5 kJ mol^{-1}, in a 9,10-dihydroanthracene two isolated benzene rings are present and so the formation of the dihydro compound only costs *ca.* 45 kJ mol^{-1} [351.5 − (2 × 153.2) kJ mol^{-1}]. Evidently naphthalene is an intermediate case between benzene and anthracene and 1,4-addition is disfavoured by *ca.* 102 kJ mol^{-1}.

The preparation of 9-substituted anthracene and phenanthrene derivatives therefore often requires an indirect approach. 9-Nitroanthracene, for example, is prepared from the 9,10-dihydro derivative (equation 90) obtained from the reaction of anthracene with nitric acid in the presence of hydrogen chloride.

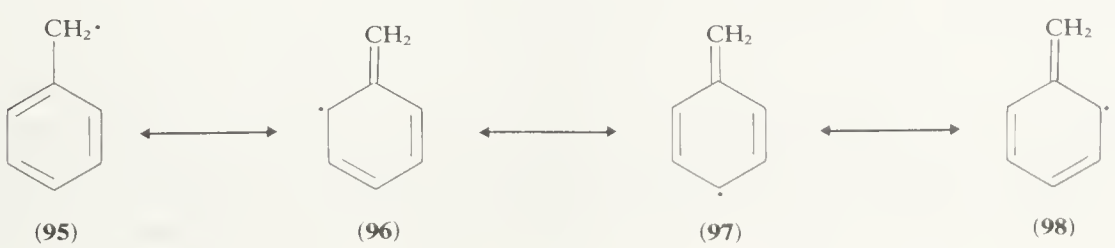


(90)

2.5.8 RADICAL HALOGENATION ON THE SIDE CHAINS OF ARENES[96]

Alkylbenzenes can react with halogens in two distinct ways. We have already discussed in Section 2.5.6 reactions carried out under ionic conditions. In radical reactions the product-determining step is almost always an abstraction. There is a considerable preference for the abstraction of a univalent atom in preference to higher-valent atoms. Thus ethane reacts with chlorine atoms to produce, initially, an ethyl radical and not a hydrogen atom. Benzene itself does not undergo this type of process because the C—H bond has extra *s* character (C_{2sp^2}—H_{1s}) compared with an alkane, and the resultant high bond strength ($DH° = 468.72$ kJ mol^{-1}) makes the abstraction of hydrogen by a chlorine atom strongly endothermic ($\Delta H° = 37.7$ kJ mol^{-1}). As well as the possibility of additions occurring with arenes under ionic conditions, this possibility also exists under conditions where radicals are generated. The addition of chlorine to benzene is well known. A mixture of isomers is obtained and one of these, the so-called γ-isomer (γ-1,2,3,4,5,6-hexachlorocyclohexane), has been widely used as an insecticide. The addition of, for example, chlorine atoms to the ring in toluene is a reversible process whereas hydrogen abstraction is irreversible. Thus the photochlorination of toluene affords benzyl chloride, but at low temperatures and high chlorine concentrations ring-addition is significant. The bromination of toluene either with mild illumination, or in the presence of peroxides, proceeds efficiently, to afford benzyl bromide. The lower bond energy of the benzyl–hydrogen bond ($DH° = 355.72$ kJ mol^{-1}) makes the abstraction of hydrogen by a chlorine atom strongly exothermic ($\Delta H° = -75.3$ kJ mol^{-1}). Bond dissociation energies ($DH°$) indicate that 79.5 kJ mol^{-1} less energy is needed to form the benzyl radical from toluene than is required to form the methyl radical from methane.

The benzyl radical is especially stable because the odd electron is delocalized into the ring — indicated by the resonance contributors (**95**)–(**98**). Although the *ortho* and *para* positions do have a significant odd-electron character, the subsequent reaction with chlorine occurs exclusively at the exocyclic position for obvious thermodynamic reasons (equations 91–93).

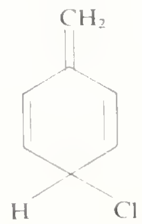


(**95**) (**96**) (**97**) (**98**)

$$\mathrm{PhCH_3 + Cl\cdot \longrightarrow PhCH_2\cdot + HCl} \qquad \Delta H^\circ = -75.3\ \mathrm{kJ\,mol^{-1}} \qquad (91)$$

$$\mathrm{PhCH_2\cdot + Cl_2 \longrightarrow PhCH_2Cl + Cl\cdot} \qquad \Delta H^\circ = -50.2\ \mathrm{kJ\,mol^{-1}} \qquad (92)$$

$\mathrm{PhCH_2\cdot + Cl_2}$ ⟶ (crossed arrow)



$+ \mathrm{Cl\cdot} \qquad \Delta H^\circ \approx +100\ \mathrm{kJ\,mol^{-1}} \qquad (93)$

Attack on a side chain usually occurs preferentially at a C—H bond α to the aryl residue. Bromine and chlorine atoms both abstract hydrogen more rapidly from toluene than from ethane. However, abstraction by a chlorine atom is faster from the secondary position in propane than from the secondary position in ethylbenzene or diphenylmethane. Bromine atoms always abstract hydrogen from a benzylic position more rapidly than from a similar alkane.[97] Some of the relevant data are summarized in Table 9.

TABLE 9

Effects of Structure on Reactivities of Alkyl and Aralkyl Hydrogen Atoms towards Bromine and Chlorine Atoms

	MeCH$_2$—H	Me$_2$CH—H	Me$_3$C—H
Cl·, 40 °C	1.0	4.3	6.0
Br·, 77 °C	1.0	2.2×10^2	1.94×10^4
	PhCH$_2$—H	Ph$_2$CH—H	Ph$_3$C—H
Cl·, 40 °C	1.3	2.6	9.5
Br·, 77 °C	6.4×10^4	1.1×10^6	6.4×10^6
	PhCH(Me)—H	PhC(Me$_2$)—H	
Cl·, 40 °C	3.3	7.3	
Br·, 77 °C	1.6×10^6	3.8×10^6	

The attack of an atom or radical on a C—H bond is believed to proceed *via* a more or less linear transition state (equation 94). However, the extent to which the C—H bond is broken in the transition state is clearly dependent upon the structure of the substrate and the attacking atom or radical. The reported primary kinetic isotope effects for α-deuteriotoluene are 1.3 for chlorination in carbon tetrachloride, 2.1 for chlorination in the gas phase, 4.6 for bromination in carbon tetrachloride, and 8.2 for bromination in the gas phase. Thus the bromination of ethylbenzene (equation 95) gives exclusively 1-bromo-1-phenylethane, while the chlorination of ethylbenzene (equation 96) affords a mixture of 1-chloro-1-phenylethane (91%) and 1-chloro-2-phenylethane (9%). One other set of data further illustrates this problem. Although toluene is more reactive towards bromination than is cyclohexane (2.5×10^2), the reactivity is reversed in the related chlorination (3.8).

$$\mathrm{R{-}H + X\cdot \longrightarrow [R\cdots H\cdots X]^{\cdot\ddagger} \longrightarrow R\cdot + HX} \qquad (94)$$

$$\mathrm{Ph{-}CH_2{-}CH_3 \xrightarrow{Br_2,\ \Delta,\ h\nu} Ph{-}CH(Br){-}CH_3 + HBr} \qquad (95)$$

$$\mathrm{Ph{-}CH_2{-}CH_3 \xrightarrow{Cl_2,\ \Delta,\ h\nu} \underset{(91\%)}{Ph{-}CH(Cl){-}CH_3} + \underset{(9\%)}{Ph{-}CH_2{-}CH_2{-}Cl}} \qquad (96)$$

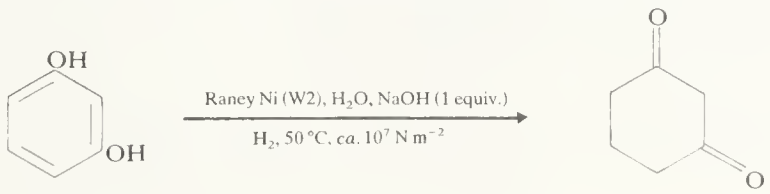
Bromination is clearly more responsive to radical-stability effects than is chlorination because less C—H bond breaking occurs in the transition state of the chlorinations. However, radical-stability arguments are clearly not the only factors to be taken into account. The low reactivity of diphenylmethane towards chlorination is usually attributed to polar factors. Since chlorine is considerably more electronegative than carbon, a chlorine atom is an electrophilic species. Thus because a phenyl group is electron attracting compared with an alkyl group it will be deactivating towards an electrophilic radical. It may be better to regard the origins of this effect in unfavourable dipolar repulsions.[98]

2.5.9 ADDITIONS TO ARENES

2.5.9.1 The reduction of arenes

As we have indicated previously, addition is strongly disfavoured in the case of benzene by *ca.* 146 kJ mol^{-1}, but in the case of anthracene addition to the 9- and 10-positions is only disfavoured by 45 kJ mol^{-1}. Naphthalene (102 kJ mol^{-1}) and phenanthrene (74.5 kJ mol^{-1}) are clearly intermediate. All types of additions will only proceed with benzene under forcing conditions, whereas with naphthalene, phenanthrene, and anthracene additions become successively more easy.

The hydrogenation of arenes to afford cycloalkanes can be achieved using a number of different heterogeneous catalyst systems.[99] Higher temperatures, and frequently higher pressures, are needed, compared with the hydrogenation of simple olefins. The reduction of alkylbenzenes over rhodium on carbon may be achieved at room temperature and at a pressure of *ca.* 4×10^5 N m^{-2}. No hydrogenolysis of the benzyl–oxygen or the benzyl–nitrogen bonds is observed using these conditions. Raney nickel is also useful in the temperature range 100–150 °C. Using Raney nickel (W2), pressures in the range 1.3–1.7×10^7 N m^{-2} are normal, while using the more active W4 catalyst, pressures of $0.6–1.0\times10^7$ N m^{-2} may be used. The reduction of phenols in the presence of a base frequently stops at the enolate anion stage and thus affords cyclohexanone derivatives (equation 97). Varying amounts of hydrogenolysis of the benzyl–oxygen bond is observed.



(97)

Phenols and phenyl ethers are converted into the respective cyclohexanol derivatives using ruthenium on carbon at temperatures of about 100–125 °C and pressures up to 10^7 N m^{-2}. The hydrogenation of aryl halides — including aryl fluorides — using all catalyst systems results in hydrogenolysis of the carbon–halogen bond as well as in saturation of the ring.

When di- or poly-substituted benzene derivatives are hydrogenated, mixtures of stereoisomers normally result. Raney nickel is the least stereoselective of all the catalysts and usually affords a mixture in which the thermodynamically favoured product predominates. The use of ruthenium, on the other hand, usually leads mainly to *cis*-1,2- and *cis*-1,3-disubstituted cyclohexanes from *ortho*- and *meta*-disubstituted benzenes, respectively.

The reduction of benzene, and other arenes, also proceeds in the presence of a wide range of 'homogeneous' catalysts.[100] Thus benzene is reduced by hydrogen to cyclohexane in *N,N*-dimethylformamide at 20 °C and 10^6 N m^{-2} in the presence of *ca.* 10^{-3} mol of a rhodium catalyst formulated as (**99**). *o*-Xylene is reduced to a mixture of *cis*- and *trans*-1,2-dimethylcyclohexane (6.5 : 3.5, respectively) using the Ziegler-type catalyst system nickel(II) 2-ethylhexanoate–triethylaluminium at temperatures in the range 150–210 °C in the presence of hydrogen at a pressure of 7×10^7 N m^{-2}. High stereoselectivity has been

reported[101] in the reduction of *o*- and *m*-xylene to the *cis*-dimethylcyclohexanes using the catalyst (**100**). Hydrogen exchange, which is frequently observed using heterogeneous catalysts, was not detected. Thus [$^2H_6$]benzene gave only [$^2H_6$]cyclohexane. Steric interference in the hydrogenation is indicated by the very low rate of hydrogenation of mesitylene to *cis,cis*-1,3,5-trimethylcyclohexane.

$H[Rh_2A_2Cl]$ $A =$ 

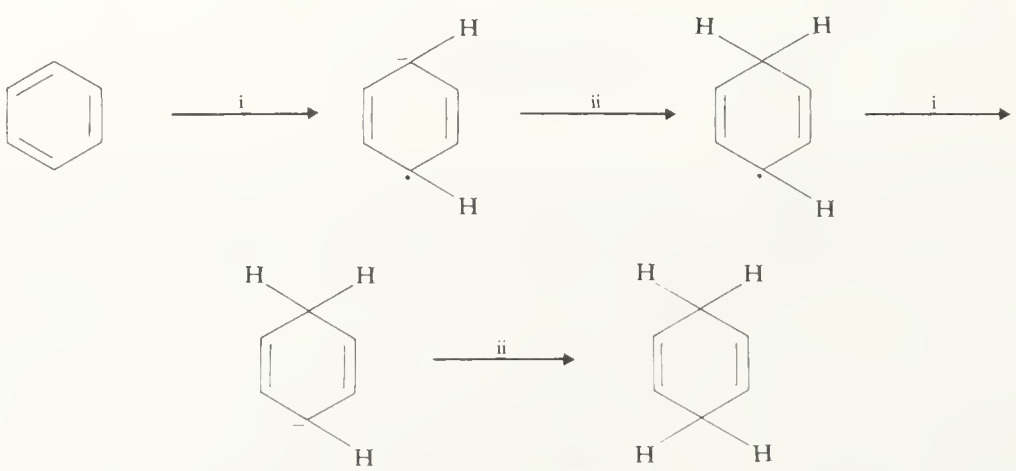
(**99**)

η-C_3H_5——$Co[P(OMe)_3]_3$

(**100**)

As expected, the initial rate of hydrogenation of polycyclic arenes increases with the number of rings present. Only one ring is saturated at a time. Thus naphthalene is reduced to 1,2,3,4-tetrahydronaphthalene using platinum oxide in acetic acid at *ca.* 50 °C under hydrogen at 4×10^5 N m^{-2}, or using Raney nickel (W2) in ethanol solution at *ca.* 100 °C and *ca.* 1×10^7 N m^{-2} hydrogen pressure. The reduction of anthracene and phenanthrene to the respective 9,10-dihydro derivatives proceeds under the same conditions as are used in the partial reduction of naphthalene. These latter reductions can also be achieved easily using sources of di-imide. Phenanthrene, for example, is reduced to 9,10-dihydrophenanthrene in high yield using a mixture of hydrazine and sodium hydrazide in benzene.[102]

When arenes are reduced by dissolving alkali metals in liquid ammonia, normally in the presence of an alcohol, 1,4-addition of hydrogen takes place. This type of reaction is known as the Birch reduction.[103] Liquid ammonia obtained commercially is frequently impure and low yields result unless the solvent is redistilled. The use of other amines as the solvent is restricted to low molecular weight aliphatic primary amines and hexamethylphosphoric triamide.[104] In these cases the reductions sometimes proceed further than those carried out in ammonia. Benzene is efficiently reduced to cyclohexa-1,4-diene by sodium in liquid ammonia containing ethanol. The probable mechanism of the reduction is shown in Scheme 42. A dianion can be involved in certain cases and is formed by the addition of a second electron to the radical anion.



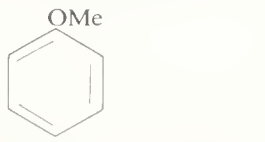
i, e^-; ii, H^+ (from EtOH).

SCHEME 42

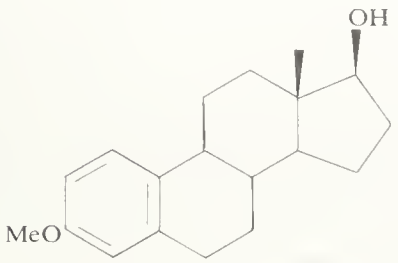
The effects of substituents are in accord with this mechanism. The presence of electron-withdrawing substituents increases the rate of reduction and protonation occurs at the 1- and 4-positions. Thus the reduction of benzamide, using sodium in liquid ammonia

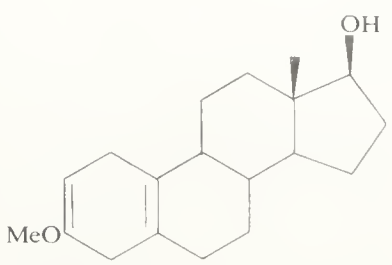
in the presence of t-butanol, affords 1,4-dihydrobenzamide. The phenyl residue in biphenyl functions as an electron-withdrawing group and effectively stabilizes the carbanion intermediate at the benzylic position. The literature concerned was originally confusing in that different results had been obtained using a variety of reaction conditions. The products obtained included 1,4- and 3,4-dihydrobiphenyl and, under more forcing conditions, tetra- and hexa-hydrobiphenols. A dianion produced at *ca.* −75 °C does give 1,4-dihydrobiphenyl,[105] and it is now clear that rapid reduction and a careful work-up does give the expected result.

Electron-releasing groups present in an arene deactivate the ring and direct the protonations to the 2- and 5-positions. The rate of reduction of alkylbenzenes decreases in the order methyl > ethyl > isopropyl > t-butyl. Similarly, the reduction of anisole affords 1-methoxycyclohexa-1,4-diene (equation 98), and oestradiol 3-methyl ether (**101**) is reduced to the diene (**102**) (equation 99).



(98)

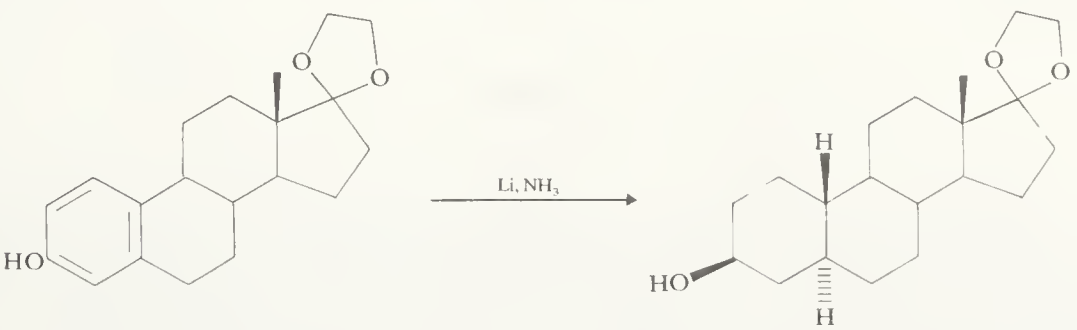




(99)

(**101**) (**102**)

Two additional cases are worthy of further discussion. They are both concerned with benzene derivatives which contain acidic functional groups and therefore give anions easily under the reaction conditions used. Monobenzenoid phenols are not reducible in liquid ammonia under the usual conditions, presumably because the phenolate anion causes extreme deactivation. On the other hand, the use of lithium at high concentrations in ammonia is successful, *e.g.* equation (100). Benzoic acid, despite the formation of the carboxylate anion, is rapidly converted, in high yield, to 1,4-dihydrobenzoic acid using sodium in liquid ammonia in the presence of ethanol.

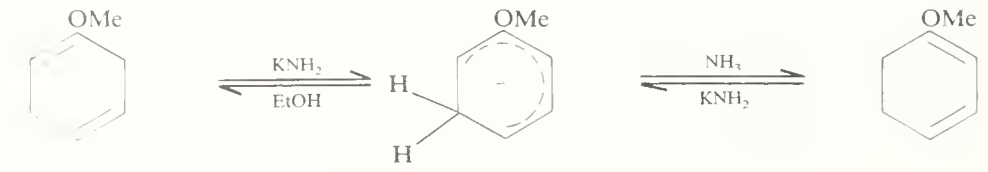


(100)

The addition of the first proton occurs at the position where the anionic charge can be localized most readily. However, another question to which we should address ourselves is concerned with the site of protonation of the carbanion which results from the addition of the second electron (Scheme 43). It is evident, from the examples above, that the initially kinetically controlled product of protonation is frequently the thermodynamically least stable product. Qualitative predictions may be based on the relative stabilities of the possible intermediate anions, using the principle of least motion. It is predicted that

protonation will occur in the middle of the mesomeric carbanion because this produces the least change in the bond orders.[106]

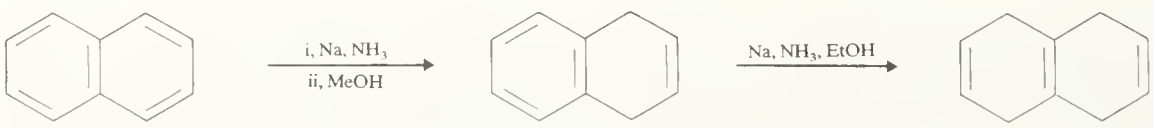
Although the 1,4-diene is normally the kinetically controlled product, it is possible, in certain cases, to obtain the thermodynamically more stable conjugated diene. The equilibration of 2,5-dihydroanisole with 2,3-dihydroanisole (equation 101) illustrates this point. The addition of more than 1 mole of potassium amide gives the salt of the anion (**104**), which on kinetic protonation affords the non-conjugated diene (**103**). On the other hand, the use of less than 1 mole of potassium amide only serves to induce the equilibration between (**103**) and the conjugated diene (**105**) and gives a ratio of (**103**):(**105**) = 2:8.



(101)

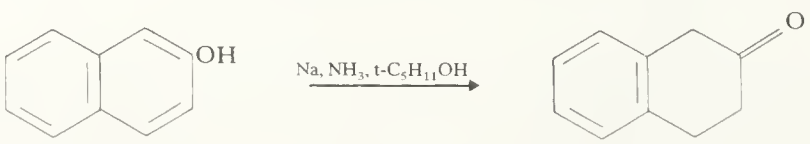
(**103**) (**104**) (**105**)

The Birch reduction of polycyclic arenes is sometimes complex, but products of considerable synthetic utility have been prepared by means of the various experimental procedures which are available. If the addition of the proton source is delayed during the experiment, the reduction of one ring can normally be achieved. Naphthalene reacts with sodium in liquid ammonia to afford a red complex which is decomposed by methanol to afford 1,4-dihydronaphthalene. If the reduction is carried out with ethanol added at the same time as the naphthalene, 1,4,5,8-tetrahydronaphthalene can be obtained in *ca.* 80% yield (equation 102). 1,4-Dihydronaphthalene is also converted into the same tetrahydronaphthalene using the same conditions. The former method was used in the first stage of the synthesis of 1,6-methano[10]annulene.[107]



(102)

Substituents in the 1-position in naphthalene afford the expected products. Thus if electron-withdrawing substituents are present the 1,4-dihydro derivative is the initial product, while in the presence of electron-releasing substituents the 5,8-dihydro derivative is formed. 2-Substituted naphthalenes undergo reduction in the substituted ring, *e.g.* equation (103).



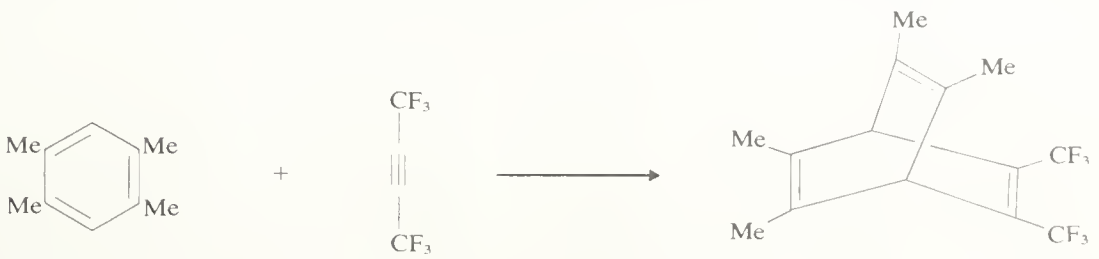
(103)

The reduction of other polycyclic hydrocarbons follows the general picture outlined above. Thus anthracene and phenanthrene afford the respective 9,10-dihydro derivatives upon treatment with sodium in liquid ammonia in the presence of iron(III) chloride. The iron(III) ion is reduced to colloidal iron, which catalyses the conversion of the excess of sodium into sodium amide. Both anthracene and 9,10-dihydroanthracene can be converted into either 1,4,9,10-tetrahydro- or 1,4,5,8,9,10-hexahydroanthracene using an appropriate quantity of lithium in liquid ammonia. 1,4,5,8,9,10-Hexahydroanthracene is the major product obtained by the reduction of anthracene using either sodium in liquid ammonia containing ethanol or of 9,10-dihydroanthracene using lithium in methylamine.[108] This is the starting material which was required for the synthesis of 1,6:8,13-propanediylidene[14]annulene,[109] and, for example, *syn*-1,6-methano-8,13-oxido[14]annulene.[110]

2.5.9.2 Thermal cycloadditions of arenes

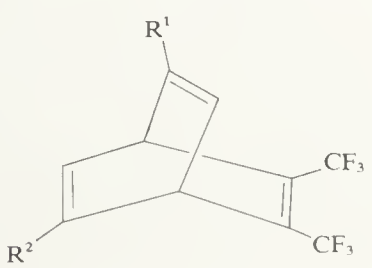
The same type of thermodynamic arguments which were used in Section 2.5.9.1 in order to predict the ease of reduction of arenes, apply to a consideration of the thermal cycloadditions of arenes with the obvious change with respect to 1,4-cycloadditions of phenanthrene.

The Diels–Alder reaction[111] only proceeds with monocyclic arenes using very electrophilic dienophiles. Even then, it is exceptional for good yields to be obtained with benzene. The presence of electron-releasing substituents on the arene increases the electron density in the particular ring and results in an increase in the yield of the Diels–Alder adduct formed under a standard set of reaction conditions. Although hexafluorobut-2-yne only affords a cycloadduct (**106**) in 8% yield with benzene at 180 °C,[112] an analogous reaction with durene (equation 104) proceeds provided it is carried out at 200 °C, and gives the indicated product in 41% yield.[113]

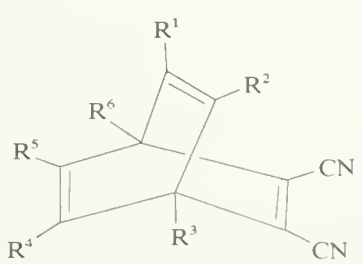


(104)

Reactions carried out with toluene and *p*-xylene at *ca.* 200 °C gave the adducts (**107**) and (**108**) in 21% and 57% yields, respectively.[112] The reactions of, for example, benzene and durene with dicyanoacetylene afford the cycloadducts (**109**) and (**110**) in low yields.[114] In the cycloadditions of dicyanoacetylene the reactions were found to be strongly accelerated by Lewis acid catalysts. Thus the adduct (**109**) was formed in 63% yield in the presence of aluminium chloride.[115] This reaction is believed to proceed *via* activation of the dienophile by complex formation with the Lewis acid. An insoluble 1 : 1 complex was obtained by mixing cyclohexane solutions of dicyanoacetylene and aluminium bromide. Whereas the reactions of hexafluorobut-2-yne gave only one adduct (**108**) with *p*-xylene, the Lewis acid catalysed reaction between dicyanoacetylene and *p*-xylene gave the two adducts (**111**) and (**112**). The ratio of (**111**):(**112**) was 2 : 8 using aluminium chloride and 1 : 1 using aluminium bromide. In the absence of a catalyst the same two adducts (**111**) and (**112**) were formed in low yield in the ratio 7 : 3. This suggests that the transition states involved in the non-catalysed reactions are product-like but that the catalysed reactions may proceed in a step-wise manner.



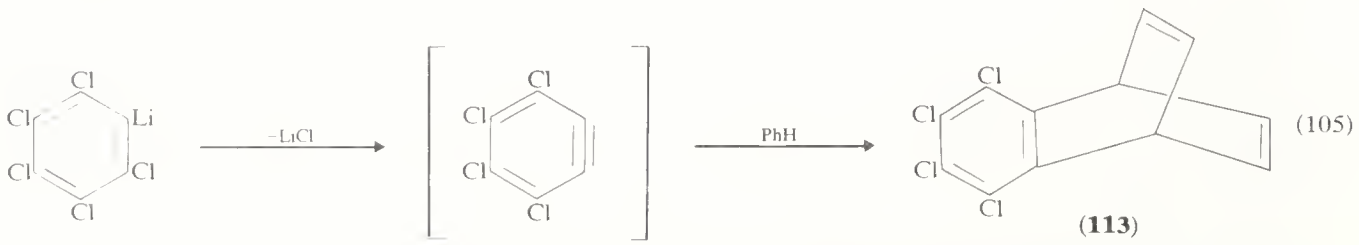
(**106**) $R^1 = R^2 = H$
(**107**) $R^1 = Me$; $R^2 = H$
(**108**) $R^1 = R^2 = Me$



(**109**) $R^1 = R^2 = R^3 = R^4 = R^5 = R^6 = H$
(**110**) $R^1 = R^2 = R^4 = R^5 = Me$; $R^3 = R^6 = H$
(**111**) $R^1 = R^4 = Me$; $R^2 = R^3 = R^5 = R^6 = H$
(**112**) $R^1 = R^2 = R^4 = R^5 = H$; $R^3 = R^6 = Me$

Benzyne also reacts with benzene to form the 1,4-cycloadduct benzobarrelene (**42**), usually in rather low yield. However, the electrophilicity of arynes can be increased in the same manner as has been exemplified above, with acetylene.[116] Highly halogenated arynes give good yields even with simple arenes such as benzene. Tetrachlorobenzobarrelene (**113**) may be prepared in 60–65% yield by allowing pentachlorophenyl-lithium to

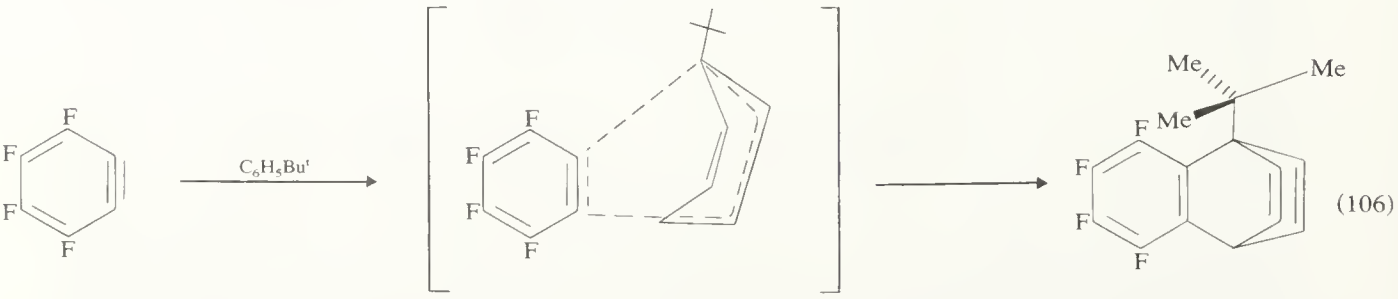
decompose in the presence of an excess of benzene (equation 105).[117] The best yield of benzobarrelene from the reaction of benzyne (from benzenediazonium-2-carboxylate) with benzene is 14%.[118] This reaction was carried out using a 1400 mole excess of benzene!



(105)

(**113**)

The reactions of the tetrahalogenobenzynes[116] with monocyclic arenes which are substituted by electron-releasing groups proceed in essentially the same way that is observed in the reactions using hexafluorobut-2-yne. It is noteworthy that using *p*-xylene and durene as the co-reactants, no adducts were detected with methyl groups at bridgehead positions. Once again, this suggests that the transition states leading to the formation of the cycloadducts are product-like. One can adduce arguments in favour of orbital-symmetry-controlled concerted reactions, although proof is impossible. In some cases it is certain that the transition state cannot be entirely symmetrical. For example, the reaction of tetrafluorobenzyne with t-butylbenzene affords a mixture of the two possible 1,4-cycloadducts in an almost statistical ratio. The adduct with the t-butyl group at a bridgehead position shows in its ^{1}H n.m.r. spectra good evidence of restricted rotation, and this leads to the conclusion that the transition state leading to its formation is not entirely symmetrical (equation 106).



(106)

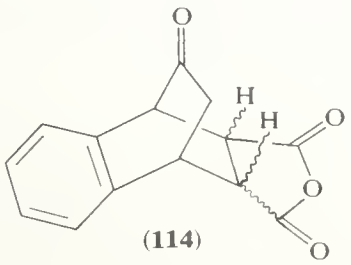
As far as the writer is aware, there are no examples of Diels–Alder reactions involving benzene or an alkylbenzene in which an olefin functions as the dienophile. Thus although a strong charge-transfer complex is formed between tetracyanoethylene and hexamethylbenzene [$K = 263$; λ_{max} 545 (ε 4390) nm], this does not collapse to a cycloadduct.

There are a very large number of reports of Diels–Alder reactions involving naphthalene, anthracene, and their simple derivatives. Despite early reports of failures, naphthalene does form a mixture of adducts with maleic anhydride, using a 30-fold excess of the dienophile at 100 °C for 30 h. Only about 1% of the adducts was isolated. The yield of the adducts (equation 107) is increased to 78% when the reaction is carried out at 100 °C and a pressure of 1×10^9 N m^{-2}.[119] With alkylnaphthalenes, attack occurs on the substituted ring.

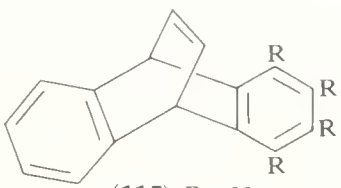
(107)

2-Naphthol forms a mixture of cycloadducts (**114**) under normal conditions in significantly better yield than is the case with naphthalene.[120] Similarly, allowing for the fact that experimental difficulties preclude the use of a very large excess of naphthalene, the reactions of other dienophiles give higher yields than is the case with benzene. Thus both benzyne and tetrachlorobenzyne, respectively, give the adducts (**115**) and (**116**) in acceptable yields.

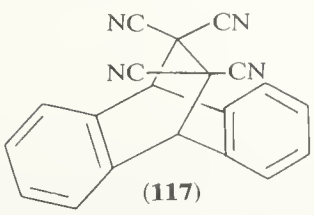
High yields of Diels–Alder adducts using anthracene have been reported over the past 50 years. Indeed, the emerald green charge-transfer complex which is formed between anthracene and tetracyanoethylene rapidly collapses to the colourless adduct (**117**). Benzyne and substituted benzynes afford triptycenes (*e.g.* **41**) in excellent yields and using anthracenes substituted at the 9-, or 9- and 10-positions allows the preparation of a wide range of derivatives of triptycene. It is of interest to note that indene can function as a dienophile — adduct (**118**) — and at high temperatures (after a [1, 5]-hydrogen shift to afford isoindene) as a diene — adduct (**119**).



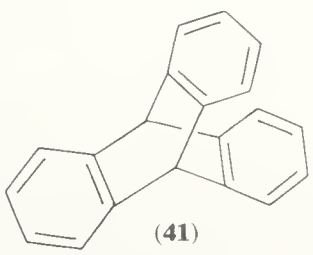
(**114**)

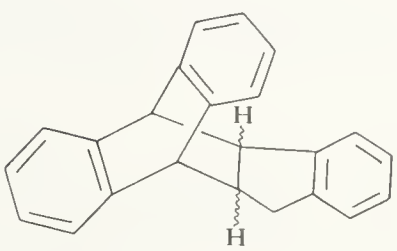


(**115**) R = H
(**116**) R = Cl

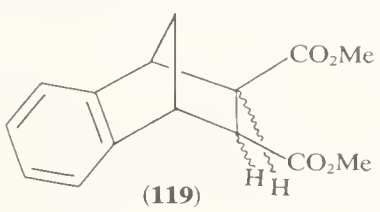


(**117**)


(**41**)

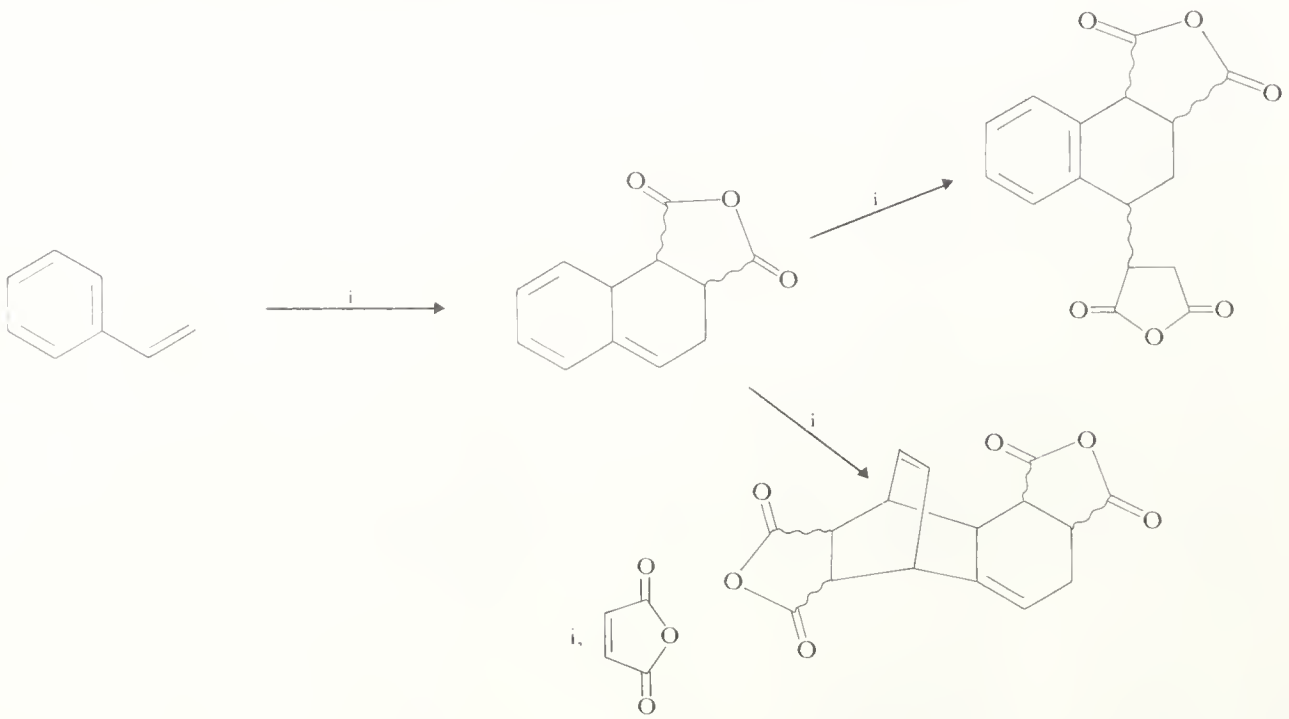


(**118**)



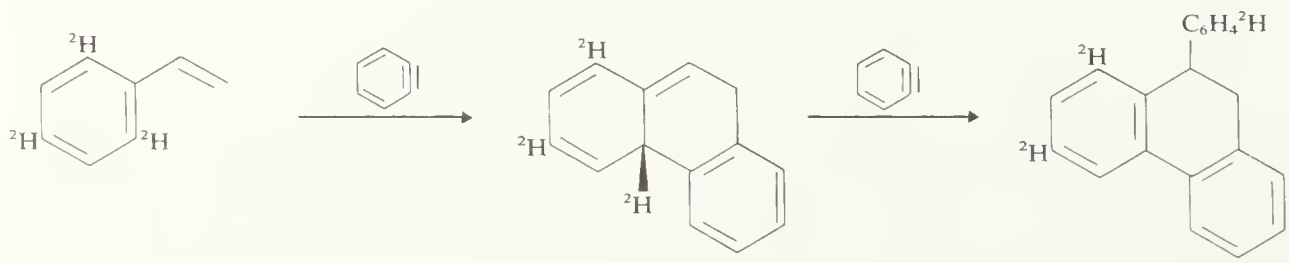
(**119**)

Styrene and substituted styrenes can function both as dienophile and as diene components in the Diels–Alder reaction. We shall only be concerned with the latter possibility. Styrene only acts as the diene component in reactions with active dienophiles. A special feature of this system is that the initial adduct is unstable and reacts further in one or more of four possible ways. Two of these processes are illustrated by considering the reaction of styrene with maleic anhydride (Scheme 43) in which the initial adduct undergoes a second Diels–Alder cycloaddition and an 'ene' reaction.



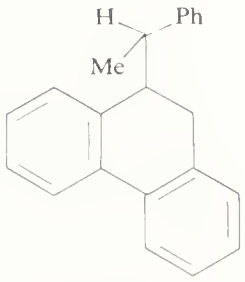
SCHEME 43

The other two possibilities are illustrated by reactions involving arynes. In fact benzyne itself reacts with styrene to give products which arise by one of the previously mentioned routes. If benzyne is generated in the presence of a moderate excess of styrene the major product is 9-phenyl-9,10-dihydrophenanthrene. That the reaction almost certainly proceeds by two successive concerted reactions — the second stage being an 'ene' reaction — is indicated (Scheme 44) by the retention of all the deuterium atoms using [2,4,6-$^2H_3$]styrene.

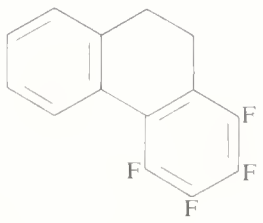


SCHEME 44

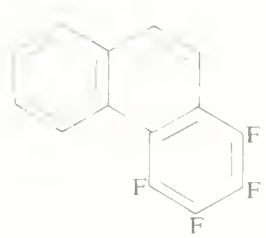
In the presence of a large excess of styrene the 'enophile' is styrene itself and a mixture of the *threo* and *erythro* isomers of the compound (**120**) are isolated.[121] The reactions of, for example, tetrafluorobenzyne with styrene can, with slight modifications to the reaction conditions, show the other two possible pathways from the initial adduct. [^{2}H]-Labelling again gave an insight into the processes involved. In the first of these, a base-catalysed 'conducted tour' leads to 1,2,3,4-tetrafluoro-9,10-dihydrophenanthrene (**121**) and, in the second, the abstraction of a hydride ion followed by deprotonation leads to the phenanthrene (**122**).



(120)

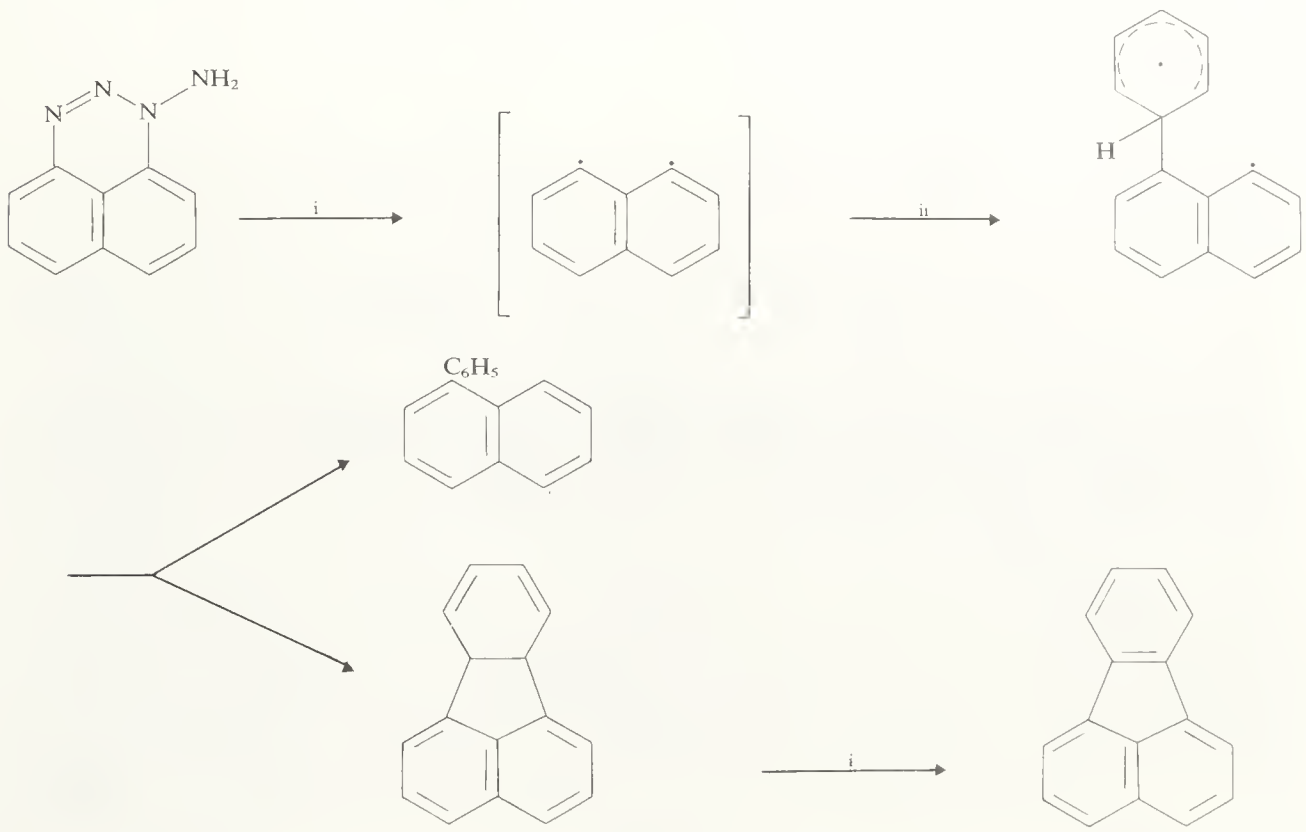


(121)



(122)

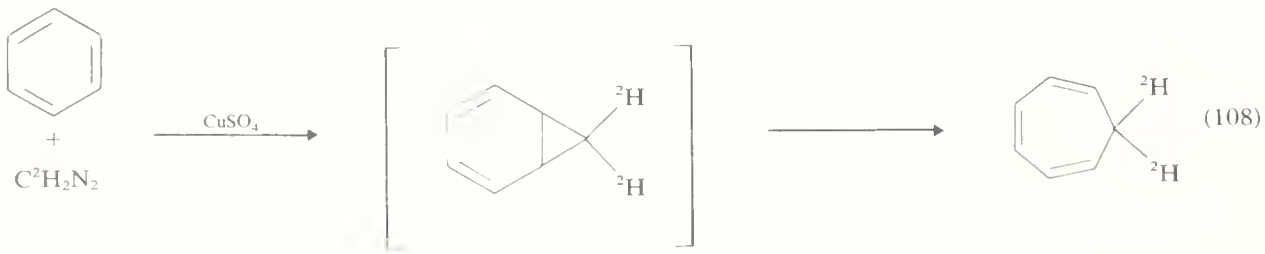
Although the reaction of benzyne (1,2-dehydrobenzene) with benzene does give some 1,2-cycloaddition, especially in the absence of silver(I) ions, this is not the normal mode of attack. On the other hand, 1,8-dehydronaphthalene reacts with benzene to give a mixture of 1-phenylnaphthalene and the 1,2-cycloadduct and its oxidation product, fluoranthene (Scheme 45).[122] Similarly, 1,8-dehydronaphthalene affords dimethyl acenaphthylene-1,2-dicarboxylate by reaction with dimethyl acetylenedicarboxylate.[123]



i, $Pb(OAc)_4$; ii, C_6H_6.

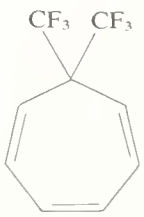
SCHEME 45

Carbenes[124] and nitrenes[125] also react with arenes to give, initially, 1,2-cycloadducts. The initial adducts can, and usually do, rearrange to the valence-isomeric seven-membered rings. Thus diazoalkanes give carbenes by photolysis, or by thermolysis in the presence of copper(II) salts, and the carbenes then react with arenes. The catalysed reaction is the method of choice for ring-expansion reactions of arenes. $[^2H_2]$Diazomethane in the catalysed reaction with benzene affords [7,7-$^2H_2$]cycloheptatriene (equation 108), but in the photolytic reaction scrambling of the deuterium occurs together with some insertion, which results in the formation of $[^2H_2]$toluene.

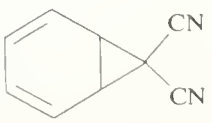


(108)

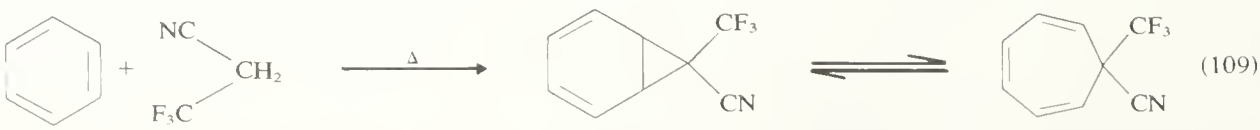
The thermolysis of bis(trifluoromethyl)diazomethane in benzene at 200 °C gave the compound (**123**) in 62% yield together with an 8% yield of the insertion product. Interestingly, the photolysis or thermolysis of dicyanodiazomethane gave the norcaradiene derivative (**124**) as the exclusive product. Not surprisingly, the thermolysis of cyanotrifluoromethyldiazomethane in benzene (equation 109) gave a product whose ^{19}F and ^1H n.m.r. spectra indicated that the norcaradiene and cycloheptatriene valence isomers are in rapid equilibrium at room temperature.



(**123**)

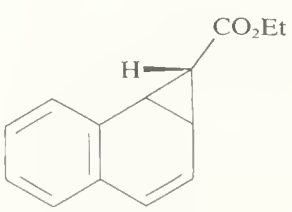


(**124**)

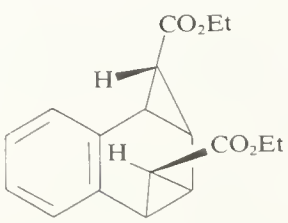


(109)

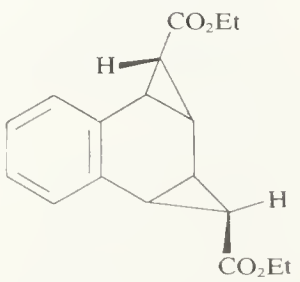
Ethoxycarbonylcarbene also reacts with benzene to afford derivatives of cycloheptatriene. In contrast, three adducts (**125**)–(**127**) containing cyclopropane rings were obtained using naphthalene. Two of these were bis-adducts, of which the major one is chiral and hence was assigned the *trans* structure (**127**).



(**125**)

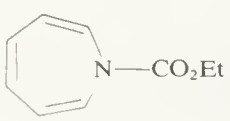


(**126**)

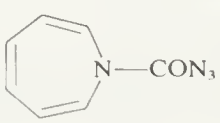


(**127**)

Carbonylnitrenes, such as ethoxycarbonylnitrene, may be generated by a number of methods, including the photolysis and thermolysis of ethyl azidoformate and the base-catalysed α-elemination from ethyl-*N*-(*p*-nitrobenzenesulphonyloxy)urethane. The nitrene reacts with benzene and affords *N*-ethoxycarbonylazepine (**128**). Similarly, carbonyl azide gives *N*-azidocarbonylazepine (**129**).



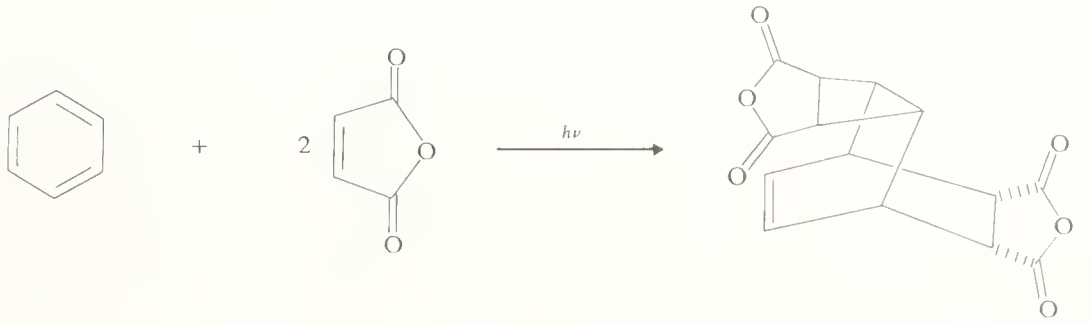
(**128**)



(**129**)

2.5.9.3 Photocycloadditions of monocyclic arenes[126]

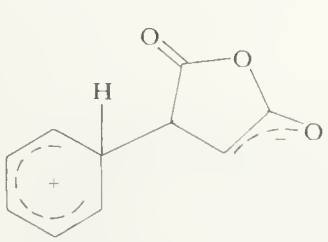
Although the first photochemical reaction of an arene — the photodimerization of anthracene — was reported over 100 years ago, it is only in the last 20 years that photoaddition and photoisomerization reactions of arenes have been studied in any detail. Many different types of photoadditions involving arenes have been discovered since the report of the formation of a 2:1 adduct of maleic anhydride with benzene (equation 110).[127] Formally, the structure of the product (**130**) looks as if it has been formed by a photochemical 1,2-cycloaddition followed by a thermal Diels–Alder reaction. In this example it is now certain that concerted 1,2-cycloaddition is not involved.



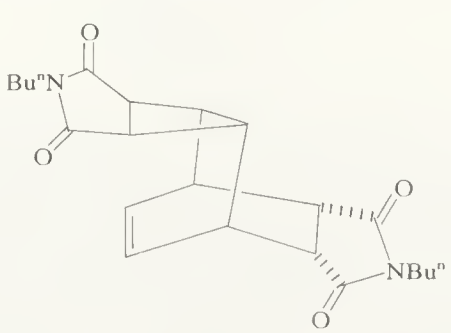
(110)

(**130**)

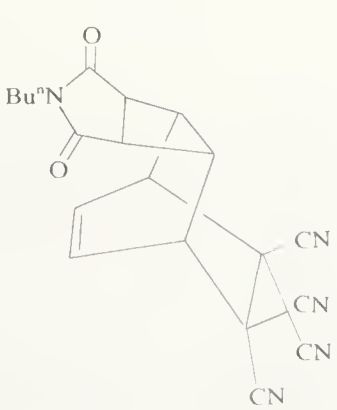
Charge-transfer bands are observed in the ultraviolet spectra of mixtures of maleic anhydride and benzene and alkylbenzenes. Photo-excitation of a charge-transfer transition is believed to lead to a zwitterion intermediate (**131**), since phenylsuccinic anhydride can be isolated from reactions carried out in the presence of proton donors. Although tetracyanoethylene is normally a much better Diels–Alder dienophile than maleic anhydride, in benzene solution it exists completely as its charge-transfer complex and this undoubtedly reduces its dienophilic properties. The irradiation of mixtures of maleic anhydride and tetracyanoethylene, either in the absence or presence of photosensitizers, was originally reported to lead only to the formation of the compound (**130**). On the other hand, although the normal 2:1 adduct (**132**) is the major product obtained from reactions of benzene and n-butylmaleimide, reactions carried out in the presence of tetracyanoethylene gave some of the 1:1:1 adduct (**133**). It is of interest to note that the benzene σ-complex formed with hexafluoroantimonic acid forms a 1,4-cycloadduct with maleic anhydride.[22a] However, it is unlikely that the maleic anhydride functions as the nucleophilic component in this Diels–Alder reaction. It is much more likely that, like the Lewis-acid catalysed Diels–Alder reactions of dicyanoacetylene mentioned in Section 2.5.9.2, the hexafluoroantimonic acid increases the electrophilicity of maleic anhydride. This explanation is consonant with the known dramatic rate enhancement of Diels–Alder reactions of anthracene carried out in the presence of aluminium chloride.[128]



(**131**)

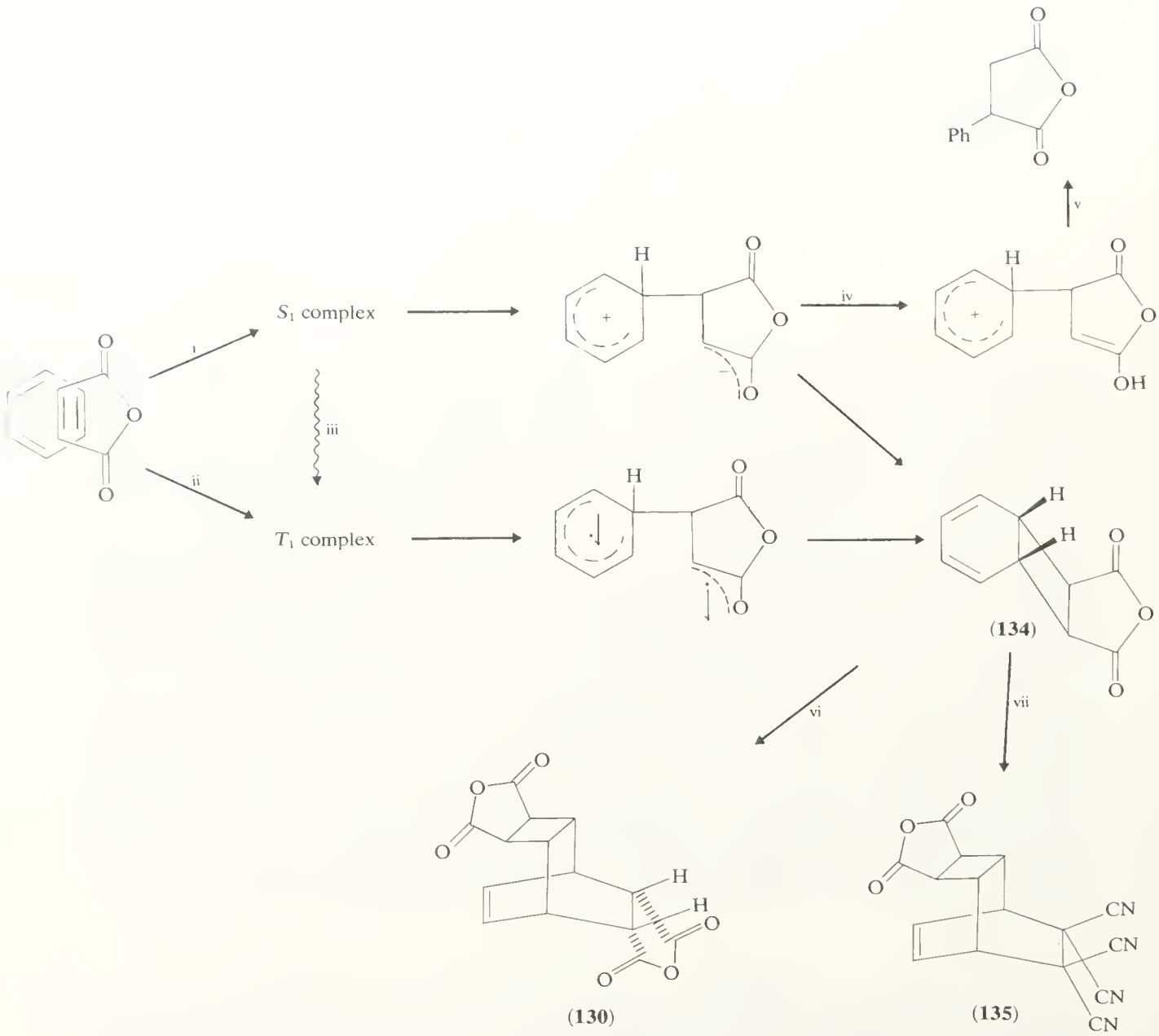


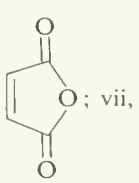
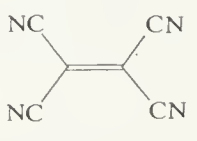
(**132**)



(**133**)

The apparent anomaly has now been resolved. The postulated bicyclic intermediate (**134**) has been prepared[129] by an alternative route and is found to be surprisingly unreactive towards tetracyanoethylene, presumably as a result of unfavourable steric interactions as well as the previously mentioned charge-transfer properties. Knowing the properties of the adduct (**135**), formed in the thermal Diels–Alder reaction of the diene (**134**) with tetracyanoethylene, has allowed experiments to be designed which have shown that the diene (**134**) is an intermediate in the photocycloadditions of benzene and maleic anhydride, both in the presence and absence of photosensitizers.[130] The results are summarized in Scheme 46.

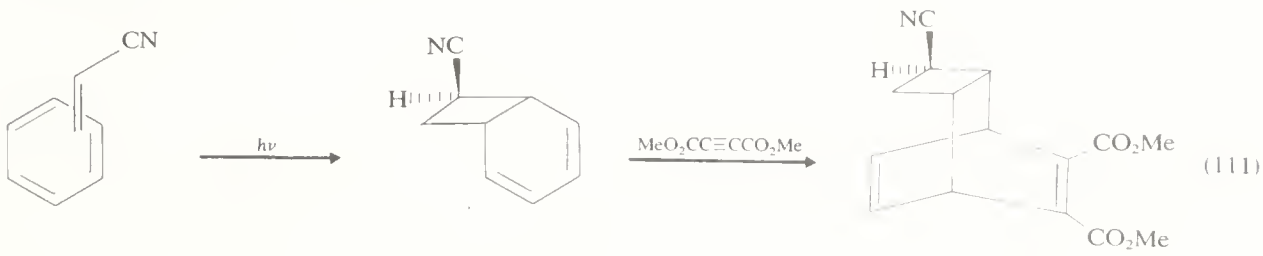


i, $h\nu$; ii, $h\nu$, Ph_2CO; iii, CH_2Br_2; iv, H^+; v, $-H^+$; vi,  ; vii, 

SCHEME 46

In spite of the above discussion, 1,2-photocycloadducts have been isolated from reactions of arenes with olefins. Thus the irradiation of a 1 : 1 mixture of benzene and acrylonitrile at 0 °C afforded the 1,2-photoadduct (**136**), which gave the stable product

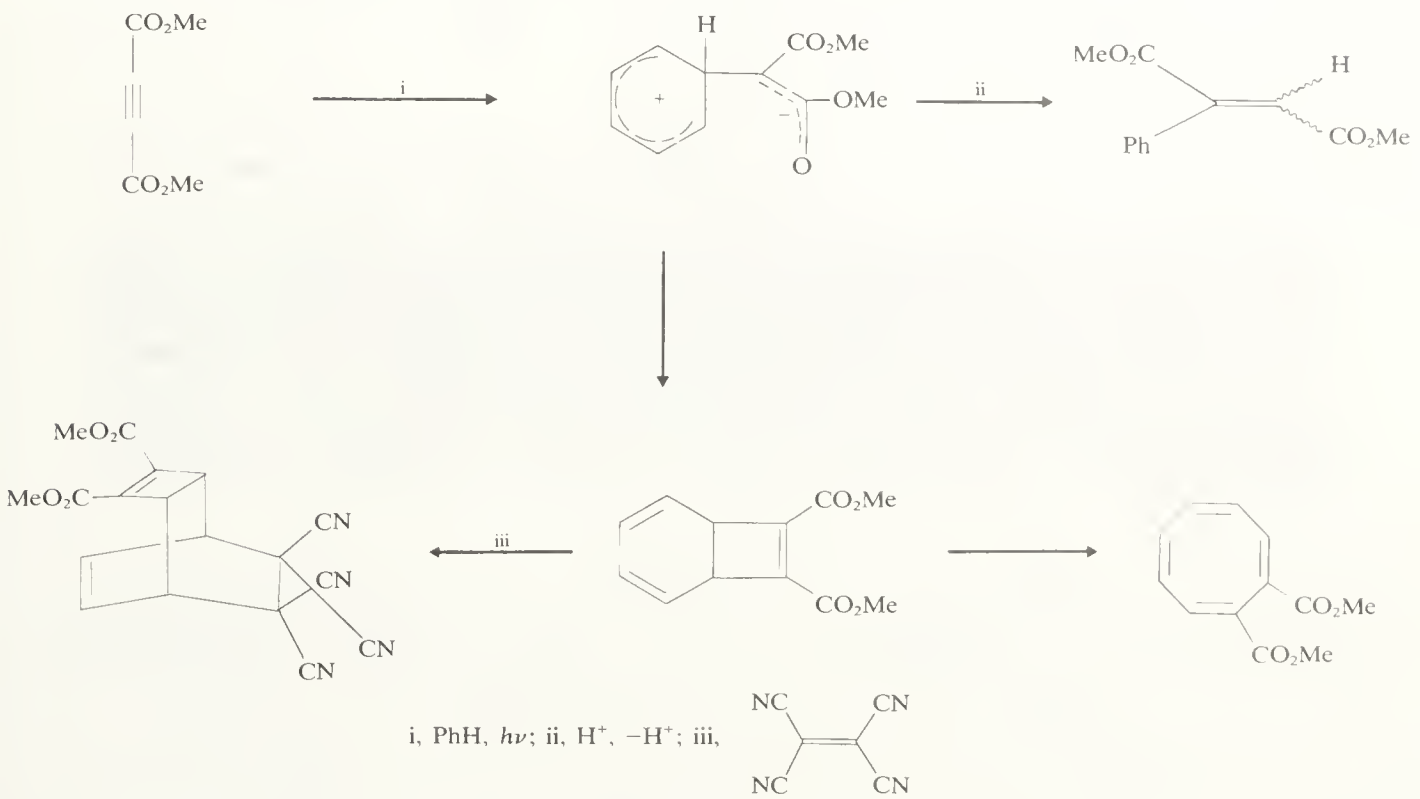
(**137**), probable stereochemically, after reaction with dimethyl acetylenedicarboxylate (equation 111).[131]



(111)

(**136**) (**137**)

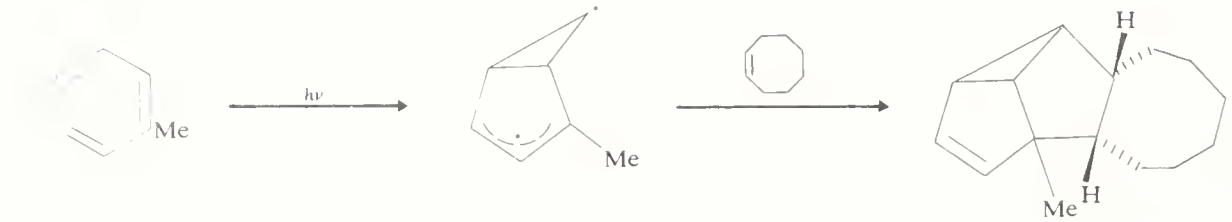
The photoreaction of benzene with dimethyl acetylenedicarboxylate also proceeds *via* a zwitterion intermediate. Dimethyl phenylfumarate and phenylmaleate were isolated in reactions carried out in the presence of proton donors. In this case the 1,2-cycloadduct, which is formed by the collapse of the zwitterion, is captured more easily by powerful dienophiles such as tetracyanoethylene. In the absence of such reagents, valence isomerization to dimethyl cyclo-octatetraenedicarboxylate occurs (Scheme 47).



SCHEME 47

The predominant photochemical process in the reactions of simple olefins with benzene and alkylbenzenes involves the formation of 1,3-cycloadducts.[132] These results have been rationalized using orbital symmetry arguments.[133] The stereochemistry of the olefin is preserved in the products, for example using *cis*- and *trans*-cyclo-octene and *cis*- and *trans*-but-2-ene. On the other hand, the amounts of the *exo* and *endo* isomers produced depends on the structure of the olefin. In many cases the *endo* isomer predominates. Thus with toluene and *cis*-cyclo-octene the *endo* adduct (**139**) is the major product. The reaction looks 'as if' the singlet pre-fulvene (**138**) is involved, and thus accounts for the location of the methyl group in (**139**) (equation 112), but there is no firm evidence on this point and an *endo* exciplex has been regarded as being product determining. The

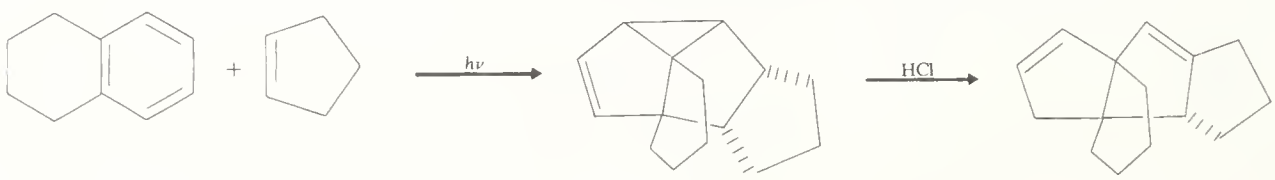
1,3-cycloaddition of functionalized olefins such as vinyl acetate,[134a] ethyl vinyl ether (with anisole),[134b] and vinylene carbonate[134c] have also been reported.



(112)

(138) (139)

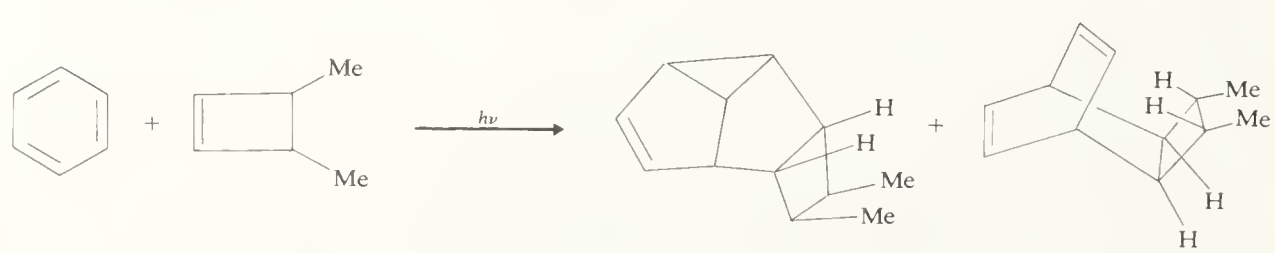
The knowledge of the regioselectivity and stereoselectivity (in many cases the stereospecificity) of the 1,3-photocycloadditions can be put to good effect in synthesis. For example, the photocycloaddition of cyclopentene to 1,2,3,4-tetrahydronaphthalene affords the adduct (**140**) which, in the presence of catalytic quantity of hydrogen chloride, gave the [4,3,3]propelladiene (**141**) (equation 113).[135]



(113)

(140) (141)

Until relatively recently it was thought that 1,3-cycloaddition was the almost exclusive process involved in the photoadditions of simple olefins with benzene. However, 1,2- and 1,4-cycloadditions as well as photo-ene reactions are now known. Thus, although the major product formed in the photochemical addition of benzene to *cis*-3,4-dimethylcyclobutene was shown to be the 1,3-adduct (**142**), a minor isomeric product was shown to be the 1,4-cycloadduct (**143**) (equation 114).[136] The stereochemistry of the compound (**143**) is probably as shown. Only in reactions of allenes is 1,4-photocycloaddition the major process.[137]

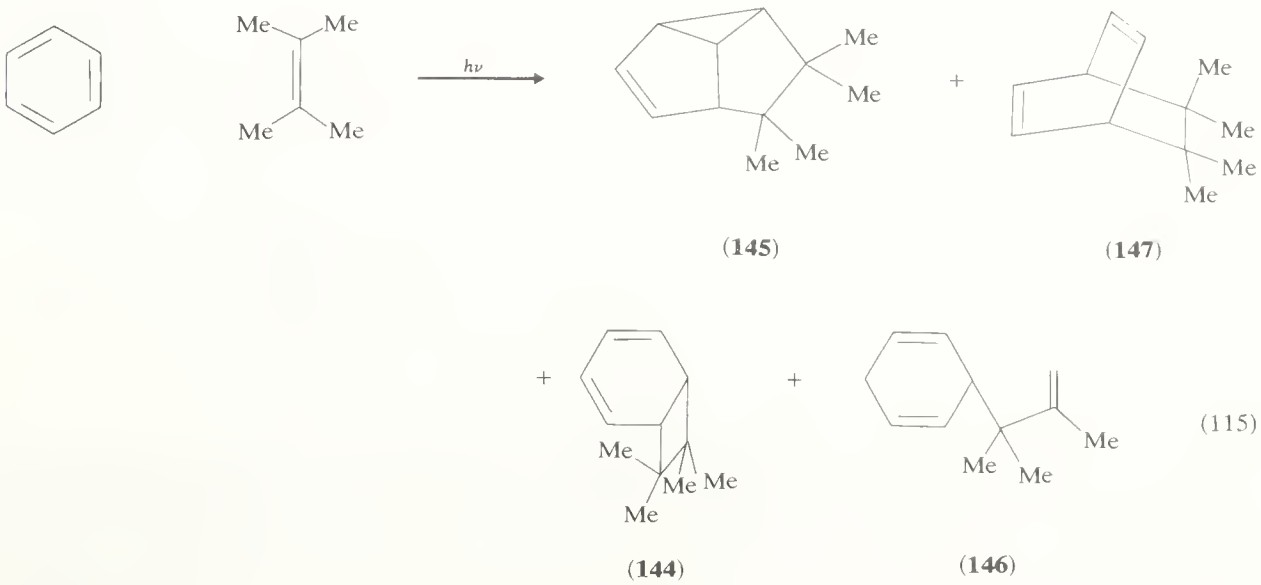


(114)

(142) (143)

We have already discussed 1,2-photocycloadditions of benzene with electrophilic olefins. It has also been shown[138] that the stereospecific formation of 1,2-photocycloadducts can be an important process with simple donor olefins. However, since photodissociation and photolysis of the initial 1,2-cycloadducts occur, they are only easily observed either during the early stages of the reactions (*i.e.* at low conversions) or by using a low-pressure mercury lamp which has little emission in the 270–290 nm range. The photoaddition of 2,3-dimethylbut-2-ene to benzene gave a mixture of three major 1:1 adducts. The minor product was shown to be the 1,2-cycloadduct (**144**), since it formed a Diels–Alder adduct with maleic anhydride, and the product of intermediate abundance was the 1,3-cycloadduct (**145**). The major product, which was eight times as abundant as the minor adduct, was shown to be the 1,4-dihydrobenzene derivative (**146**)

(equation 115). The 'ene' product is formed non-stereospecifically and its formation is catalysed by proton donors. In addition to the products mentioned above, the 1,4-cycloadduct (**147**) is also obtained.[126c]

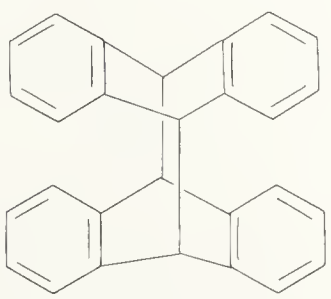


(**145**) (**147**)

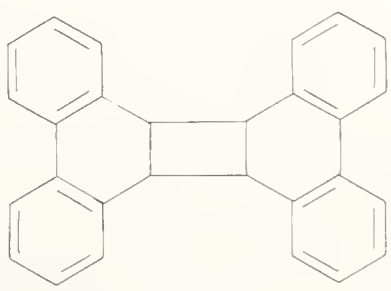
(**144**) (**146**) (115)

2.5.9.4 Photochemical reactions of polycyclic arenes

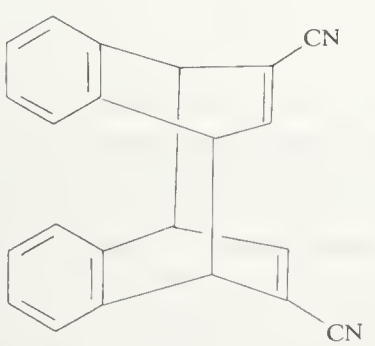
The photodimerization of anthracene, and its derivatives, proceeds to afford products of structural type (**148**).[139] Mixed dimerizations of substituted anthracenes have been reported using, for example, 9,10-dimethylanthracene and 9-cyanoanthracene. Other 'acenes' such as naphthacene also undergo mixed dimerization. Recently,[140] reports of the photodimerization of phenanthrenes have appeared; products of type (**149**) result.



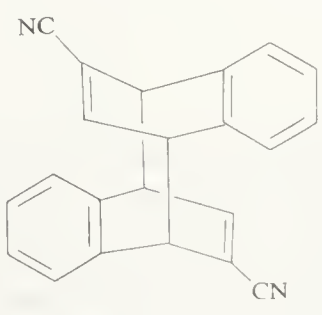
(**148**)



(**149**)

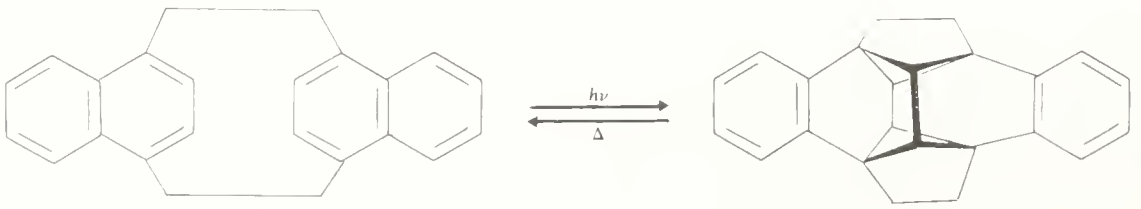


(**150**)



(**151**)

Naphthalene itself does not appear to photodimerize, but some substituted naphthalenes do. There has been some confusion concerning the structures of the photodimers of 2-methoxy- and 2-cyano-naphthalene. In the case of naphthalene-2-carbonitrile, a mixture of (**150**) and (**151**) is obtained.[141] Mixed dimers have also been reported.[142] Intramolecular photodimerization occurs with the [2,2]paracyclonaphthane (**152**) and affords the heptacyclic hydrocarbon (**153**) (equation 116).[143] Both the *syn* and *anti* forms of the compound (**152**) undergo the reaction, but (**153**) is thermally labile and decomposition gives the more stable *anti*-[2,2]paracyclonaphthane.

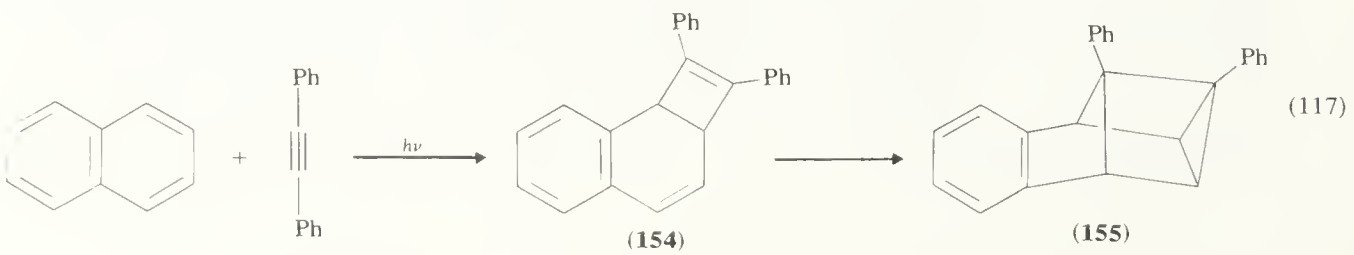


(116)

(**152**) (**153**)

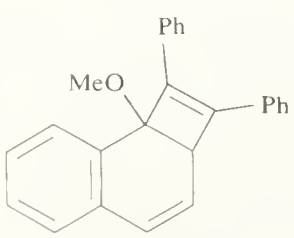
The photoadditions of unsaturated compounds with benzene have been shown to proceed to afford an interesting range of structures. The range of possibilities has also been shown to be large using naphthalene and other polycyclic hydrocarbons.[144]

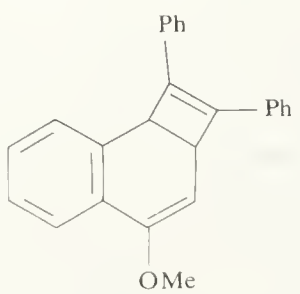
The photoaddition of diphenylacetylene to naphthalene involves the exciplex formed between singlet naphthalene and the ground state of the acetylene. Apparently the initial product is the 1,2-adduct (**154**), which then undergoes intramolecular cyclization to (**155**) (equation 117). A large number of analogous photocycloadditions have been reported using substituted naphthalenes and other acetylenes. 1,4-Dimethoxynaphthalene affords the analogues of (**154**) and (**155**).[145] Interestingly, the photocyclization of compound (**156**) proceeds more slowly than the isomer (**157**).



(117)

(**154**) (**155**)

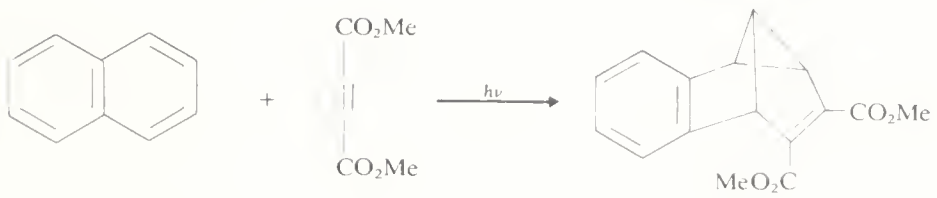




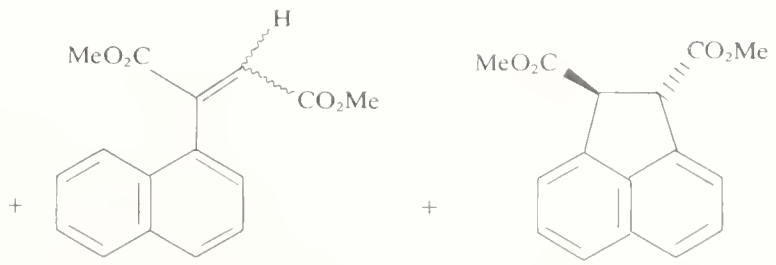
(**156**) (**157**)

The photocycloaddition of dimethyl acetylenedicarboxylate to naphthalene is much more complex than the corresponding reaction with benzene. The main photoproducts are shown in equation (118). The acenaphthene derivative is formed from the dimethyl (1-naphthyl)fumarate and is the main 1:1 adduct formed in methanolic solution. The benzo-semibullvalene derivative (**158**) is probably the first example of a 1,3-photoaddition of an acetylene to an arene.

The photoadditions of polycyclic arenes proceed with olefins to afford either 1,2- or 1,4-cycloadducts, and with dienes to yield 1,4-cycloadducts. Both singlet and triplet exciplexes are involved in the photoaddition of dimethyl fumarate to phenanthrene

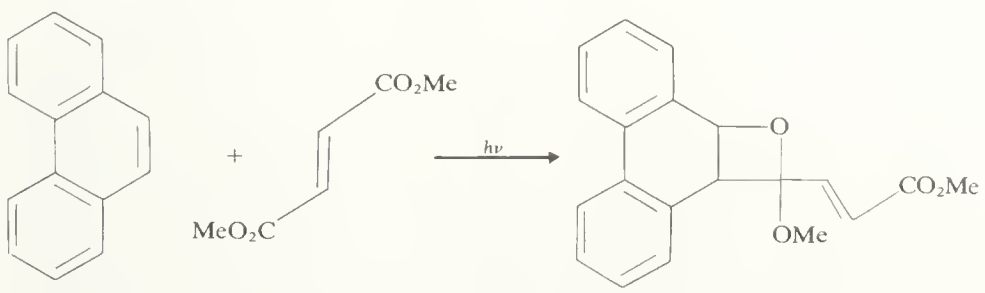


(**158**)

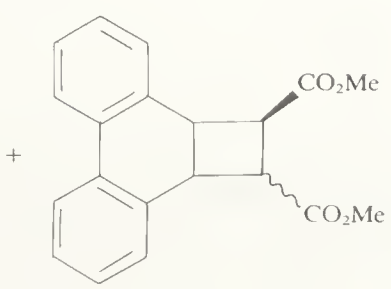


(118)

(equation 119). The singlet exciplex yields the oxetan (**159**) and the cyclobutane derivative (**160**) (stereospecifically), while the triplet exciplex affords both stereoisomers of the cyclobutane (**160**).[146]



(**159**)



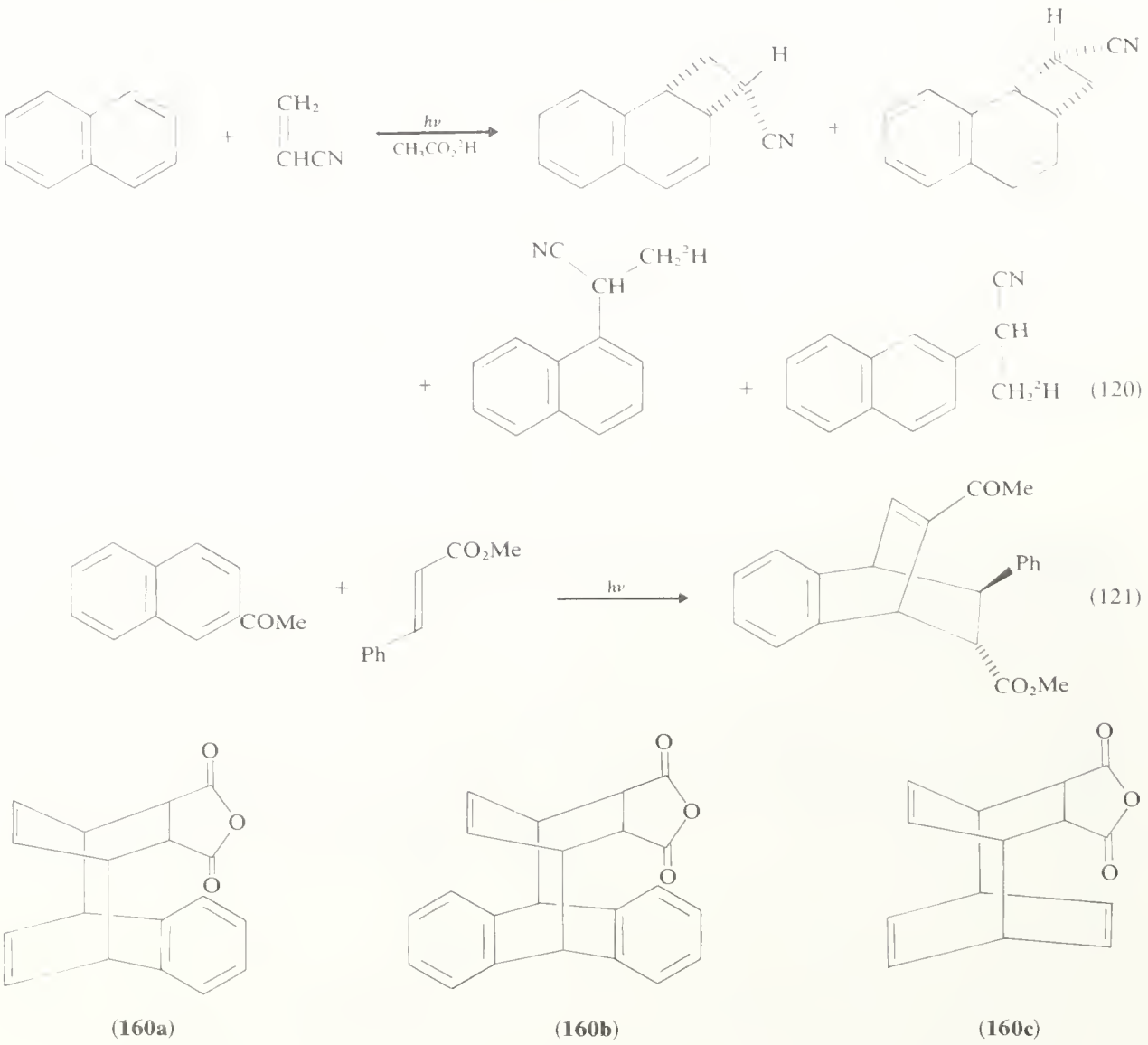
(119)

(**160**)

The photoaddition of acrylonitrile to naphthalene, like the reaction with benzene, results in 1,2-cycloaddition, probably *via* a polar exciplex. However, and not surprisingly, two adducts are formed (equation 120), together with, in the presence of a source of a deuteron (*O*-deuterioacetic acid), the two substitution products with deuterium in the methyl group.[147]

Perhaps one of the most remarkable photocycloadditions to have been reported is that between 2-acetylnaphthalene and methyl cinnamate. In view of the rapidity with which a photo-equilibrium is attained between the *cis*- and *trans*-esters, the stereospecificity (equation 121) is amazing for this slow reaction.

A number of 1,4-cycloadditions of 1,2-dihydrophthalic anhydride have been reported.[148] Not only are the compounds (**160a**) and (**160b**) obtained from naphthalene and anthracene respectively, but also, using benzene, the compound (**160c**) was obtained. Oxidative decarboxylation of the corresponding dicarboxylic acids should allow the synthesis of what are formally 1,4–1,4-dimers.

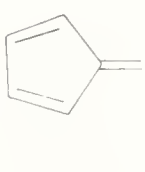


(160a) (160b) (160c)

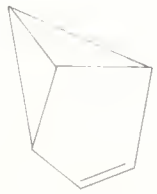
2.5.10 PHOTOISOMERIZATIONS OF ARENES[126b]

The irradiation of liquid benzene at 254 nm gives a mixture of fulvene (**161**) and benzvalene (**162**) *via* the first excited singlet state, but no trace of Dewar-benzene (**163**). In neat benzene the reaction to give fulvene and benzvalene proceeds most efficiently in the range 50–60 °C and the chemical yield of both of the isomers is improved by carrying out the irradiation in dilute solution using an alkane such as hexadecane. Some of the fulvene may arise from the benzvalene by a catalytic process involving quartz. Benzvalene is less base-sensitive than fulvene, but more acid-sensitive. The thermal reversion of benzvalene to benzene proceeds slowly at room temperature, but the reversion is sensitized by triplet benzene. A very efficient thermal synthesis of benzvalene and naphthvalene involves the interaction of cyclopentadienyl- or indenyl-lithium with dichloromethane and an alkyl-lithium reagent.[149] This availability of benzvalene has enabled its intermediacy in the photohydration of benzene to be confirmed. The use of deuterium oxide gave (**164**). In contrast to the results obtained by irradiating liquid benzene at 254 nm, when an oxygen lamp (165–200 nm) is used Dewar-benzene is formed, along with fulvene and benzvalene (ratio 1 : 2 : 5), together with a small amount of biphenyl. Irradiation of benzene vapour at 165–200 nm affords fulvene and the open-chain isomer *cis*-hexa-1,3-dien-5-yne which is subsequently photoisomerized to the *trans* isomer. It is worth noting at this point that benzene readily forms a photo-oxidation product in

aqueous solution. There has been controversy concerning the structure of this product and even whether oxygen is necessary for its formation. All the workers agree that benzvalene is an intermediate.



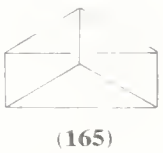
(161)



(162)

(163)

(164)



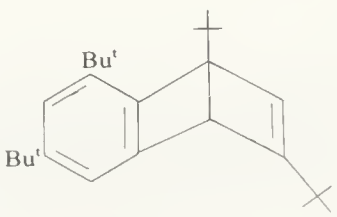
(165)

The photo-isomerizations of substituted benzenes can be considered under two headings. Firstly, those involving the formation of fulvenes, benzvalenes, Dewar-benzenes, and prismanes (**165**). The second category involves the formation of constitutional isomers in which the substituent has *apparently* migrated to a new position. In fact the substituent does not migrate. In contrast to the results obtained with benzene, hexafluorobenzene gives hexafluoro-Dewar-benzene and is the only isomer formed by irradiation using wavelengths in the range 212–265 nm. These results and those relating to the perfluoroalkylbenzenes are discussed in Chapter 3.

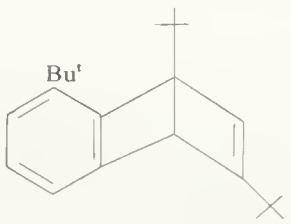
The major process which occurs on irradiation of the dialkylbenzenes (for example, the xylenes and the di-t-butylbenzenes) involves 1,2-alkyl shifts which result from the transposition of the ring-carbon atoms. These transpositions largely, and perhaps exclusively, involve the rearomatization of substituted benzvalenes. It is interesting to note that irradiation of an ethereal solution of *o*-di-t-butylbenzene leads to the total disappearance of this isomer. The steric hindrance which results from the presence of two *ortho* t-butyl groups evidently reduces the thermodynamic stability of this isomer very considerably. An analysis of ring-carbon transpositions in terms of 12 possible ring-permutation patterns has been suggested.[150] It was pointed out that the intermediacy of benzvalenes, Dewar-benzenes, and prismane intermediates has been proposed more frequently than they have been established.

The presence of two neighbouring bulky substituents evidently favours the formation of non-planar Dewar-benzene derivatives. Thus irradiation of 1,2,4-tri-t-butylbenzene leads to the less-overcrowded Dewar-benzene (**166**).[151] Similarly, irradiation of 1,3,6,8-tetra-t-butylnaphthalene and 1,3,8-tri-t-butylnaphthalene leads to the hemi-Dewar-naphthalenes (**167**) and (**168**), respectively.[152] Interestingly, only one of the two possible isomers was formed in the latter case. In the case of 1,2,4-tri-t-butylbenzene, benzvalene and prismane derivatives are formed, and with 1,3,5-tri-t-butylbenzene, the benzvalene derivative is the primary product.

(166)

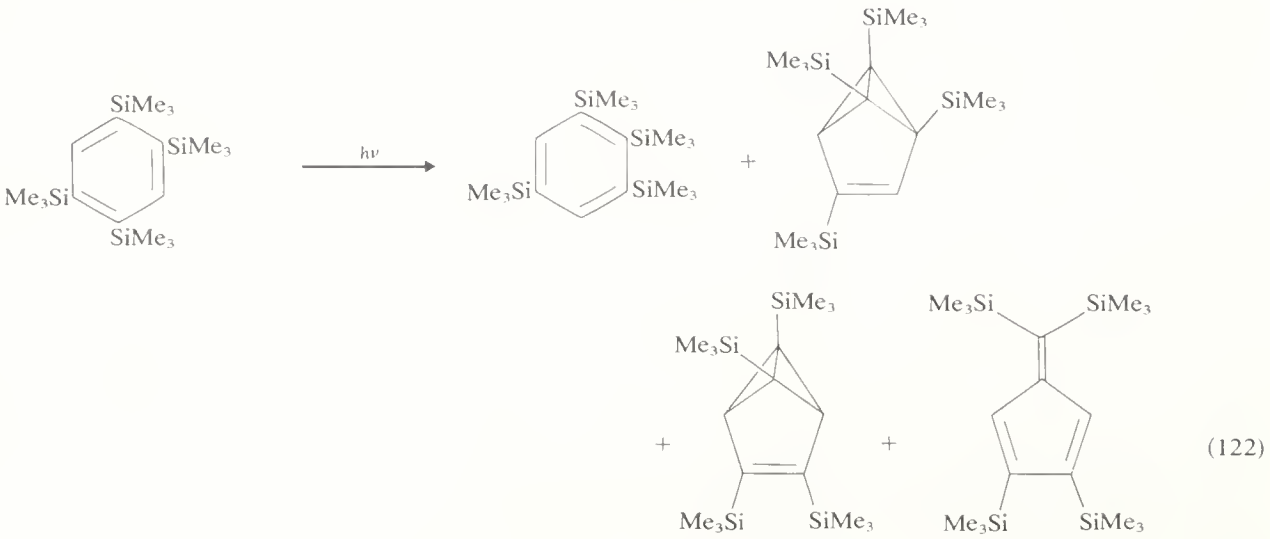


(167)



(168)

The photoisomerizations of 1,2,4,5-tetra-t-butylbenzene and 1,2,4,5-tetrakis-(trimethylsilyl)benzene have been studied and produce complementary results. Whereas, in the former case, two products, 1,2,3,5-tetra-t-butylbenzene and 1,2,3,5-tetra-t-butyl-Dewar-benzene, are produced, with the silicon compound, five products are obtained (equation 122), none of which is a Dewar-benzene derivative. This effect is probably a reflection of the longer C—Si bond, compared with the C—C bond, which reduces the steric distortion in the starting material when compared with the tetra-t-butylbenzene.



(122)

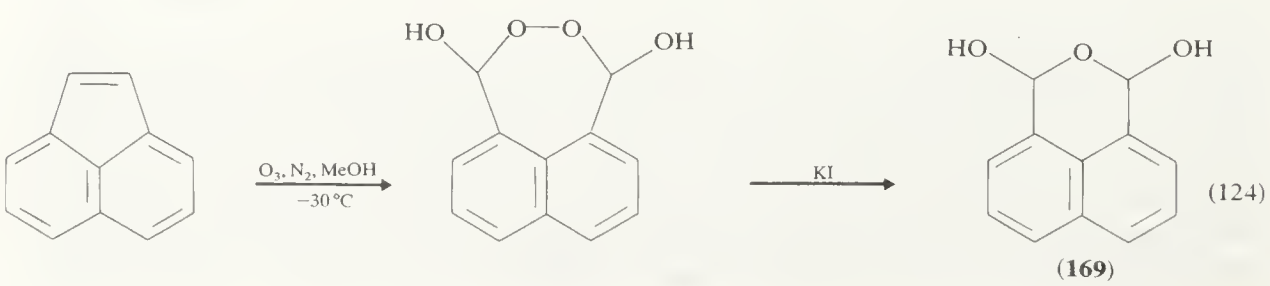
2.5.11 THE OXIDATION OF ARENES[153]

We have already considered certain oxidations of arenes in Section 2.5.6.7. In this section we shall be mainly concerned with the oxidation of side-chains in arenes and the oxidation of arenes to quinones. The oxidation of unsubstituted aromatic rings, with the resultant loss of the stabilization energy, requires vigorous conditions, and from what has been written previously (Section 2.5.7) is only likely to be of preparative value with polycyclic hydrocarbons. This is the case.

Thus the ozonization of anthracene using a mixture of ozone and nitrogen affords, after an alkaline hydrogen peroxide work-up, 9,10-anthraquinone in 73% yield. Phenanthrene, by ozonolysis in methanolic solution followed by treatment with potassium iodide to remove the peroxidic intermediate, gives biphenyl-2,2′-dicarboxaldehyde in excellent yield. The ozonolysis of pyrene (equation 123), provides, in reasonable yield, a point of entry into the synthesis of phenanthrene derivatives which are substituted at the 4- and 5-positions. These compounds are otherwise difficult to obtain.

(123)

Although it does not involve the ozonolysis of an aromatic ring it is worth noting that acenaphthylene, absorbed on silica gel, reacts smoothly with a mixture of ozone and nitrogen to give the bis-hemiacetal (**169**) in 73% yield after desorbtion from the silica gel (equation 124).

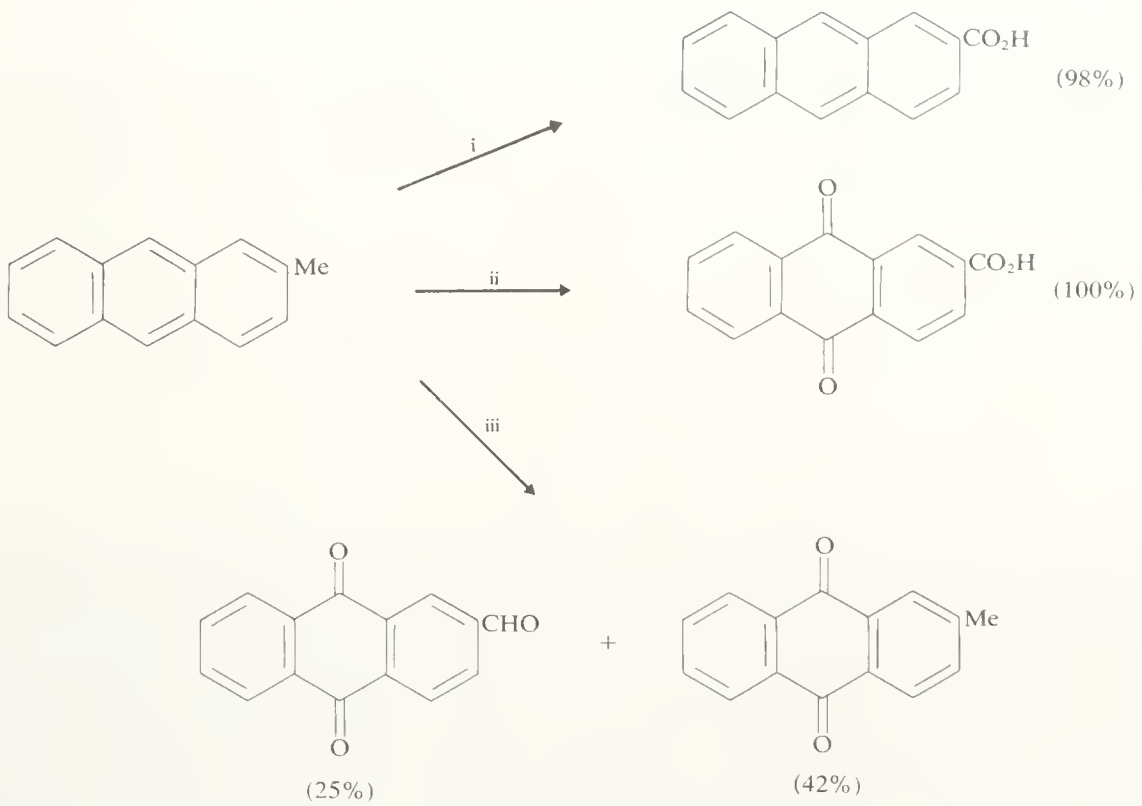


(124)

(**169**)

Naphthalene undergoes ozonolysis and affords phthalic acid in good yield. However, this method would never be used as a route to phthalic anhydride since both naphthalene and *o*-xylene are oxidized cheaply and efficiently using aerial oxidation over a vanadium pentoxide catalyst at 400–500 °C.

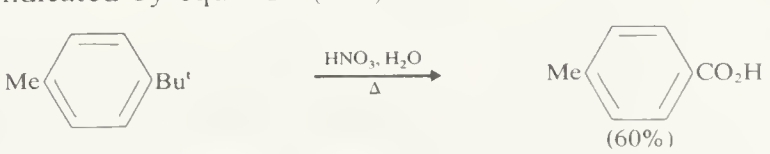
Chromium(VI) is undoubtedly the most versatile of all the oxidizing agents used in reactions with arenes. Chromium trioxide and sodium dichromate are both converted into the chromium(III) ion with a net transfer of three electrons to each chromium atom. By a suitable choice of the reagent and reaction conditions it is possible to convert side chains selectively to aldehydes, ketones, diacetates, or carboxylic acids. Under other conditions, polynuclear arenes are converted into quinones. Thus ethylbenzene is converted into benzoic acid (85% yield) by means of chromium(III) oxide in aqueous sulphuric acid, but gives acetophenone (50% yield) using dichromate in water at 250 °C. Ethylbenzene gives mainly phenylacetaldehyde using chromyl chloride. Chromyl acetate oxidizes *p*-nitrotoluene to *p*-nitrobenzaldehyde diacetate in 65% yield. Reactions of 2-methylanthracene (Scheme 48) further illustrate the generalizations given above. In the present context, pyridinium chlorochromate[154] promises to become a valuable addition to the present methodology for the oxidation of primary and secondary alcohols to carbonyl compounds. Benzhydrol is oxidized to benzophenone quantitatively.



i, $Cr_2O_7^{2-}$, H_2O, 250 °C; ii, $Cr_2O_7^{2-}$, H_2SO_4, 90 °C; iii, CrO_2Cl_2, CCl_4, 25 °C.

SCHEME 48

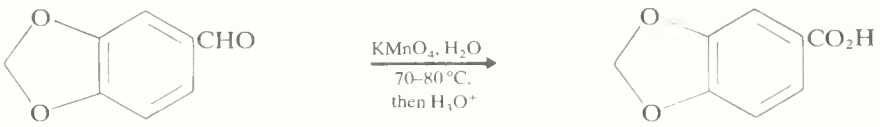
Chromic acid will not attack side chains which lack an α-hydrogen. However, nitric acid will do so, as is indicated by equation (125).



(125)

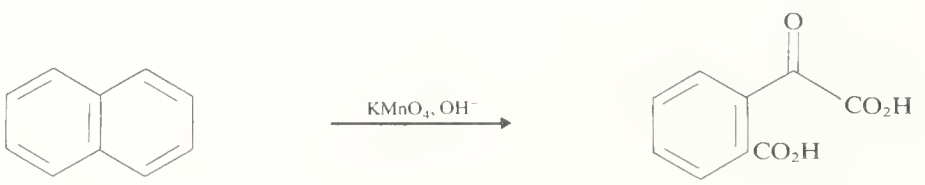
Manganese(VII) is a vigorous oxidizing agent for arenes. A net transfer of five electrons in acidic media results in the production of the manganese(II) ion. In neutral or basic

media, manganese dioxide is formed as a result of a net transfer of three electrons. In many cases, some degradation of the aromatic rings occurs, particularly when using an excess of the permanganate. Careful control can, however, give synthetically useful results, as is indicated by the example in equation (126).

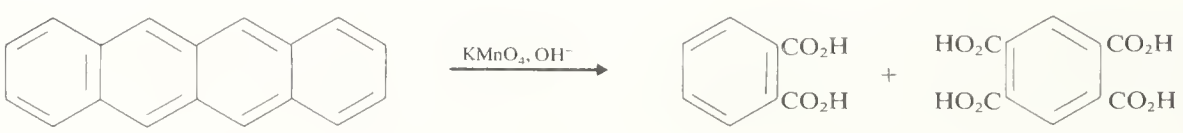


(126)

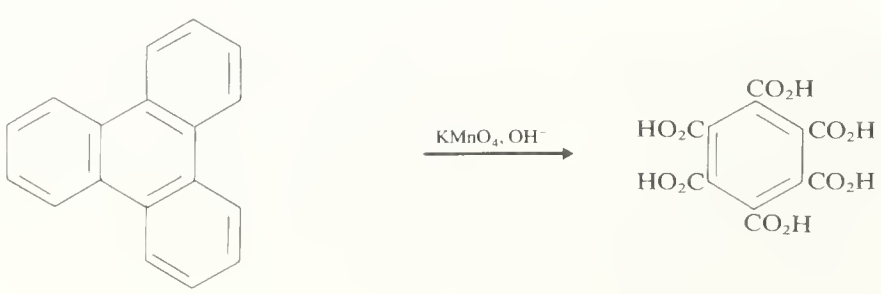
One or more rings are oxidized using permanganate in basic media. For example, naphthalene gives phthalonic acid (equation 127), naphthacene gives mainly phthalic acid together with some pyromellitic acid (equation 128),[128] and triphenylene gives exclusively mellitic acid (equation 129).



(127)



(128)



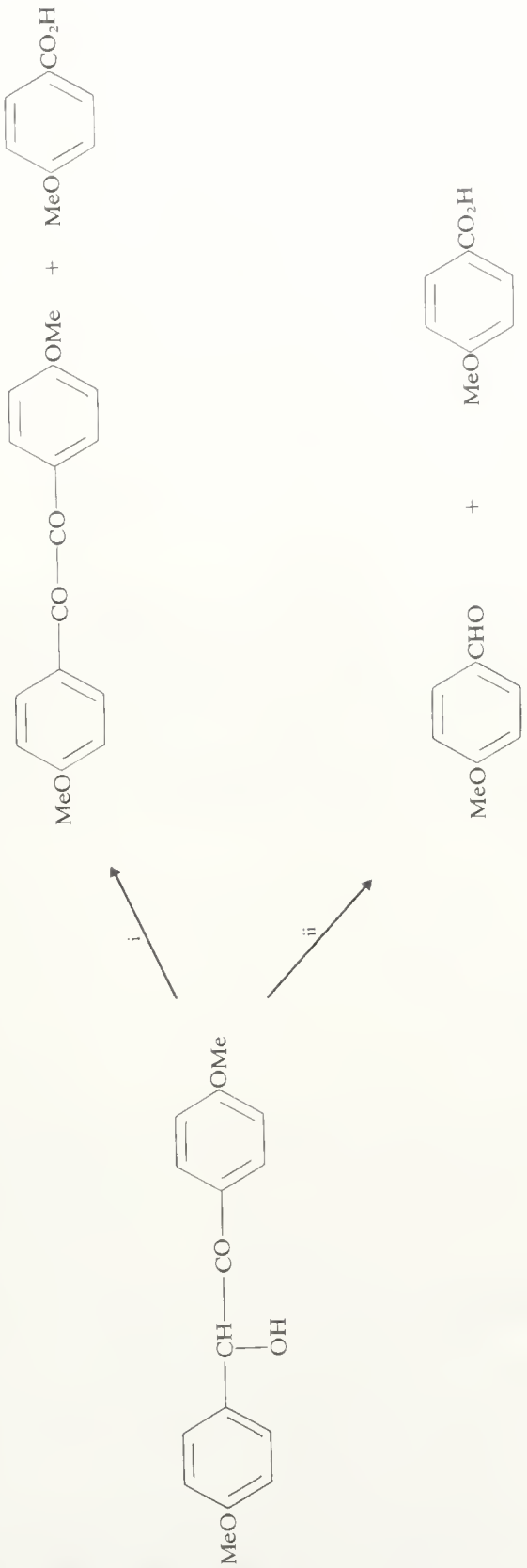
(129)

The primary use of lead(IV) acetate has been in connection with the oxidative cleavage of 1,2-diols, α-hydroxy ketones, and α-hydroxy acids. In its reactions with alkylarenes it normally affords benzylic alcohols, after hydrolysis of the corresponding acetoxy compounds. Thus lead(IV) acetate reacts with 4,4′-dimethoxybenzoin in dry acetic acid at 50 °C to afford the corresponding benzil in 75% yield, together with 4-methoxybenzoic acid in 20% yield. Using aqueous acetic acid results in cleavage, possibly *via* the hydrate of the benzoin, and gives 4-methoxybenzoic acid and 4-methoxybenzaldehyde in 77% and 83% yield, respectively (Scheme 49). The oxidation of acenaphthene gives the benzylic alcohol acenaphthen-7-ol in good yield by hydrolysis of 7-acetoxynaphthene (equation 130).

In certain cases, particularly those with hydrogen on a carbon atom γ to a monohydric alcohol, cyclic products may be obtained. Thus 5-phenylpentan-1-ol affords a 50% yield of 2-benzyltetrahydrofuran, presumably *via* abstraction of γ-hydrogen by the alkoxy radical. Interestingly, none of the possible product from ε-abstraction was detected even though this would involve a benzylic radical.

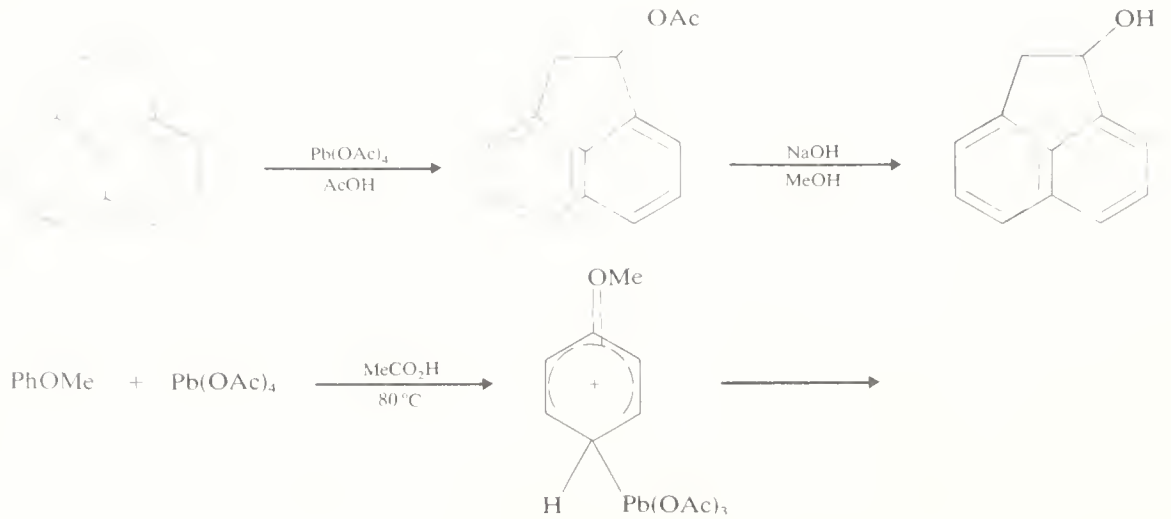
Acetoxylation of ring carbon atoms is restricted to benzene derivatives which contain strong electron-releasing substituents and may proceed by way of electrophilic plumbylation. Anisole affords 4-methoxyphenyl acetate as shown in equation (131). A radical mechanism was suggested for the final step.

Polycyclic arenes lacking substituents are attacked by lead(IV) acetate, usually at a *meso* position. For example, anthracene gives 9-acetoxyanthracene in 70% yield.

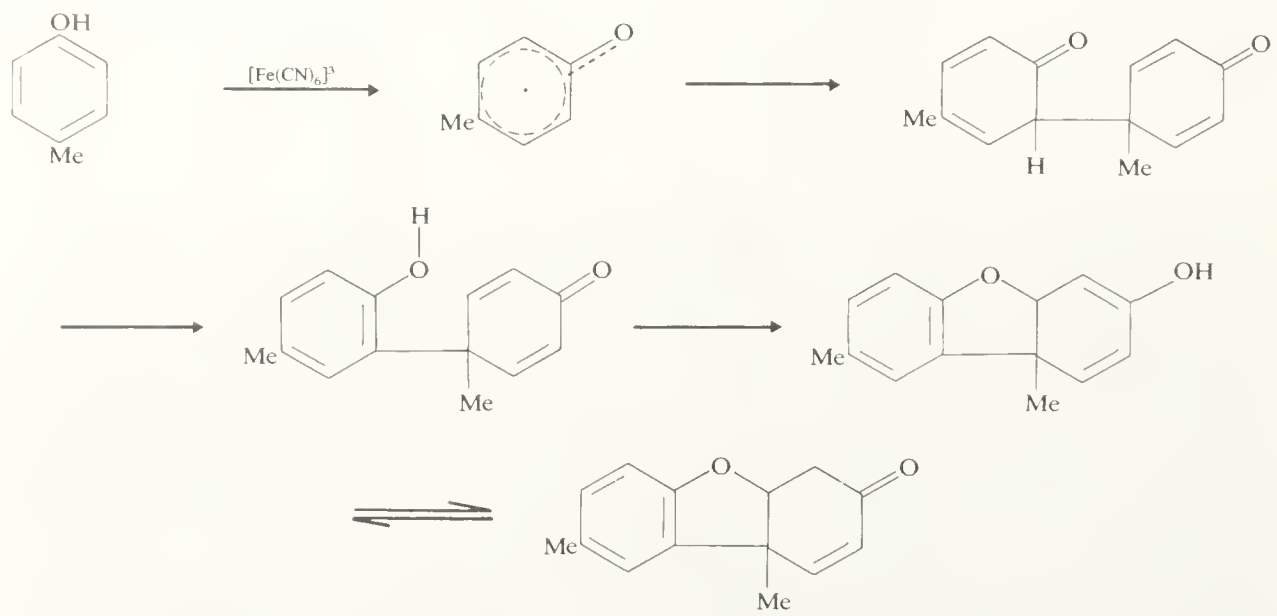


i, $Pb(OAc)_4$, CH_3CO_2H, 50 °C; ii, $Pb(OAc)_4$, CH_3CO_2H, H_2O, 50–55 °C.

SCHEME 49

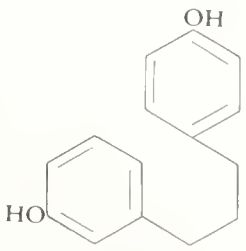


The aromatic rings of phenols react avidly with one-electron oxidants such as iron(III) species since the removal of a hydrogen atom gives a delocalized aryloxy radical. The fate of the radical depends on its precise structure. 2-Naphthol, for example, is converted into 2,2′-dihydroxy-1,1′-binaphthyl, but *p*-cresol gives, in addition to the dimer formed by 2,2′-coupling, Pummerer's ketone which is formed (Scheme 50) by way of 2,4′-coupling. Much use has been made of phenol oxidative coupling in *in vitro* syntheses modelled on biosynthetic reactions.[155] Mild one-electron oxidants must be used.

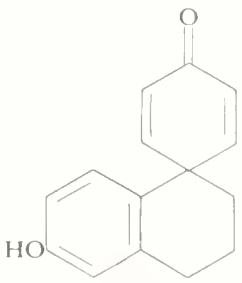


SCHEME 50

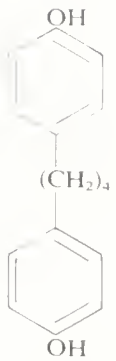
The use of vanadium oxytrichloride in the intramolecular oxidative coupling of diphenols has been used and sometimes gives very good results.[156] For example, the diphenol (**170**) gave the dienone (**171**) in only 4% yield using alkaline ferricyanide whereas 76% yield was obtained using vanadium oxytrichloride. The range of possible coupling products is further exemplified by the oxidation of the diphenol (**172**) to the bisdienone (**173**).[157]



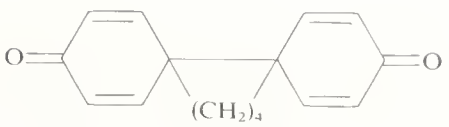
(**170**)



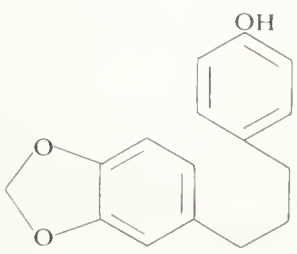
(**171**)



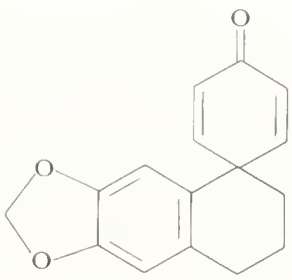
(**172**)



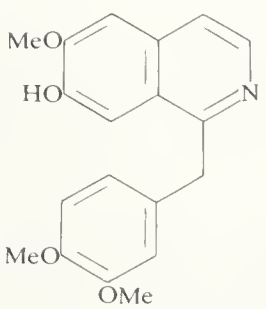
(**173**)



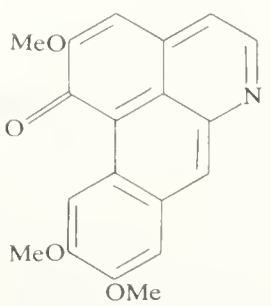
(**174**)



(**175**)



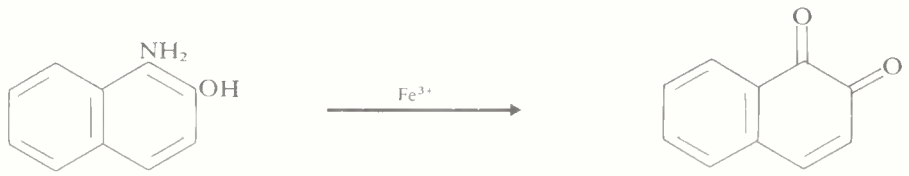
(**176**)



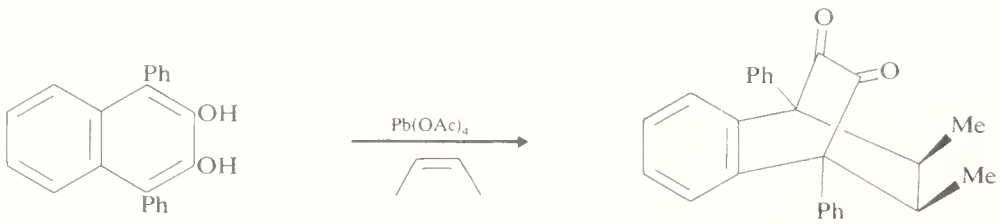
(**177**)

The intramolecular coupling of monophenolic compounds has also been reported. Thus the oxidation of the monophenol (**174**) to the dienone (**175**) in 87% yield was achieved using thallium(III) trifluoroacetate.[158] The coupling of 7-hydroxy-1-benzylisoquinolines has been achieved using a variety of oxidizing agents, including cerium(IV), thallium(III), and chromium(VI). Vanadium oxytrifluoride and molybdenum oxytetrachloride were particularly successful in converting the 1-benzylisoquinoline (**176**) into the quinonoid oxoaporphine (**177**) in 59% and 62% yield, respectively.[159]

We have already seen that a number of polycyclic hydrocarbons may be oxidized to quinones directly. This generalization applies particularly to the formation of 1,4-naphthoquinone, 9,10-anthraquinone, and 9,10-phenanthraquinone. Compounds such as the benzoquinones and 1,2-naphthoquinone are normally prepared by the oxidations of appropriate phenols or amines. Thus 1-amino-2-naphthol hydrochloride is oxidized by iron(III) chloride in aqueous hydrochloric acid and affords 1,2-naphthoquinone in *ca.* 95% yield (equation 132). *p*-Benzoquinone is obtained on an industrial scale by the oxidation of aniline using manganese dioxide in sulphuric acid. The oxidation of phenol by peracetic acid occurs *via* *o*- and *p*-hydroxylation, but whereas the *p*-dihydroxybenzene affords *p*-benzoquinone, catechol (*o*-dihydroxybenzene) is oxidized to hexa-2,4-dienoic acid.[160]



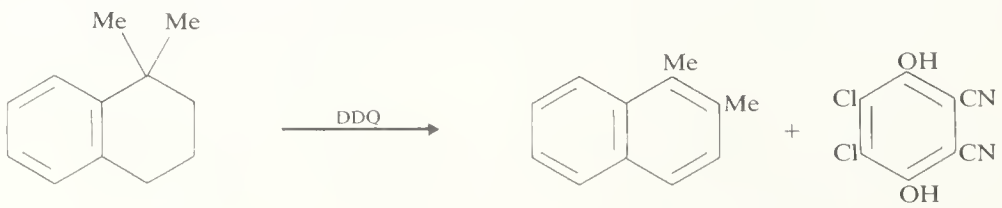
(132)



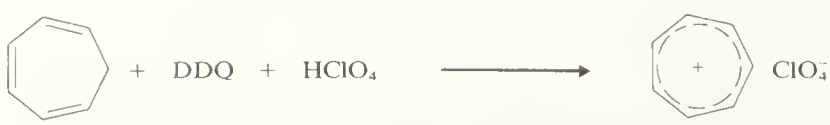
(133)

The oxidation of catechol to *o*-benzoquinone requires the use of carefully controlled conditions. The use of silver(I) oxide suspended in ether, together with a drying agent, is common, although other oxidizing agents such as periodate have been used. 2,3-Naphthoquinone and its derivatives are of considerable interest, but none has been isolated. The oxidation of 1,4-diphenylnaphthalene-2,3-diol with lead(IV) acetate leads to the formation of trimers of the expected quinone. On the other hand, oxidation at low temperature in the presence of trapping agents, such as *cis*-but-2-ene (equation 133) led to the isolation of the expected adduct.[161]

Benzoquinones are oxidizing agents and are particularly useful when electron-withdrawing substituents are present to increase the potential. Both tetrachloro-*o*- and tetrachloro-*p*-benzoquinone find use in this connection. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) is frequently used as a dehydrogenating agent, as is indicated in equations (134)–(136).



(134)

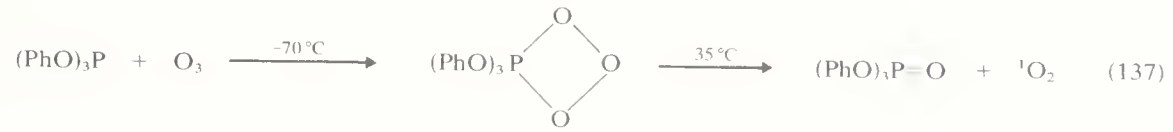


(135)

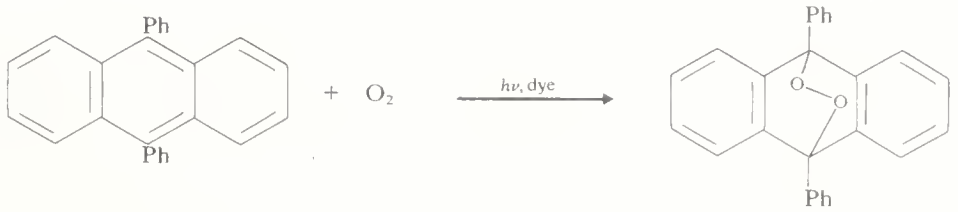
(136)

2.5.12 REACTIONS OF ARENES WITH SINGLET OXYGEN[162]

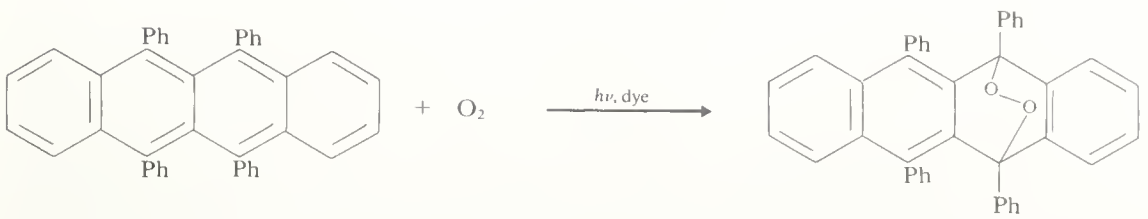
Acenes react with singlet oxygen to afford 1,4-cycloadducts of the Diels–Alder type. Reaction occurs exclusively at *meso* positions but no reaction is observed with, for example, naphthalene and phenanthrene. The classical photochemical method used for the generation of singlet oxygen involves the use of a dye as a sensitizer. The dye absorbs light to give an excited singlet state and then intersystem crossing to the excited triplet occurs. The excited triplet dye then transfers energy to ground-state molecular oxygen (triplet) to afford excited singlet oxygen ($^1O_2$). Singlet oxygen can also be generated by allowing the adduct of triphenyl phosphite and ozone to decompose at −35 °C (equation 137). Similarly, the adduct of singlet oxygen and 9,10-diphenylanthracene can be used to generate singlet oxygen thermally.



(137)



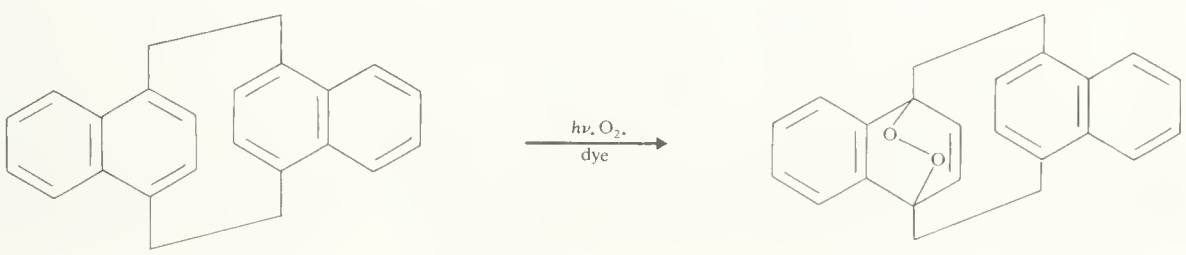
(138)



(139)

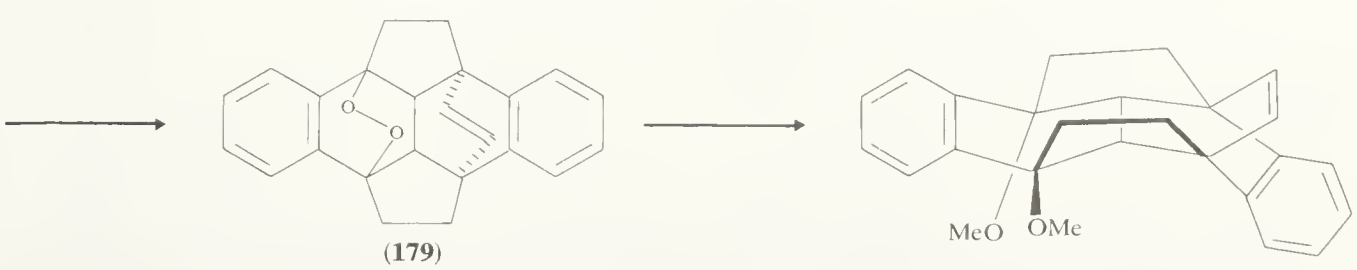
A very large number of photo-peroxidations of anthracene and naphthacene derivatives have been reported. They are all of the type indicated in equations (138) and (139) for 9,10-diphenylanthracene and rubrene, respectively.

anti-[2,2]Paracyclonaphthane reacts with singlet oxygen in methanol (equation 140).[163] The reaction is thought to proceed by an intramolecular Diels–Alder reaction of the initial transannular peroxide (**178**) to give (**179**), which is then solvolysed to the final product.



(**178**)

(140)

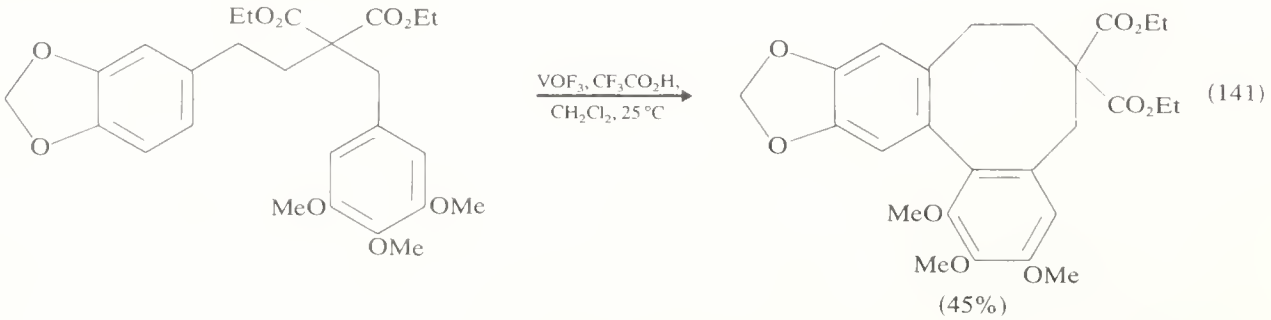


(**179**)

2.5.13 THE PREPARATION OF BI- AND POLY-ARYLS

We have already mentioned certain reactions which lead to the formation of biaryls. Thus in Section 2.5.11 the oxidative coupling of phenols was discussed. Recent work directed towards the oxidative coupling of non-phenolic arenes has been successful. Two approaches will be mentioned. An electrochemical oxidation has been shown to be extremely successful on a preparative scale.[164] Thus the oxidation of (±)-laudanosine, at platinum in a three-compartment cell at 1.1 V in acetonitrile in the presence of sodium carbonate, gave *O*-methylflavinantine in 52% yield. The yield in this reaction was increased to 62% in the presence of bis(acetonitrile)palladium(II) chloride. The success achieved in the oxidative coupling of monophenols using vanadium oxytrichloride prompted its use as the oxidant in the intramolecular coupling of non-phenolic aryl residues. Once again, using (±)-laudanosine as the example, it was shown that (±)-glaucine could be

isolated in 43% yield by carrying out the coupling at −30 °C in a solution in methylene chloride containing fluorosulphuric acid and trifluoroacetic acid.[165] This method has been used in a key stage (equation 141) in a synthesis of the anti-leukemic biphenyl lignan lactone precursor steganone.[166]

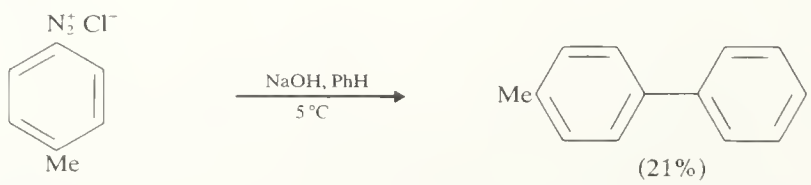


(141)

A number of classical methods are available for the preparation of biaryls. These will be briefly reviewed, paying particular attention to variations which have been introduced recently. That constitutionally symmetrical biaryls are prepared by the Ullmann reaction and constitutionally unsymmetrical biaryls by the Gomberg–Bachmann–Hey reaction is a facile conclusion which is not entirely justified.

The replacement of the diazonium group in arenediazonium salts by an aryl residue under alkaline conditions is known as the Gomberg–Bachmann–Hey reaction.[167] The intramolecular version is known as the Pschorr reaction.[168] The mechanistic details are discussed in Chapter 2.8.

Diazotization of the arylamine may be carried out in the usual way (Chapter 6.3 and Chapter 6.5), except that a minimum amount of water is used. The solution is made basic using sodium hydroxide and/or sodium acetate and the cold concentrated aqueous solution is efficiently stirred with a liquid aromatic compound. The yields obtained are frequently rather poor (equation 142), but, since arylamines are usually available in large quantities, this reaction has found widespread use. The normal reaction involves the formation of the *p*-methylphenyl radical which is formed from the anhydride (**178**) (equation 143).[169]



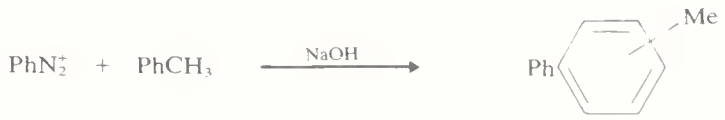
(142)

(143)

A useful variant involves the aprotic diazotization of the arylamine using an alkyl nitrite such as pentyl nitrite and using the arene which is to be arylated as the solvent.[170] 4-Methoxybiphenyl was prepared in this way in 33% yield. Other compounds containing N—N bonds have been used as precursors of aryl radicals and these include triazenes, azo compounds, and *N*-nitrosoamides. With *N*-nitrosoamides the reactions are sometimes complex (see Chapter 2.8),[171] and can lead to products derived from aryl radicals and arynes. The intervention of aryl cations has also been implicated.[172]

Because the reaction normally involves aryl radicals the directional effects of substituents on the arene co-reactant are not those discussed in Section 2.5.7. Almost all substituents tend to promote predominant attack at *ortho* and *para* positions. It is because mixtures of products are invariably obtained (equation 144) that the arene to be substituted should be kept as simple as possible. Clearly, one can use arenes that are 'symmetrically' substituted.

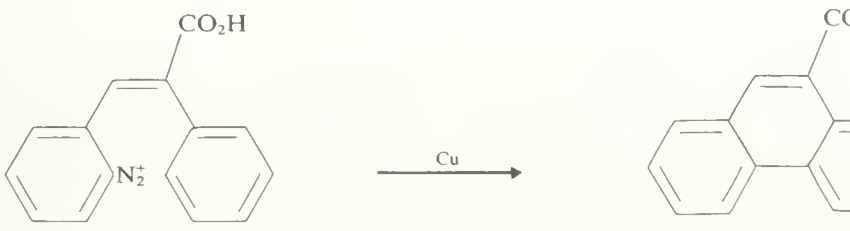
The Pschorr reaction, as originally devised, was applied to the synthesis of phenanthrene derivatives in which the key step is that shown in equation (145). It has been



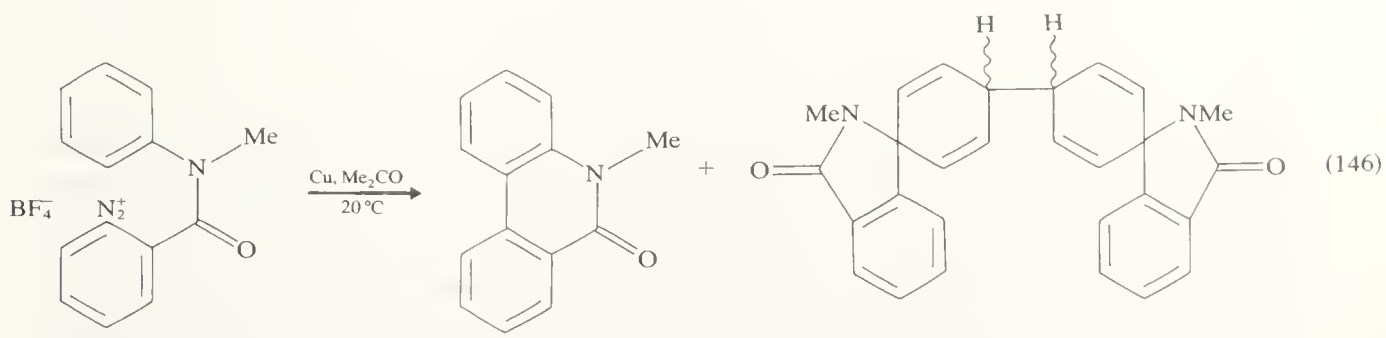
(144)

o-, 66%; *m*-, 19%; *p*-, 14%

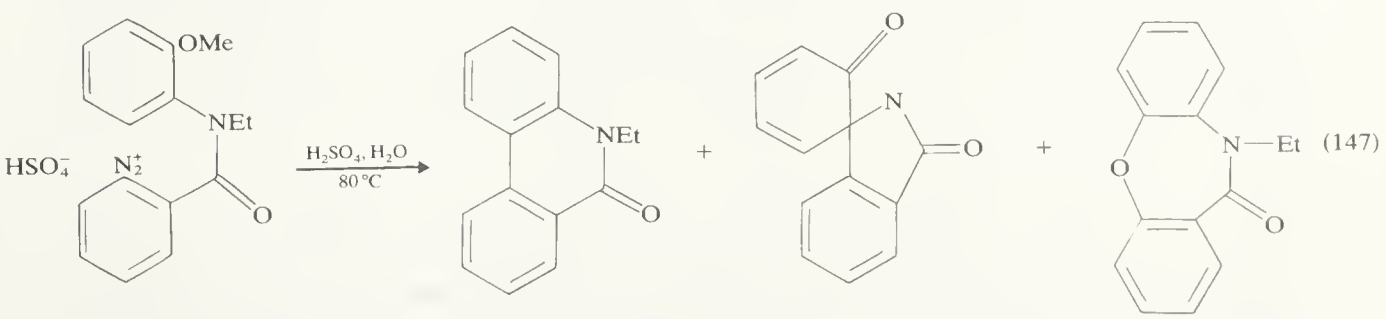
extended for example to the synthesis of fluorenone and its derivatives and to the preparation of n-alkylphenanthridones (equation 146). Interesting results involving spirodienyl radicals have been obtained.[173] The nature of the products obtained from the diazotization of arylamines frequently depends upon the precise experimental conditions used. The results using 2-amino-*N*-alkylbenzanilides are no exception. For example, the thermal decomposition at 80 °C of an aqueous solution of the diazonium sulphate prepared from 2-amino-2′-methoxy-*N*-ethylbenzanilide gave the results shown in equation (147). These conditions favour a heterolytic mechanism. On the other hand, the decomposition of the diazonium salt by the addition of copper powder in acetone at 20 °C, conditions which favour a homolytic mechanism, give rise to two major products (equation 146). The decomposition of the diazonium salt derived from 2-amino-*o*-terphenyl gives triphenylene in good yield (equation 148). The best yield (94%) was obtained under acidic conditions and this implicates the intermediacy of an aryl cation.[174]



(145)



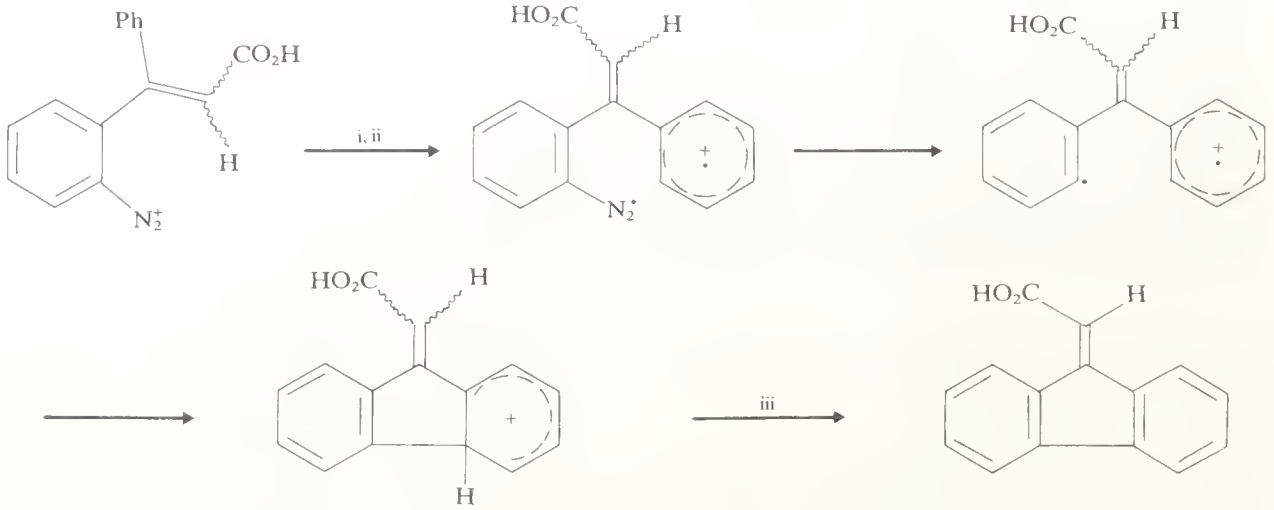
(146)



(147)

(148)

The photochemical equivalent of the Pschorr cyclization has also been studied using *N*-alkyl-2-iodobenzanilides and is, in broad outline, very similar to the process outlined in equation (146). Once again two basic mechanisms, the one involving an aryl cation and the other an aryl radical, have been invoked to explain the Pschorr reaction. An alternative, intramolecular one-electron redox mechanism has been suggested recently.[175] Thus, for example, the electrolytic reduction of diazonium salts provides a useful insight into this problem. The decomposition of diazonium salts derived from 2-aminobenzophenone in the presence of iodide ion leads mainly (95%) to 2-iodobenzophenone with little fluorenone being produced. On the other hand, in a case which is sterically more favourable (Scheme 51), the major product (90%) is the fluorene derivative.

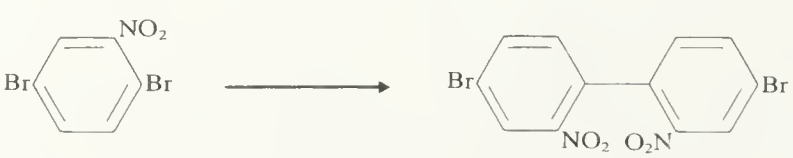


i, e^-; ii, $Pr_4N^+ I^-$; iii, $-H^+$.

SCHEME 51

The Ullmann reaction in which two molecules of aryl halide react with finely divided copper to form a biaryl and copper(II) halide has been used to prepare 'symmetrical' and 'unsymmetrical' biaryls, to effect ring closures, and to prepare oligophenylenes.[176] The method is evidently related to a series of reactions in which copper is used as a catalyst or where organocopper compounds are produced or are presumed intermediates.

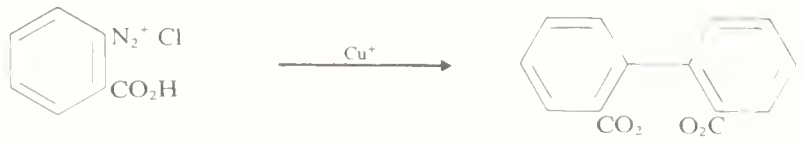
Strong electron-withdrawing groups such as nitro and methoxycarbonyl, particularly when they are present in an *ortho* position, markedly activate an aryl halide towards the Ullmann reaction. Thus, for example, 2,2′-dinitrobiphenyl can be prepared in good yield from *o*-chloronitrobenzene, and 2,5-dibromonitrobenzene reacts with copper in *N*,*N*-dimethylformamide to afford 4,4′-dibromo-2,2′-dinitrobiphenyl in 76% yield (equation 149).



(149)

The presence of substituents such as hydroxy, amino, and carboxy, as well as the presence of bulky substituents *ortho* to the halogen, inhibit or prevent the reaction from proceeding in the normal way. The protection of the hydroxy and carboxy groups as the methyl ethers and esters, respectively, does not pose a major problem since the protecting group can be removed.

It is interesting to note here that biphenyl-2,2′-dicarboxylic acid may be prepared in *ca.* 80% yield by reducing an aqueous solution of benzene diazonium-2-carboxylate hydrochloride with copper(I) in aqueous ammonia (equation 150). This reaction works efficiently with a number of other arylamines.



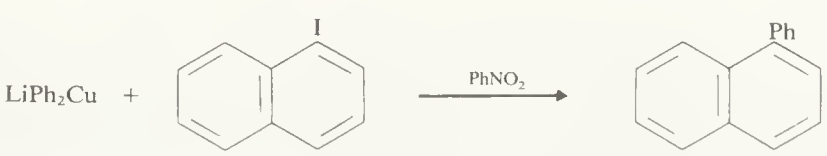
(150)

An analysis of the results obtained in a large number of attempted preparations of 'unsymmetrical' biaryls leads to the conclusion that the best yields are obtained when one of the aryl halides is activated and the other is relatively unreactive. It is well known that the duplication of yields is especially difficult in Ullmann reactions. The major problem is probably connected with the efficiency of stirring in the two-phase reactions. 2-Methoxy-2′-nitrobiphenyl, which is a useful intermediate in the preparation of the Meerwein reagent *O*-methyldibenzofuranium fluoroborate,[177] is prepared from *o*-bromonitrobenzene and *o*-iodoanisole in 58% yield (equation 151).[178] Yields as high as 80% have been obtained in this reaction by using a copper stirrer which sweeps the whole volume of the reaction vessel.[179]

(151)

Although a mechanism involving radicals on the metal surface has been postulated in order to explain the results obtained in Ullmann reactions, the present view is that organocopper compounds are involved.[180] The slow step in the reaction would normally involve the displacement of the halogen from the second molecule of the aryl halide. This suggests that the formation of organocopper compounds by alternative routes, followed by reaction with the aryl halide, should constitute the best procedure for carrying out mixed Ullmann reactions. The experimental facts lend some support to this suggestion, but rapid halogen–metal interconversion does in some cases complicate the picture. Pentafluorophenylcopper can be prepared by the reaction of copper(I) bromide with pentafluorophenylmagnesium bromide, and the copper reagent does give 2,3,4,5,6-pentafluorobiphenyl in 87% yield (equation 152) after reaction with iodobenzene.[181] On the other hand, the reaction of phenylcopper with [4-^{2}H]iodobenzene gave a statistical distribution of deuterium in the biphenyl which was formed. These results suggest that, as is the case with organolithium compounds, the precise position of an equilibrium between the two possible arylcopper compounds and the two aryl halides will depend upon electronegativity differences in the aryl residues.

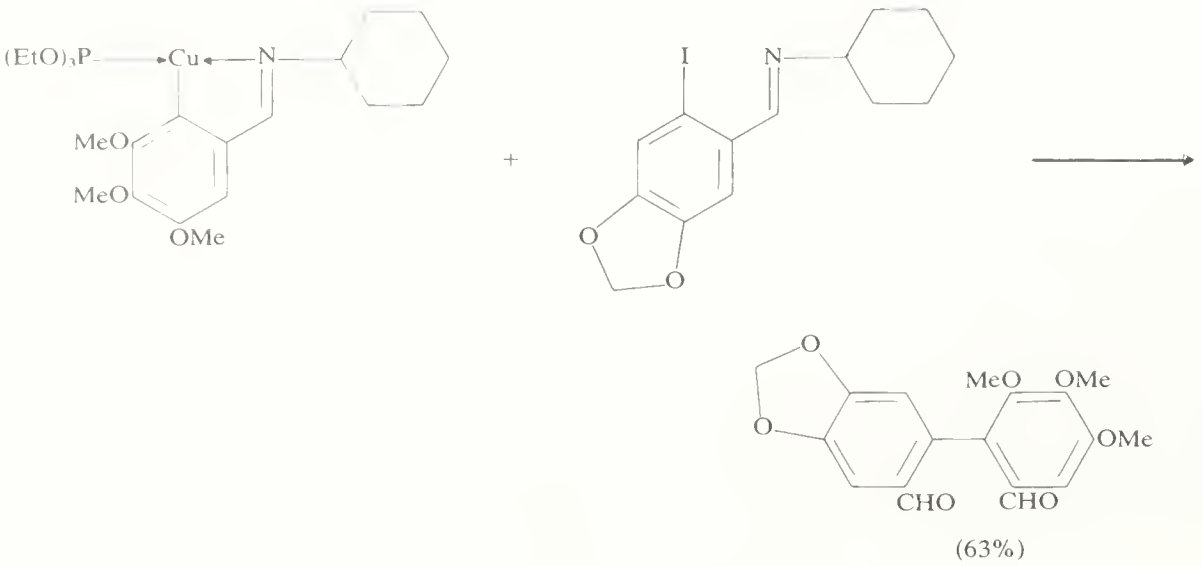
$$C_6F_5Cu + C_6H_5I \longrightarrow C_6F_5—C_6H_5 \qquad (152)$$



(153)

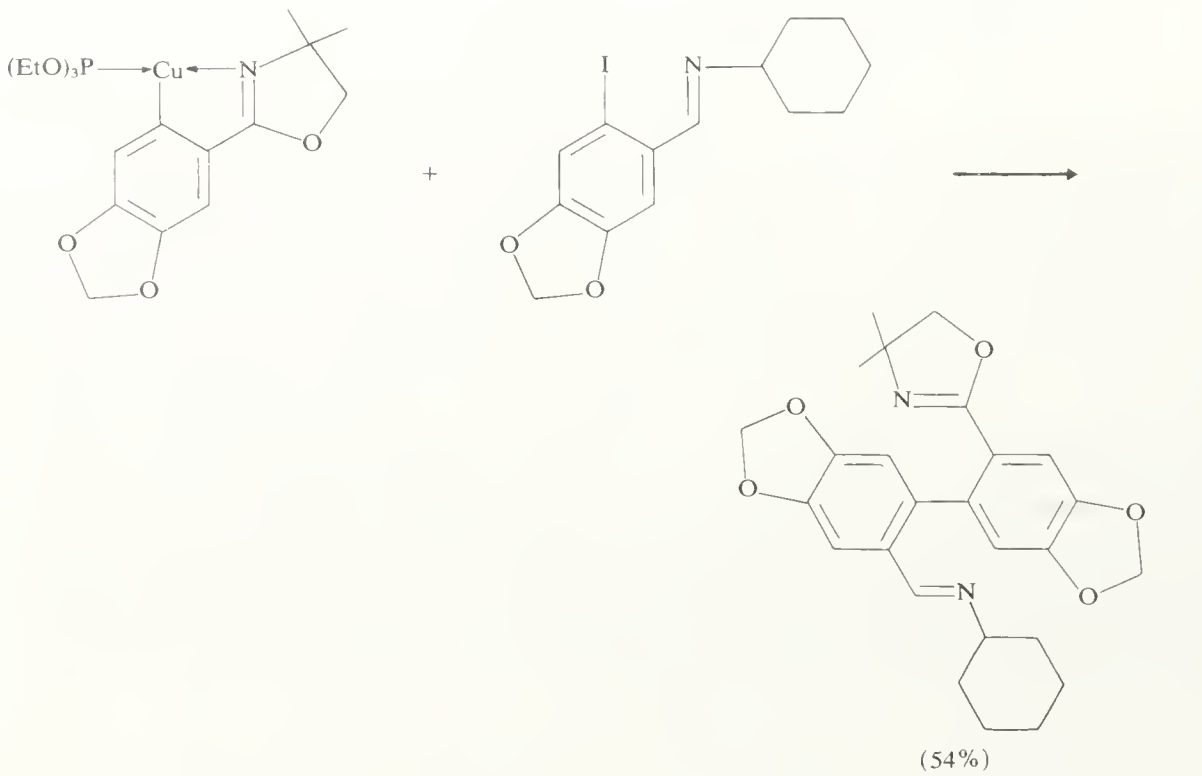
Lithium diarylcuprates also react with aryl iodides in ether by competing metal–halogen exchange and coupling. High yields of coupled products can be obtained by the oxidation of the equilibrium mixture either with oxygen or nitrobenzene. Lithium diphenylcuprate gives 1-phenylnaphthalene in 90% yield, as shown in equation (153).[182]

Biaryls have also been prepared in good yield by the displacement of the methoxy group in 2-(*o*-methoxyphenyl)oxazolines by means of Grignard and organolithium reagents,[183] and this method has been extended to reactions involving arylcopper species and the displacement of halide.[184] The presence of an aldimine function *ortho* to copper can be replaced by an oxazolinyl residue and hence affords biaryls with protected aldehyde or ester or carboxylic acid groups. Two examples are given in equations (154) and (155), which indicate the scope of the method.



(154)

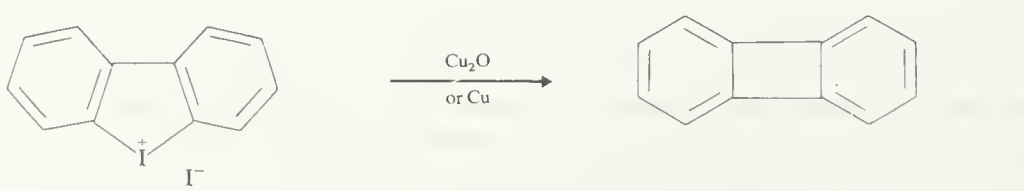
(63%)



(155)

(54%)

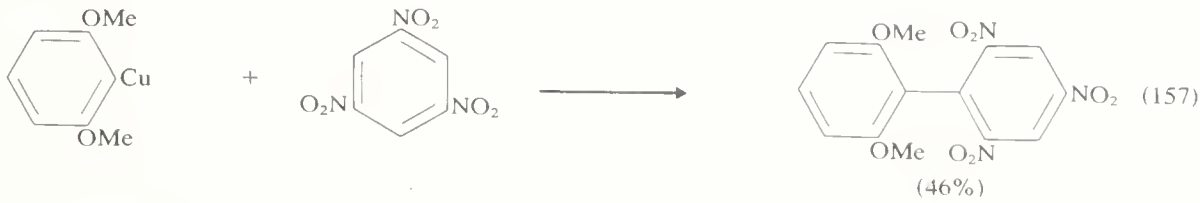
The early work[185] on the preparation of biphenylene and its derivatives from a 2,2′-di-iodobiphenyl or biphenyl-2,2′-yliodonium iodide suggested that copper(I) oxide was a necessary reagent and that the reaction differed in mechanism and scope from the Ullmann reaction. It is now known that copper can be used and that, in some examples, better yields are then obtained (equation 156).[186]



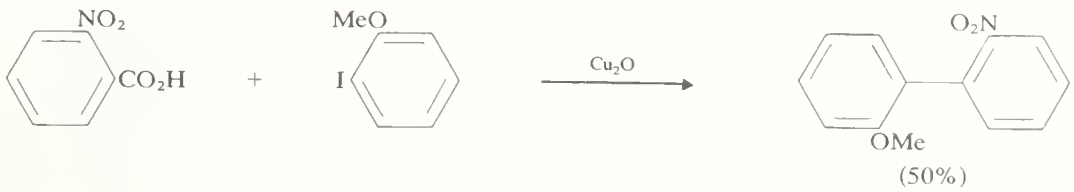
(156)

Copper-promoted arylations, *e.g.* equation (157), have been studied in some detail and are sometimes more useful than conventional Ullmann reactions.[187] Decarboxylative coupling in the presence of copper(I) oxide is evidently related (equations 158 and 159),

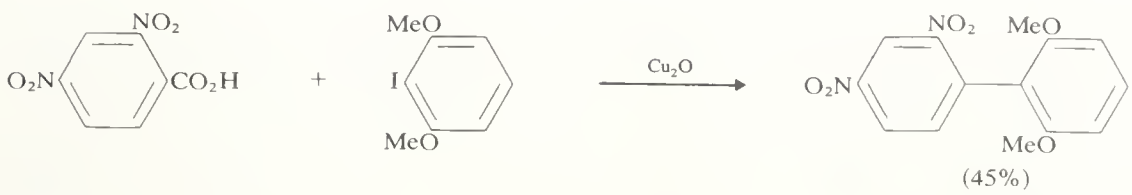
but we should note that the biaryl may not be formed exclusively by linking at the position from which the carboxyl group is displaced.[188]

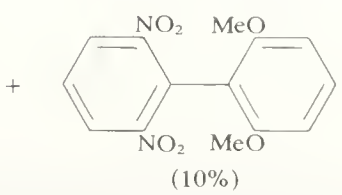


(157)



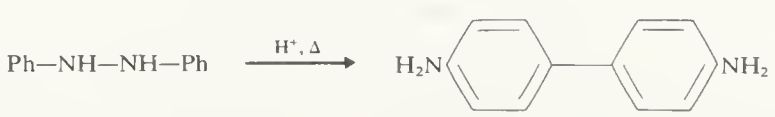
(158)



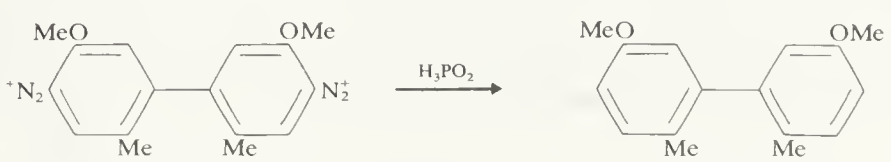


(159)

Two other reaction types which result in the formation of an aryl–aryl bond are worthy of a brief mention at this point. The first of these is the benzidine rearrangement (see Chapter 6.5).[189] The advantage of this reaction (equation 160) is that it places amino groups at the 4,4′-positions in the biphenyl which can be replaced by other functional groups *via* the tetrazonium salts. The amino groups can, of course, be removed (equation 161).

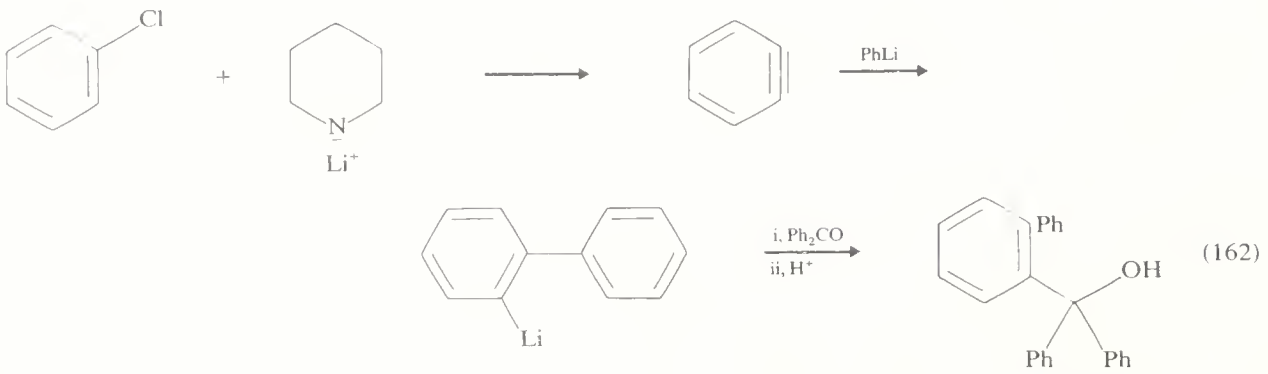


(160)

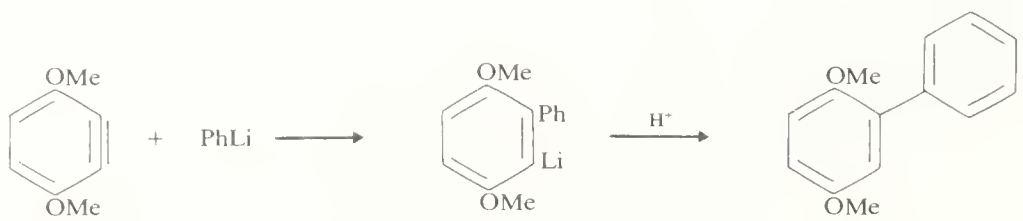


(161)

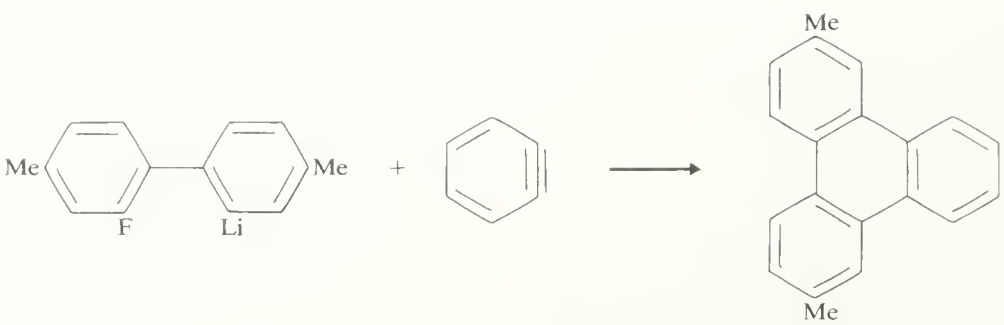
The second reaction type involves the addition formally of an aryl carbanion (usually a Grignard or an organolithium reagent) to an aryne (see Chapter 2.8).[116a] When benzyne is generated from an aryl halide using phenyl-lithium the addition of the latter to the aryne cannot be completely suppressed by the addition of other nucleophiles. The initial product, a 2-lithiobiphenyl, can be intercepted by electrophiles (equations 162 and 163). The reaction with a suitable aryl-lithium can be synthetically useful, as in the synthesis of triphenylenes, *e.g.* equation (164).



(162)



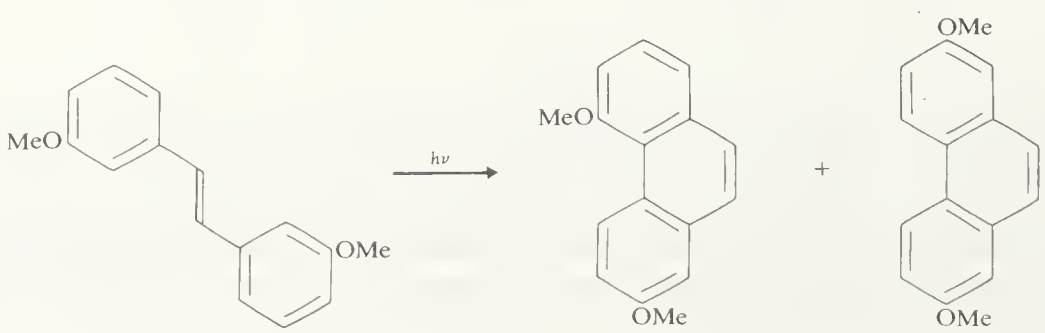
(163)



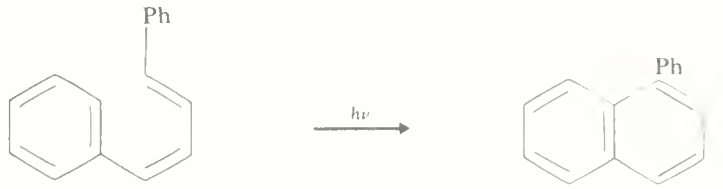
(164)

2.5.14 INTRAMOLECULAR PHOTOCYCLIZATIONS LEADING TO POLYCYCLIC ARENES[144a,190]

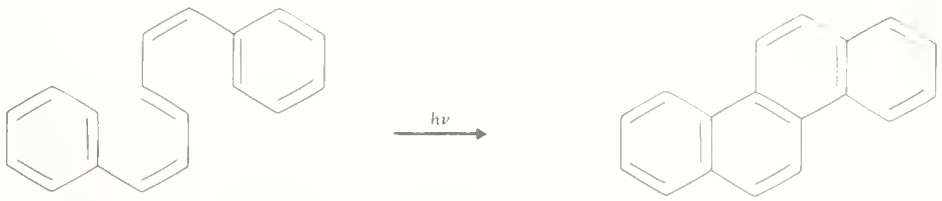
The photocyclodehydrogenation of *cis*-stilbene which gives phenanthrene has been known for over 40 years. The photoisomerization of *trans*- to *cis*-stilbenes and *vice versa* produces an equilibrium mixture and hence for photocyclization purposes either isomer is a satisfactory precursor of the phenanthrene. Steric factors are important, as is evident from the results obtained using 3,3′-dimethoxystilbene (equation 165). The absence of 4,5-dimethoxyphenanthrene illustrates this point. Stilbene analogues which have low values for the free-valence indices, for the first excited state, at the atoms between which the new bond would form on cyclization, fail to photocyclize. The value of $\sum F^*$ must be greater than unity. Similarly, substituents, such as acetyl and nitro, which promote a high degree of intersystem crossing also prevent photocyclization. This type of cyclization has been extended to give other ring systems. For example, the irradiation of 1,4-diphenylbuta-1,3-diene and 1,6-diphenylhexa-1,3,5-triene give 1-phenylnaphthalene (equation 166) and chrysene (equation 167), respectively.



(165)

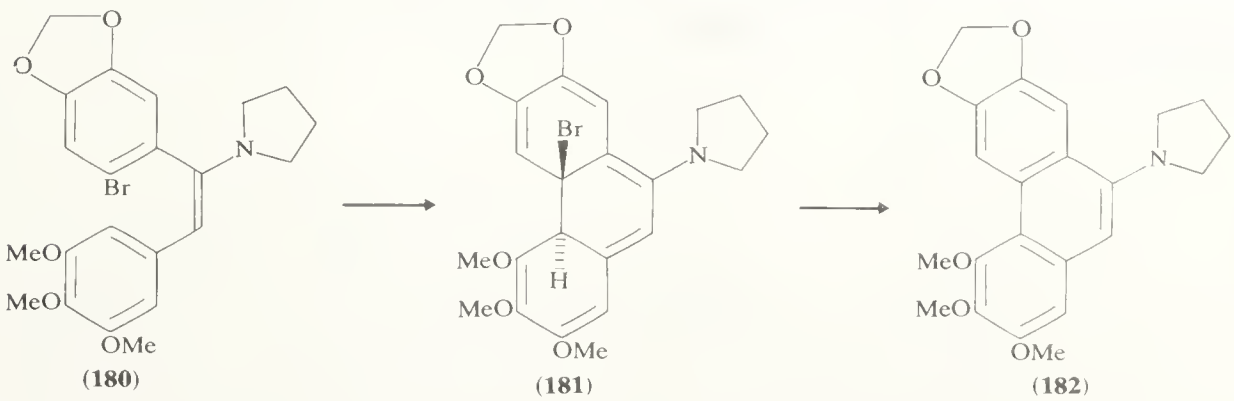


(166)



(167)

We mentioned in Section 2.5.12 the photochemical equivalent of the Pschorr cyclization in connection with the preparation of phenanthridones. 2-Iodostilbenes do photocyclize to phenanthrenes but the ready photolysis of the carbon–iodine bond suggests that this reaction is not related mechanistically to our present considerations. On the other hand, the higher bond strength of the aryl C—Br bond suggests that the photocyclization of 2-bromostilbenes may be related. Thus the photolysis of the stilbene derivative (**180**) affords the phenanthrene (**182**) by elimination of hydrogen bromide from the presumed intermediate (**181**) (equation 168).[191]

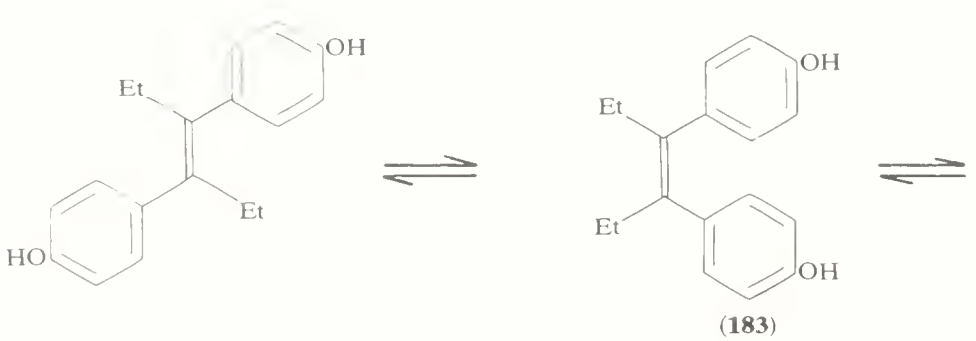


(168)

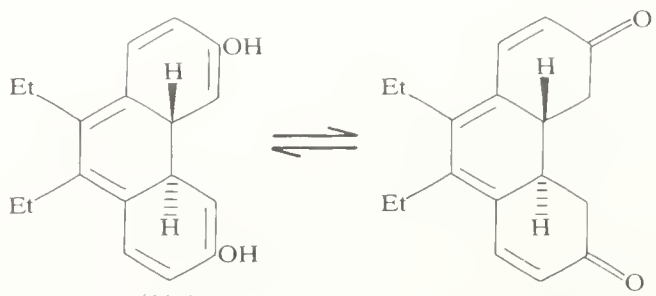
Although the stereochemistry of the enamine was not established, evidently the (*E*)-diastereoisomer shown in (**180**) was the one involved. We should break off our discussion at this point in order to establish the stereochemical convention which defines (**180**) as *E* (German, entgegen, across) for the *seqtrans* isomer. Stereoisomers which do *not* bear a mirror image relationship to each other are evidently not enantiomers. They are therefore diastereoisomers (see Part 1). The sequence rules[192] apply to diastereoisomers just as they apply to enantiomers. The carbon atom at one end of the double bond in (**180**) is substituted by a hydrogen atom and an aryl residue; the aryl group takes precedence. The carbon atom at the other end of the double bond is substituted by an amino group and by an aryl residue; the amino group takes precedence. The diastereoisomer (**180**) is therefore sequence-*trans*. The other diastereoisomer (not shown) would be sequence-*cis* (*seqcis*) and the symbol *Z* (German, zusammen, together) would then be used.

Although the conversion of stilbene into phenanthrene is thought to proceed by a conrotatory cyclization, to afford initially the *trans*-4a,4b-dihydrophenanthrene, the intermediate has not been isolated. Hydrogen is not eliminated and so an oxidant must be present. The oxidants used include oxygen, sulphur, and iodine. The photocyclization of (*Z*)-α,α′-diethyl-stilbene-4,4′-diol (**183**) does afford the dihydro derivative (**184**), which does not suffer oxidation because of the particular stability of the diketone (**185**) (equation 169).[193]

The photocyclization of the three isomeric distyrylbenzenes proceeds as expected. Thus

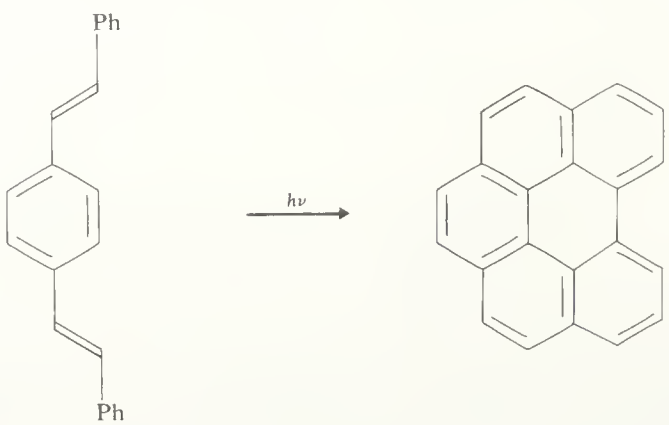


(**183**)

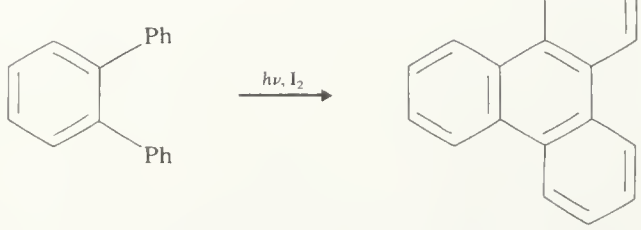


(**184**) (**185**) (169)

1,4-distyrylbenzene gave benzo[*g*,*h*,*i*]perylene (equation 170) on irradiation. The ethylenic portion of the stilbene may be part of, for example, a benzene ring, as is exemplified by the conversion of *o*-terphenyls to triphenylenes, *e.g.* equation (171), in the presence of iodine.



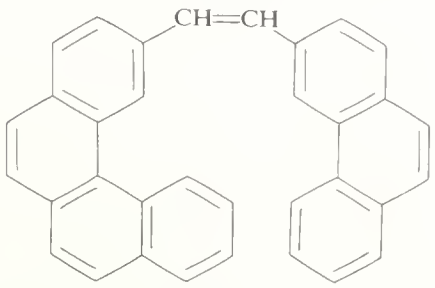
(170)



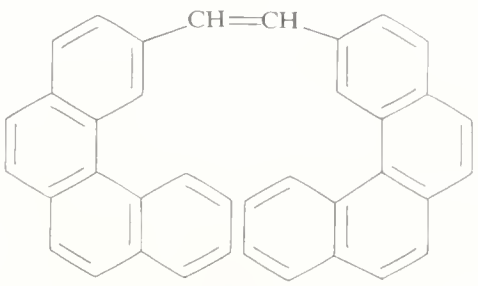
(171)

The use of the photocyclization of stilbene analogues in the preparation of helicenes confirms the synthetic potential of this general reaction.[194] The name 'helicene' is used to describe the benzologues of phenanthrene in which the additional *ortho* condensed rings give rise to a regular cylindrical helix because of the molecular overcrowding which makes a planar molecule impossible, *e.g.* octahelicene (**187**). The first helicene, hexahelicene, was prepared over 20 years ago by a classical 12-stage synthesis starting with 1-naphthaldehyde.[195] The most significant advance in helicene syntheses involved the realization that 1,2-diarylethylenes could be satisfactory precursors. Results obtained about ten years ago showed that hepta-, octa- (**187**), and nona-helicenes could be prepared by this method. An alternative naming of these last three compounds describes them as [7]-, [8]-, and [9]-helicene.

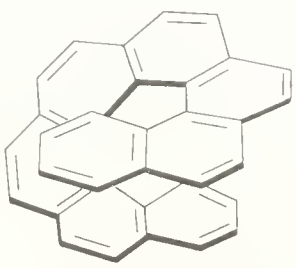
Double helicenes can also be prepared by photocyclizations, and are of two distinct types. They can have either the same or opposite helicity. In the majority of cases the helicene is the only cyclized product obtained. The photocyclization of the compound (**186**) gave [8]helicene (**187**), and (**188**) gave [9]helicene. A rare exception is indicated in equation (172) in which the olefin (**189**) gave the polycyclic arene (**190**) in 67% yield together with [7]helicene in 20% yield.



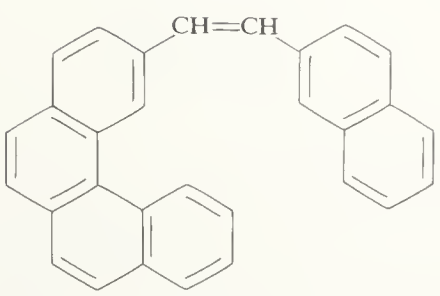
(**186**)



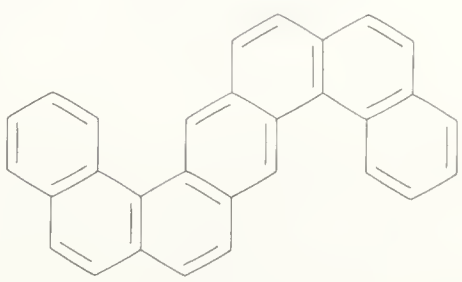
(**188**)



(**187**)



(**189**)



(**190**)

(172)

Similarly, the photocyclization of 8-phenyldi-β-naphthylethylene affords initially 1-phenyl[5]helicene and 10-phenylnaphtho[1,2-*a*]anthracene. A third product, benzocoronene (**191**), was isolated in 42% yield and arises by the photocyclization of 1-phenyl[5]helicene, which involves the rearrangement of the phenyl group shown in Scheme 52.[196]

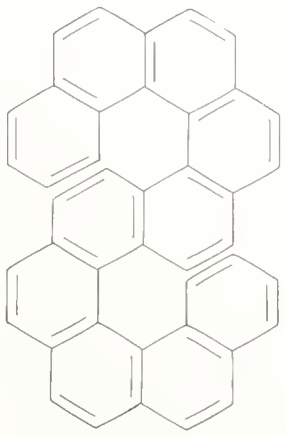
The double helicene (**192**) was prepared by the bis-photocyclization of 2,6-bis-(3-phenanthrylethenyl)naphthalene and [13]helicene (**193**) from 3,6-bis-(3-benzo[g]phenanthrylethenyl)phenanthrene. [14]Helicene has also been prepared.

The photocyclization reactions of 1,2-diarylethylenes can, in principle, give rise to a number of constitutional isomers, *e.g.* equation (172). Double cyclizations are more complex. The photocyclization used in the preparation of [13]helicene could have given ten isomers. ^{1}H N.m.r. spectroscopy has played a particularly important role in determining the structures of the photocyclization products.

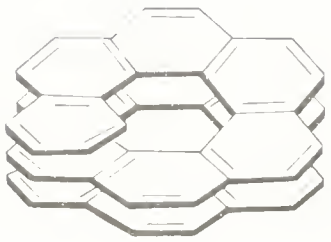
The double helicene (**192**) is capable of existing as a *meso*-form (**194**) and (+)- and (−)-rotatory forms (**195**) and (**196**). Helicity is a special case of chirality.[192] The unsubstituted 'all-benzene-helicenes' are chiral in which a right- or left-handed helicity associates a right- or left-handed turn with axial translation away from the observer. The unsubstituted 'all-benzene-helicenes' are also palindromic. If the helix is identified as left-handed,

i, *hν*; ii, I_2

SCHEME 52

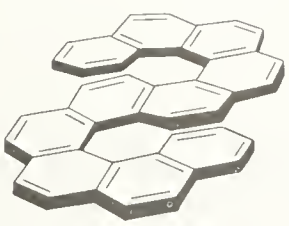


(**192**)

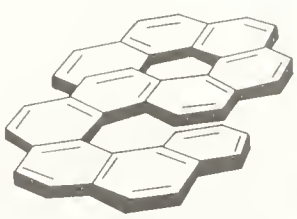


(**193**)

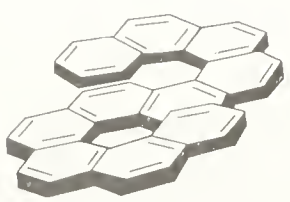
it is designated as 'minus' and denoted by *M*. The reverse case is designated as 'plus' and denoted by *P*. The determination of the absolute configurations of a number of helicenes has been achieved both by means of chemical correlations and by the use of physical methods such as X-ray diffraction and long-wavelength optical activity. All of the studies lead to the conclusion that the (−)-rotatory isomers belong to the *M*-series. The same relative helicity is shown by optical rotatory dispersion and circular dichroism studies.



(**194**)



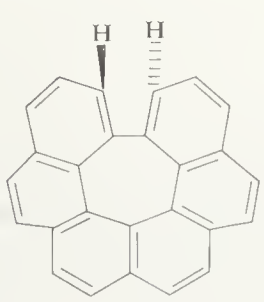
(**195**)



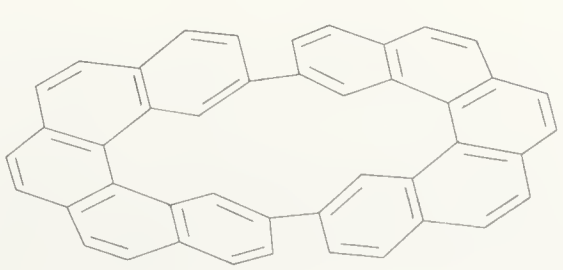
(**196**)

[7]Helicene has been obtained in an optically active form by spontaneous resolution; one of the crystals was optically pure $\{[\alpha]_D^{20} = 6200 \pm 200°\}$! High-performance chromatography has been used to obtain the rapid and complete resolution of the helicenes on columns containing optically active charge-transfer agents such as 2-(2,4,5,7-tetranitro-9-fluorenylideneamino-oxy)propionic acid.[197] Asymmetric syntheses have been achieved using a chiral substituent in the precursor and also using circularly polarized light. Kinetic data are available for the thermal racemization of a number of helicenes. It is believed that the thermal racemization is a conformational process and therefore leads one to the conclusion that the helicenes are considerably more flexible than was at one time thought. π-SCF force-field calculations are in accord with these data.[198]

Two interesting compounds which are related to the helicenes have been prepared recently. They are 1,16-didehydro[6]helicene (**197**),[199] which is probably saddle-shaped, and the bis-2,13-didehydro[5]helicene (propellicene) (**198**), which is shaped like a two-bladed propeller.[200] Both of these compounds are chiral.



(**197**)

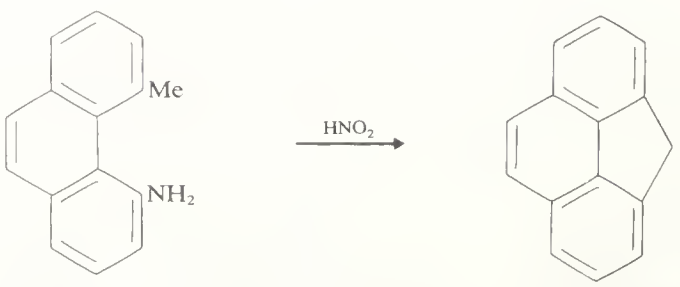


(**198**)

2.5.15 INTRAMOLECULAR CYCLIZATIONS OF DISUBSTITUTED ARENES

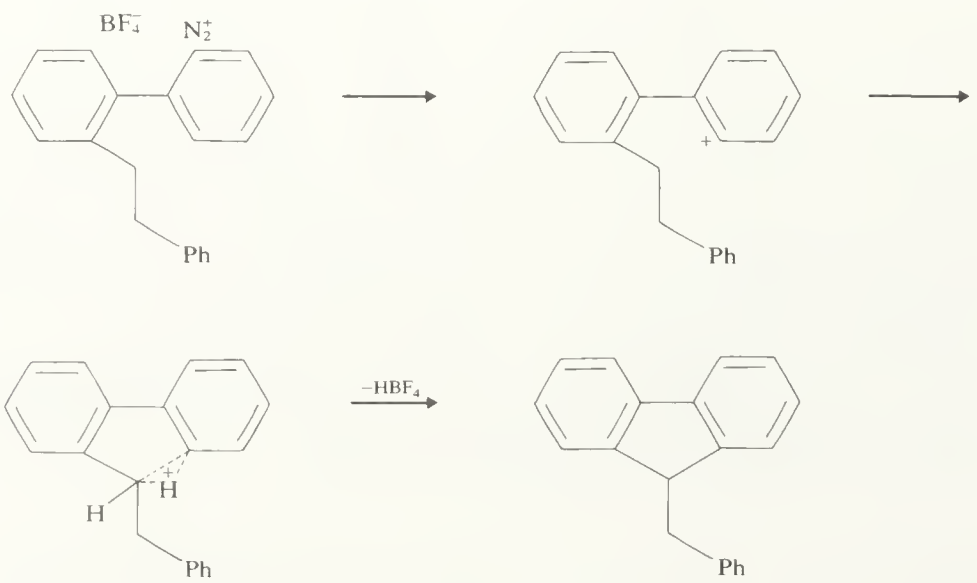
The close spatial interactions between substituents in the 2,2′-positions in biaryls lead to a large number of reactions.[201] Some of these reactions have been dealt with previously and a number of others which lead to the formation of heterocyclic rings are outside the scope of the present chapter. We shall concentrate our attention on the Mascarelli reaction, in which a 2-alkylbiphenyl-2′-yldiazonium salt is converted into a fluorene derivative, and intramolecular cyclization reactions of arylacetylenes.

The Mascarelli reaction gives good yields of fluorene derivatives with a wide range of 2-alkylbiphenyl-2′-yldiazonium salts.[201,202] The reaction is particularly successful if alkyl groups are absent from the 6,6′-positions, difficult with 6-monosubstituted compounds, and fails with 6,6′-disubstituted 2-alkylbiphenyl-2′-yldiazonium salts. Evidently a planar intermediate — or transition state — is involved. This latter point is emphasized by the formation of 4,5-methanophenanthrene in 50% yield from 4-methyl-5-aminophenanthrene (equation 173).[203]



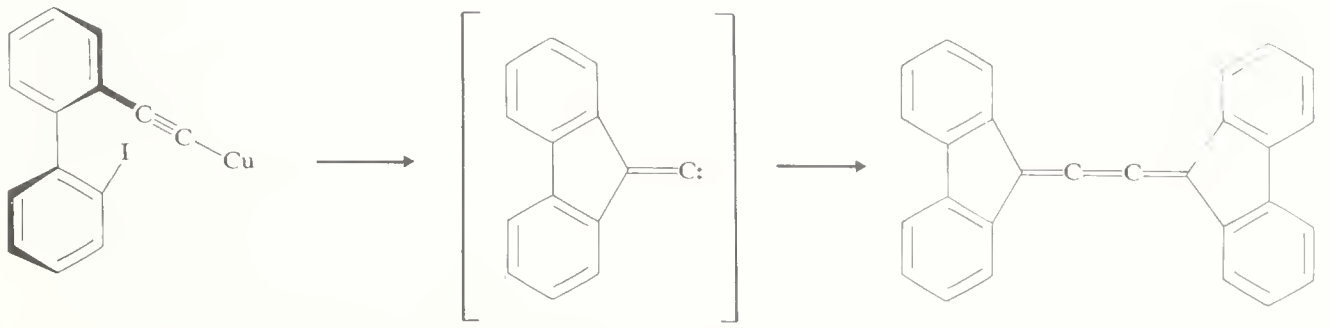
(173)

A number of mechanistic proposals have been made, including the intervention of arylcarbenes and benzyl cations, formed by 1,5-hydride shifts. It is of interest to note that 2-β-phenylethylbiphenyl-2′-yldiazonium salts cyclize to give exclusively 9-benzylfluorene (Scheme 53).[33] No 9-phenyl-9,10-dihydrophenanthrene was obtained. In the writer's opinion the most likely mechanism involves a penta-coordinate carbocation (Scheme 53).



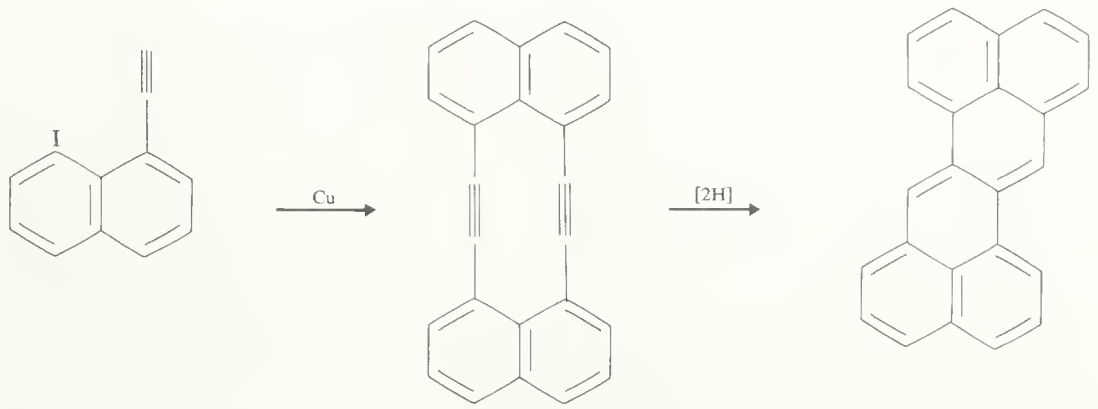
SCHEME 53

The intramolecular reactions of arylacetylenes have attracted attention in recent years. For example, 2-ethynyl-2′-iodobiphenyl forms a copper(I) salt which eliminates copper(I) iodide to form the cumulene (equation 174), presumably *via* a carbene.[204] 2,2′-Diethynylbiphenyl reacts with hydrogen bromide to form 9,10-bisbromomethylphenanthrene.



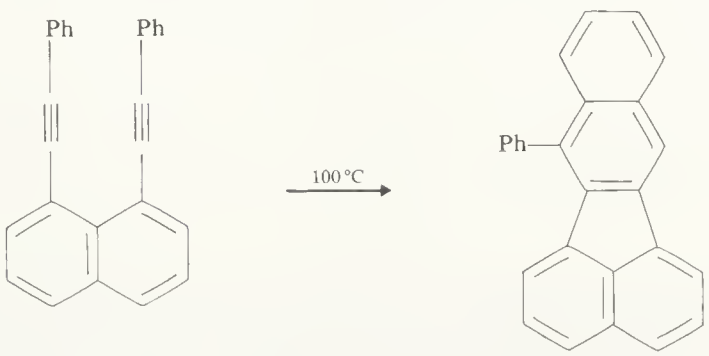
(174)

A more spectacular reaction involves the isolation of the polycyclic arene (zethrine) from the reaction of 1-ethynyl-8-iodonaphthalene with copper (equation 175).[205] The same product is formed from a reaction of 1,8-di-iodonaphthalene and 1,8-diethynylnaphthalene with copper. Both of these reactions are presumed to involve the reductive cyclization of the diacetylene shown in equation (175).



(175)

Related to this latter reaction is the rearrangement of 1,8-bis(phenylethynyl)-naphthalene, which affords 7-phenylbenzo[*k*]fluoranthene (equation 176) at 100 °C.[206]

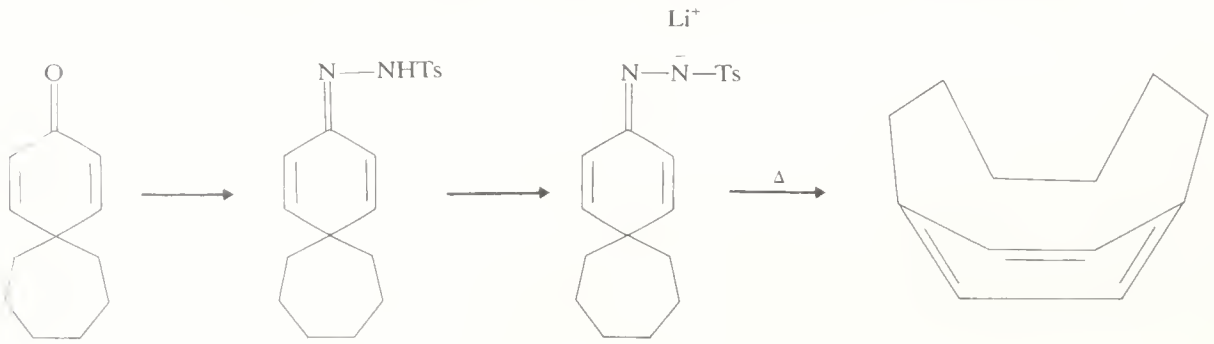


(176)

2.5.16 CYCLOPHANES

Benzene is flat and the extraordinary stability of benzene is associated with the cyclic overflap of the six *p*-orbitals. However, we saw in Section 2.5.13 that the thermal racemization of the helicenes is a conformational process and therefore we must conclude that the benzene rings are flexible. How much bending can a benzene ring withstand without giving up its aromatic character? The most successful experimental approach to this question has been through the preparation of meta- and para-cyclophanes. We shall consider [*m*]-meta- and -para-cyclophanes and [*m*, *n*]-meta- and -paracyclophanes. All of these series of compounds have been studied for some considerable time.

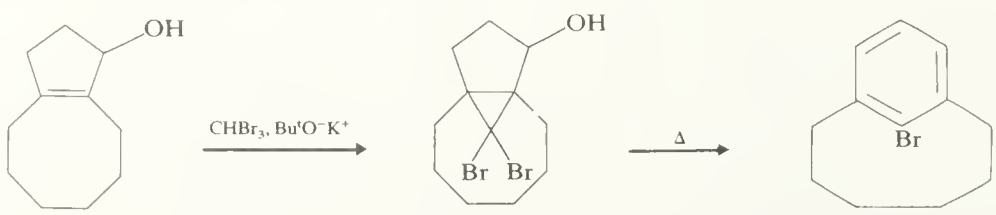
A successful approach to the preparation of [*m*]paracyclophanes, where *m* is a low number, was suggested by the observation that 4,4-dimethylcyclohexadienylidene rearranged to *p*-xylene on generation in the gas phase. This method has been used to prepare [7]paracyclophane[207] and [6]paracyclophane (equation 177),[208] each in *ca.* 10% yield. The latter compound contains the smallest *para* bridge known at present.



(177)

The ultraviolet spectra of both [7]- and [6]-paracyclophane show the expected hypsochromic shifts of the benzene absorption bands and which reflect the deviation from planarity of the benzene rings. The ^{1}H n.m.r. spectra show that the diamagnetic ring-current effects are still important in both [7]- and [6]-paracyclophane. In the latter compound, multiplets (4H's) were observed at $\delta = 0.33$, 1.15, 2.49, and 7.17 p.p.m. [7]Paracyclophane-3-carboxylic acid has been prepared from [8]paracyclophane-3-carboxylic acid.[209] The former compound shows, in its ^{1}H n.m.r. spectrum, that one of the hydrogens is forced into close proximity with the π-electrons of the benzene ring; it was observed at very high field ($\delta = -1.4$ p.p.m.). The structure of [7]paracyclophane-3-carboxylic acid was also determined by X-ray crystallography. The *para* carbons of the benzene ring were found to be *ca.* 17° out of the plane of the other benzene carbons, while the benzyl carbons were 24° from that same plane.

The preparation of [*m*]metacyclophanes, with *m* as a low number, have also attracted attention recently. [6]Metacyclophane and the [7]-homologue have been prepared by the route indicated (equation 178) for the former compound.[210] Various derivatives are available *via* halogen–metal interconversion to the lithio compounds.

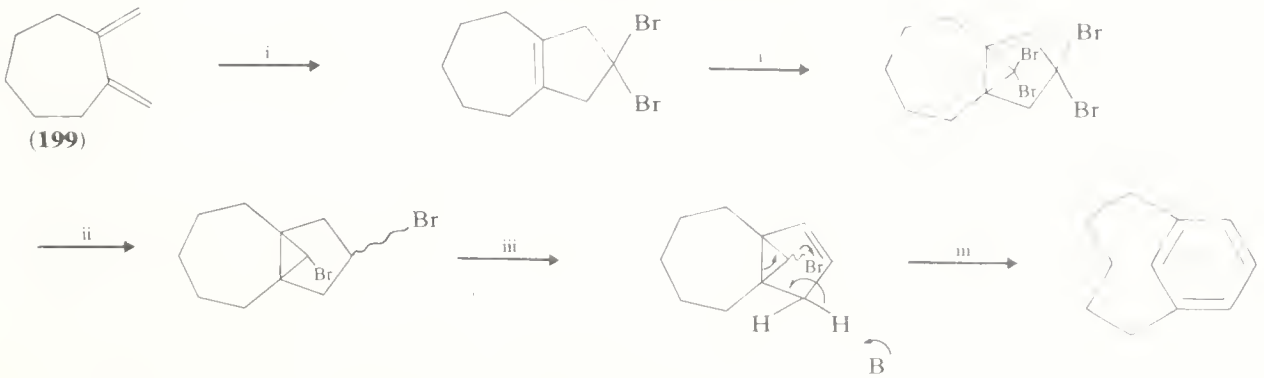


(178)

Even [5]metacyclophane has been reported (Scheme 54).[211] In connection with the synthesis of bridged bicyclopropenyls the diene (**199**) was allowed to react with dibromocarbene in order to generate two cyclopropane rings. Evidently some initial 1,4-cycloaddition of the dibromocarbene occurs and the subsequent steps in the bicyclopropenyl synthesis are also in the correct sequence for the [5]metacyclophane synthesis! The yield of the product was 5%.

The unusually high strain in [5]metacyclophane is indicated by the u.v. spectrum, which shows a distorted benzene chromophore, and by the ^{1}H n.m.r. spectrum, which shows one aromatic proton at δ 7.85 and one proton from each of the two β-methylene groups at δ 0.04–0.54 p.p.m. [5]Metacyclophane is also thermally unstable and rearranges at *ca.* 150 °C to the *ortho* isomer, possibly *via* the benzvalene as shown in equation (179).

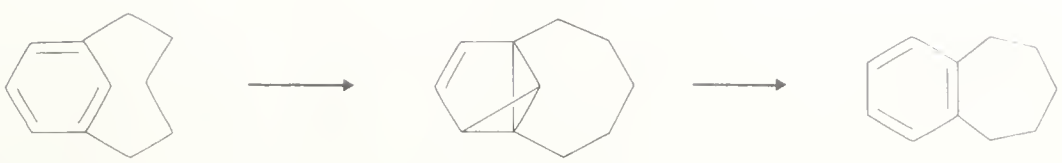
[*m*,*n*]Cyclophane chemistry has been reviewed on a number of occasions.[212] With two arene residues three series are possible: para-para-, meta-meta-, and meta-para-cyclophanes. All three series are known, *e.g.* (**200**)–(**202**). Stacked cyclophanes are also known (Section 2.5.5).



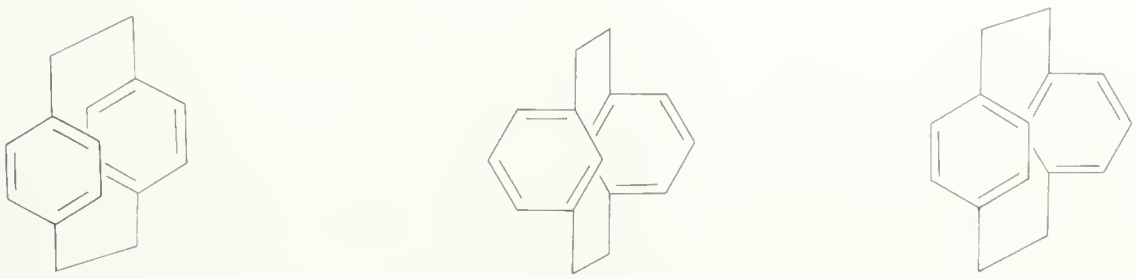
(**199**)

i, $\ddot{C}Br_2$; ii, R_3SnH; iii, $Bu^tO^-K^+$, DMSO.

SCHEME 54



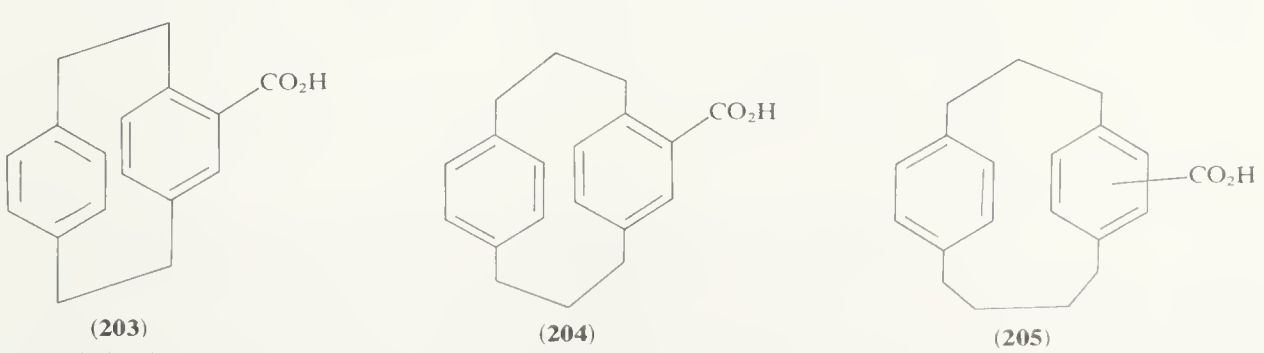
(179)



(**200**) (**201**) (**202**)

[2,2]Paracyclophane was first isolated as a minor component obtained from the pyrolysis (*ca.* 950 °C) of *p*-xylene. It is now used as a monomer for the production of poly-*p*-xylylene. A rational synthesis involves the generation of *p*-quinodimethane (*p*-xylylene) by a 1,6-Hofmann elimination using 4-methylbenzyltrimethylammonium bromide.[213] [2,2]Paracyclophane has also been prepared by a photochemical method which involves the extrusion of carbon dioxide from *p*-xylylene-1,4-benzenediacetate.[214] This method promises to be a useful addition to the available synthetic procedures. X-ray crystallography revealed that [2,2]paracyclophane, in which the bridges are both etheno residues, does have a rigid face-to-face geometry.

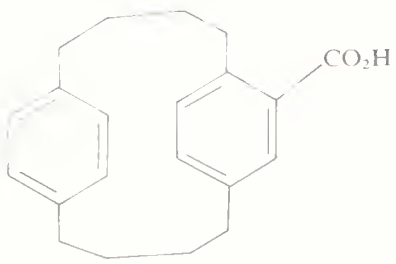
The possibility of ring rotation has been investigated since, if the energy barrier to rotation is sufficiently high, monosubstituted [*n*,*m*]paracyclophanes will be chiral. The carboxylic acids (**203**), (**204**), and (**205**) have been resolved, but (**206**) was not resolvable. The diacetyl [4,4]paracyclophane (**207**) showed a temperature-dependent ^1H n.m.r. spectrum from which the energy barrier to ring rotation was estimated as *ca.* 63 kJ mol^{-1}.



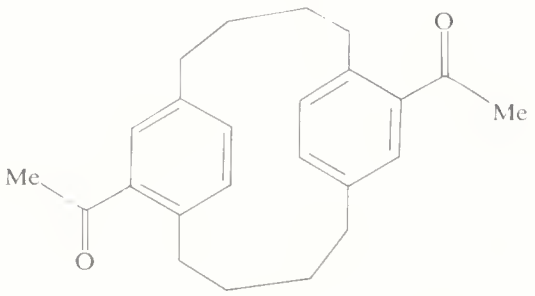
(**203**)
(+)-(*S*)

(**204**)

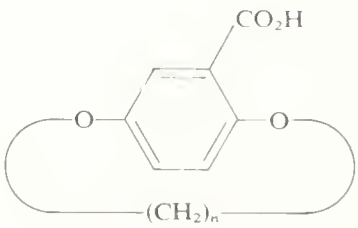
(**205**)



(206)



(207)

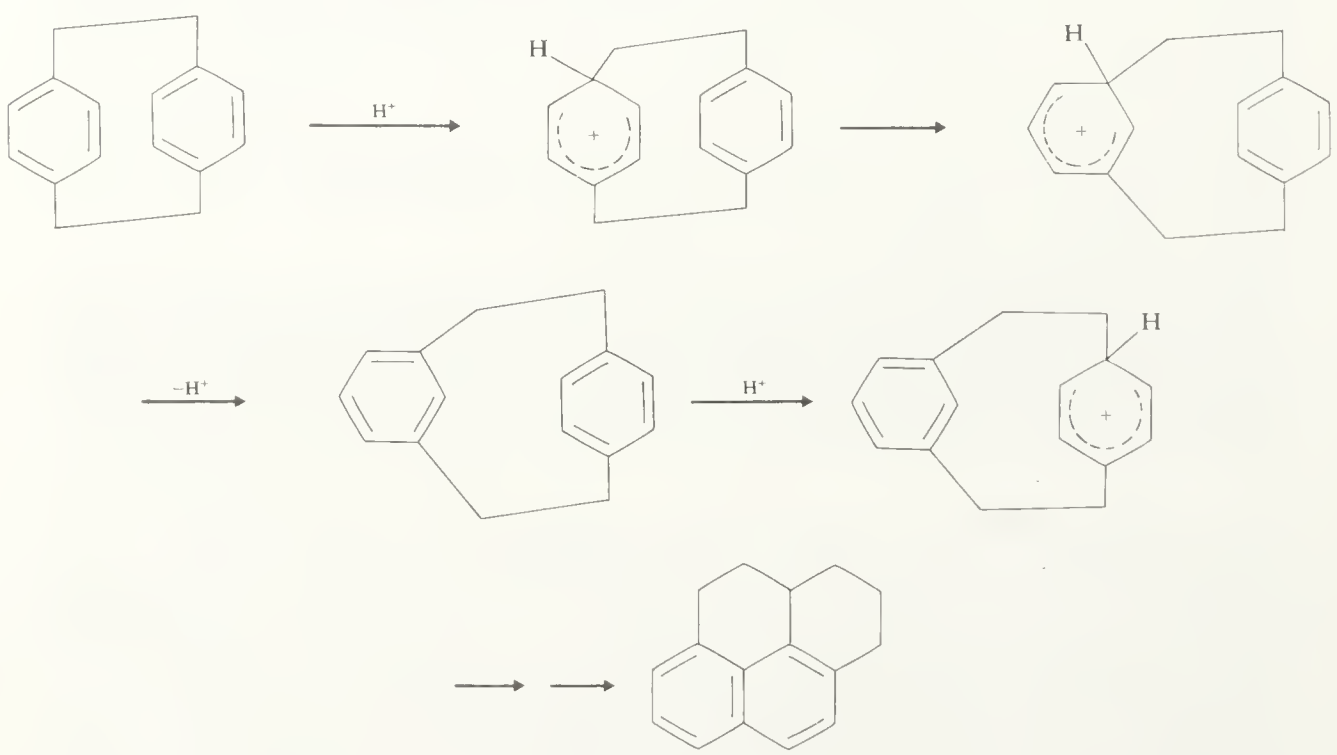


(208)

The optical stability of the ansa compounds ([*m*]paracyclophanes) of the type (**208**) also depends on the value of *m*.

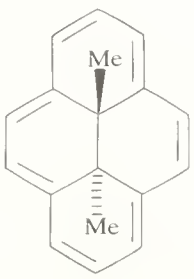
[2.2]Metacyclophane (**201**) does not undergo inversion at temperatures up to 180 °C, which indicates that the activation energy for such a process is $>113\ kJ\ mol^{-1}$. Ring rotation in [2,2]metaparacyclophane (**202**) is complicated by the possibility that each of the different rings may rotate with respect to the other ring. A combination of n.m.r. and optical techniques have been used to investigate this problem. *p*-Ring rotation was not detected and an activation energy for *m*-ring rotation in compound (**202**) was found to be $86.1\ kJ\ mol^{-1}$.

We have already discussed certain reactions which proceed easily because of the strain which is present in the [2,2]paracyclophane systems (in. for example, Sections 2.5.9.4 and 2.5.12). A number of other interesting reactions are known but we shall restrict ourselves to interconversion reactions. The strain energy of [2,2]paracyclophane is $129.6\ kJ\ mol^{-1}$, and, for (**202**) and (**201**), the values are *ca.* 32.4 and $14.3\ kJ\ mol^{-1}$ respectively. It is not surprising, therefore, that [2,2]paracyclophane rearranges in strongly acidic media to afford [2,2]metaparacyclophane (44% yield) together with 1,2,3,3a,4,5-hexahydropyrene (10% yield) (Scheme 55). The relief of the strain in [2,2]paracyclophane on *ipso* protonation is evident in that the ion is readily observed in the ^1H n.m.r. spectrum in $HF–SbF_5–SO_2ClF$ at −78 °C and is stable at temperatures up to *ca.* −10 °C. The quantitative rearrangement of [2,2]metacyclophane to 1,2,3,3a,4,5-hexahydropyrene occurs in benzene solution at 60 °C in the presence of iodine.[215]

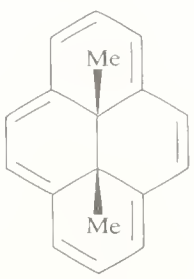


SCHEME 55

The reaction of 2,6-dibromomethyltoluene with 2,6-bis(thiomethyl)toluene affords a mixture of the *syn*- and *anti*-2,11-dithia-9,19-dimethyl[3,3]metacyclophanes. Each of these compounds was converted into the bis-sulphonium salts which, after Stevens rearrangement followed by Hofmann elimination, gave the corresponding *syn*- and *anti*-[2,2]metacyclophane-1,9-dienes.[216] The *anti* isomer may not undergo spontaneous valence isomerization but it is converted into *trans*-15,16-dimethyldihydropyrene (**209**) after chromatography over silica gel, or by irradiation or heating. On the other hand, attempts to form the *syn*-diene gave *cis*-15,16-dimethyldihydropyrene (**210**) directly.

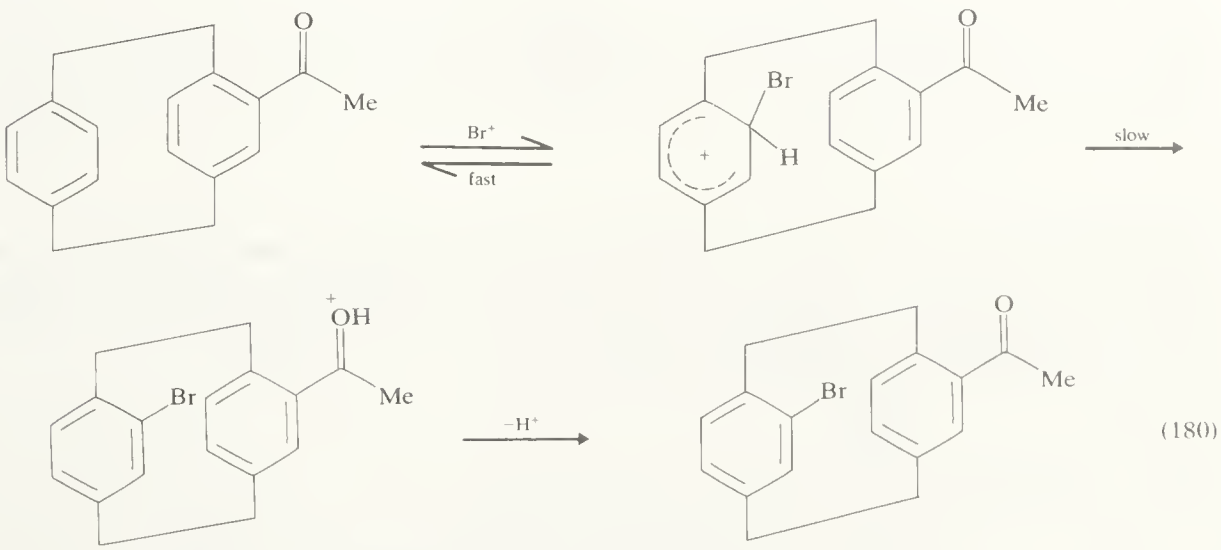


(**209**)



(**210**)

Electrophilic addition-with-elimination reactions of [*m*,*n*]paracyclophanes have highlighted a number of interesting effects. The directive effects of a substituent in one ring on the position of attack by the second ring is particularly unusual. Thus the bromination of both acetyl- and nitro-[2,2]paracyclophane leads exclusively to the *pseudo-geminally* substituted product. This reflects attack *pseudo-gem* to the most basic position or substituent already present on the substituted ring. In the rate-determining step, proton transfer to the acceptor site on the already substituted ring occurs, *e.g.* equation (180). The cyano group does not have the geometry necessary for it to function as a proton acceptor and therefore no *pseudo-gem* product is formed. This mechanism also accounts for the transfer of deuterium from the *para* position to the *pseudo-para* position when 4-methyl-[7-^{2}H][2,2]paracyclophane was brominated. The product 4-bromo-7-methyl[2,2]paracyclophane retained just over 50% of the deuterium at the 12-position. A kinetic isotope effect $k_{1H}/k_{2H} = 3.7$ was observed.



(180)

2.5.17 CONFORMATION AND CHIRALITY IN ARENES

van't Hoff, in his classic paper published in 1874, predicted the existence of dissymmetric molecules which do not contain centres of asymmetry associated with single atoms. Restricted rotation can give rise to perpendicular dissymmetric planes, and compounds

which have two dissymmetric planes are chiral (Figure 6). The groups A and B must be different, as also must the groups C and D. The groups C and D can be the same as the groups A and B. Such compounds are characterized as having a chiral axis (see Part 1). Interchanging the positions of the groups C and D (in Figure 6) produces the enantiomer with the opposite configuration. It would be equally correct to say that the two forms differ in conformation, assuming that the bond linking the two sub-structures is a single bond. The term 'atropisomerism' has also been applied to this type of stereoisomerism. The two main classes of compounds containing a chiral axis which are relevant to our present considerations are to be found in biaryls[217] and allenes.[218] We have already mentioned chiral helices (Section 2.5.14).

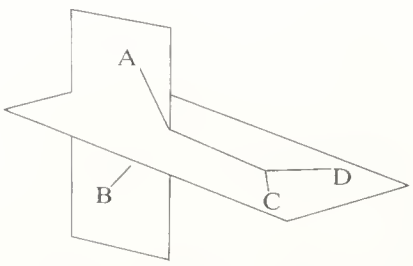
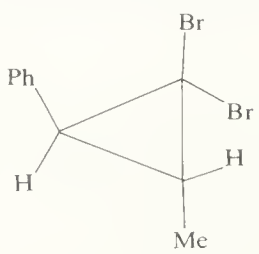


Figure 6

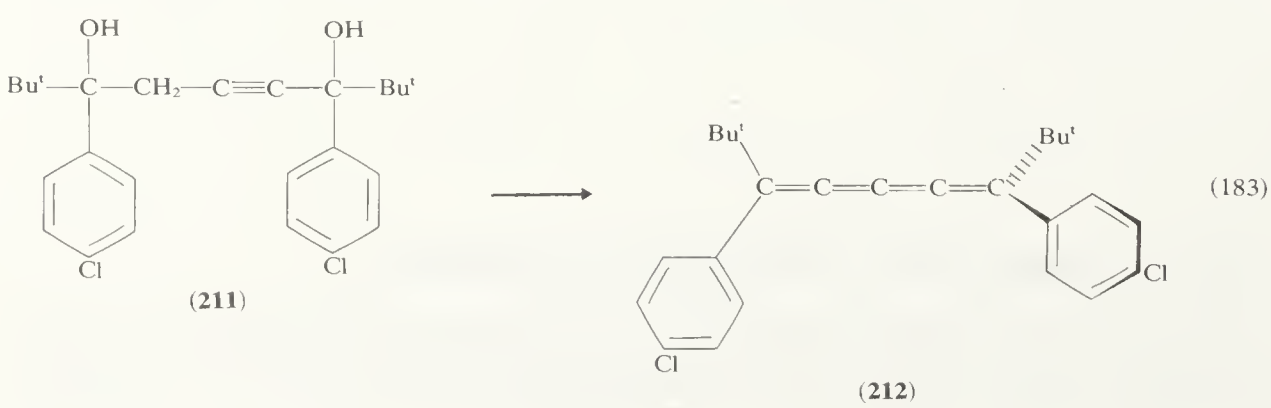
A large number of chiral 1,3-diarylallenes (1,3-diarylpropa-1,2-dienes) are known, the preparations of which have frequently involved partial asymmetric syntheses. Thus benzylphenylacetylene was converted into optically active 1,3-diphenylallene by the prototropic rearrangement shown in equation (181), and 1,1-dibromo-2-methyl-*trans*-3-phenylcyclopropane was converted into optically active 1-methyl-3-phenylallene using n-butyl-lithium in the presence of (−)-sparteine (equation 182).

$$Ph—CH_2—C{\equiv}C—Ph \xrightarrow[\text{on } Al_2O_3]{\text{brucine}} Ph—CH{=}C{=}CH—Ph \qquad (181)$$



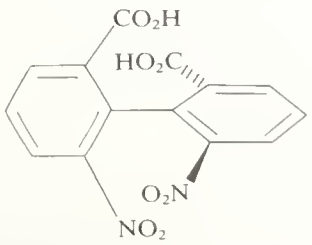
$$\xrightarrow[Bu^nLi]{(-)\text{-sparteine}} Ph—CH{=}C{=}CH—Me \qquad (182)$$

Whenever an even number of cumulative double bonds are present in a molecule the situation is analogous to that in the allenes and a chiral axis can exist. Thus the acetylenic diol (**211**) is dehydrated by (+)-bromocamphorsulphonic acid to afford the chiral pentatetraene (**212**) (equation 183).

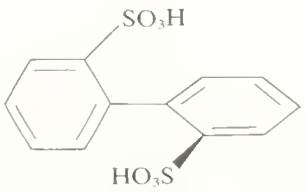


(183)

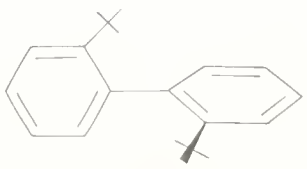
Biphenyl can exist in a number of different conformations which are achieved by rotation about the bond joining the two phenyl groups. Biaryls which contain four large groups in the *ortho* positions cannot freely rotate about the central bond because of steric hindrance. A chiral axis is once again possible. The first biaryl to be resolved was 2,2′-dicarboxy-6,6′-dinitrobiphenyl (**213**). It is not always necessary for four large groups to be present in order to restrict rotation sufficiently to allow the isolation of enantiomers. Thus biphenyl-2,2-disulphonic acid (**214**) was resolved some 45 years ago; it racemizes rapidly on heating. On the other hand, the enantiomers of 2,2′-di-t-butylbiphenyl (**215**), which were prepared from the corresponding optically active 6,6′-di-t-butylbiphenyl-3,3′-dicarboxylic acids, were found to have high optical stability.



(**213**)

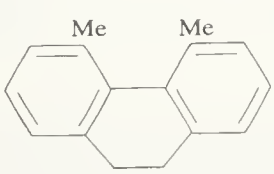


(**214**)

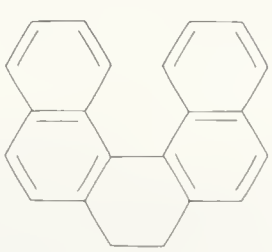

(**215**)

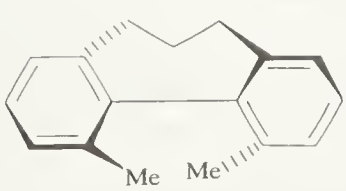
1,1′-Binaphthyl is also resolvable. It was first obtained in an optically active form by the deamination of (+)-4,4′-diamino-1,1′-binaphthyl. Spontaneous resolution of racemic 1,1′-binaphthyl has recently been demonstrated by heating the solid at temperatures between 105–150 °C.[219]

When the two rings in the biaryl are linked by a bridge, rotation is impossible. If the bridge is made by a single atom the molecule is flat and therefore achiral. However, with larger bridges the possibility of conformational isomerism or atropisomerism again exists.[220] Thus 4,5-dimethyl-9,10-dihydrophenanthrene (**216**) and 9,10-dihydrodibenzo[*c*,*g*]phenanthrene (**217**) have both been prepared in optically active forms. The latter compound has the higher optical stability. Skewed biphenyls are inherently dissymmetric chromophores. The electronic transition which gives rise to the so-called conjugation band in the u.v. spectrum is strongly optically active. The sign of the relevant Cotton effect is related to the chirality of the biphenyl. A biphenyl whose sense and extent of twist is that shown in the compound (**218**) has a negative Cotton effect of large rotational strength which is centred at the conjugation band. The chiral binaphthyl derivative (**219**) is readily resolved and has been used with bases, some of which are normally difficult to resolve.

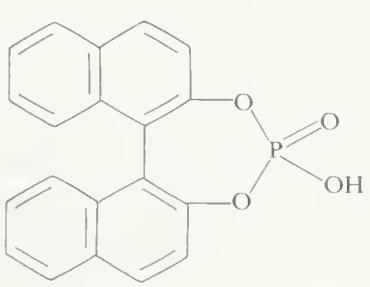


(**216**)


(**217**)



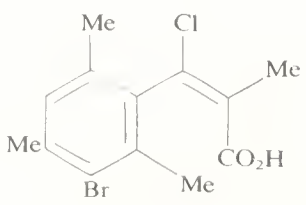
(**218**)



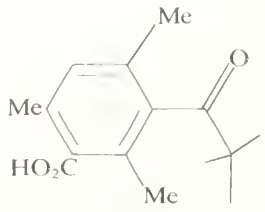
(**219**)

In order to assign the configurational symbol (*cf.* Part 1), a biaryl must be viewed along the chiral axis and four relevant substituents projected on a plane at right angles to the axis.[192] In order that the projection can be considered in the same way as an asymmetric atom, the near groups take precedence over the far groups. It does not matter which end of the chiral axis is considered; however, we must remember that in order to draw a Fischer projection the near groups must occupy horizontal positions. Thus the representation (**213**) is of (*R*)-2,2′-dicarboxy-6,6′-dinitrobiphenyl, and of (**218**), the (*S*)-enantiomer.

Related to biaryl atropisomerism is the hindered rotation of other sterically crowded molecules. Examples include the styrene (**220**) and the pivalophenone[221] (**221**).

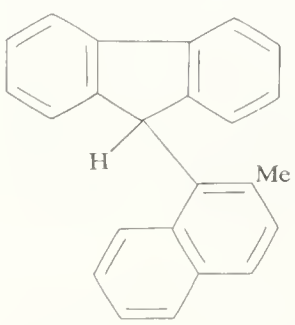


(**220**)

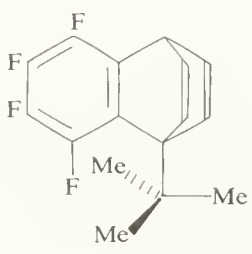


(**221**)

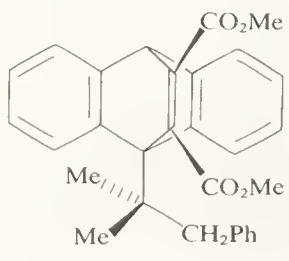
The use of variable-temperature n.m.r. spectroscopy has resulted in an increased interest in dynamic conformational processes. Unusually high barriers to rotation involving sp^3 hybridized carbon atoms have been studied in considerable detail in the past decade.[222] Aryl residues are found in many examples. For example, 9-arylfluorenes have been investigated by using line-shape analyses. The compound (**222**) shows an energy barrier of 124.6 kJ mol^{-1}.[223] The first example of restricted rotation about an sp^3–sp^3 bond which resulted in a high energy barrier to rotation (*ca.* 83.5 kJ mol^{-1}) was given by the compound (**223**).[116b] In order to be able to isolate stable rotamers the substituent must be as bulky as a t-butyl group, but it must not have local threefold symmetry. The compound (**224**) is such a compound and evidence for a *meso* and a racemic form has been obtained.



(**222**)



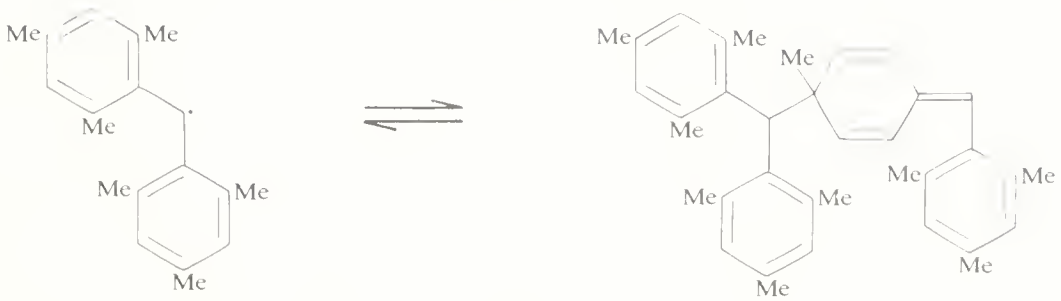
(**223**)



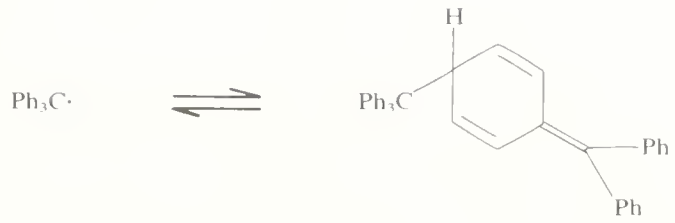
(**224**)

The mechanism of enantiomer and diastereoisomer interconversion in triarylmethyl cations has been studied using a *m*-difluoromethyl group as a diastereotopic probe. The trityl propeller conformation interconverts by way of a two-ring flip transition state.[224] We should note here that, although planar triarylmethyl cations would have the maximum stabilization due to delocalization of the charge, steric interactions can evidently preclude this possibility. Steric effects are also evident in the chemistry of benzyl radicals. The well-known dimerization of the triphenylmethyl radical does not give hexaphenylethane because such a molecule would be excessively overcrowded.[225] In fact the previously supposed ethane derivatives which are obtained from diarylmethyl and triarylmethyl radicals, and which readily afford the radicals in solution, are methylenecyclohexa-1,4-diene derivatives (equations 184 and 185).

The conformational behaviour of certain medium-sized ring systems have also been investigated in some detail using n.m.r. lineshape methods.[226] The n.m.r. spectrum of 5,6,11,12-tetrahydrodibenzo[*a*,*e*]cyclo-octene (**225**) shows, at low temperatures, two sets

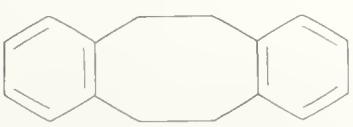


(184)

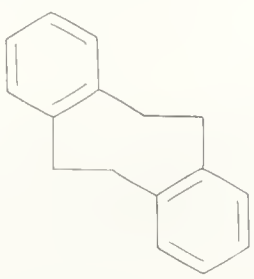


(185)

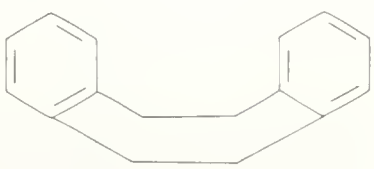
of aromatic proton signals and two sets of methylene proton signals. These sets of signals correspond to two conformations which are present in a ratio of *ca.* 1 : 1. One of the conformations is a rigid *chair* (**226**) and the other conformation is mobile and belongs to a set of boats (*e.g.* **227**). Similar analyses have been carried out with the analogues, dibenzo[*a*,*e*]cyclo-octene and 5,6-dihydrodibenzo[*a*,*e*]cyclo-octene.



(**225**)



(**226**)



(**227**)

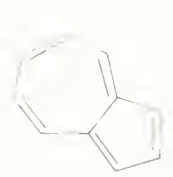
Other investigations have centred on other relative positions of the two benzo groups and on compounds where certain of the methylene groups have been replaced by heteroatoms. The work has also been extended to larger ring systems taking advantage of the *rigid-group principle*. This principle makes use of the fact that torsionally rigid groups — such as the *ortho*-disubstituted benzene residue — facilitate the formation of medium and large rings from acyclic precursors.

2.5.18 AZULENE AND NON-BENZENOID ARENES[227]

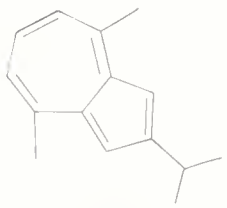
Azulene (**24**) is isomeric with naphthalene. The aromatic stabilization energy is high (72 kJ mol^{-1}), though considerably less than naphthalene (133 kJ mol^{-1}). Part of the reason is undoubtedly due to strain in the σ framework of azulene which is absent in naphthalene. Certain derivatives of azulene are available in relatively large quantities by the dehydrogenation of sesquiterpenes. Thus, for example, 4,8-dimethyl-2-isopropylazulene (**228**) is obtained from β-vetivone (**229**), which is a constituent of vetiver oil from *Vetiveria zizanoides*.

Much interesting work on the synthesis and properties of azulene and related compounds has been published recently.[228] For example, the thermolysis of the fulvene (**230**) in the presence of base affords azulene (equation 186). Aceheptylene (**232**) can be prepared in a similar way (equation 187) using the dienamine (**231**).

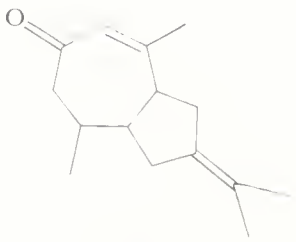
Many attempts to prepare pentalene (**233**), a bicyclic analogue of cyclo-octatetraene, have met with failure. This is not surprising since a planar 8π-electron species would be at



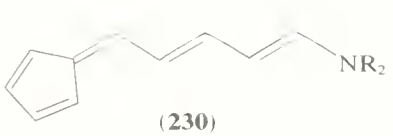
(24)



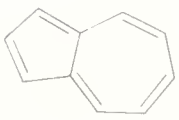
(228)



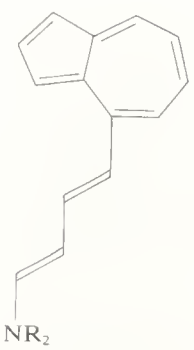
(229)



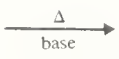
(230)

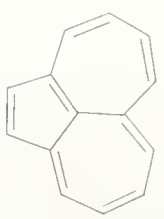


(186)



(231)

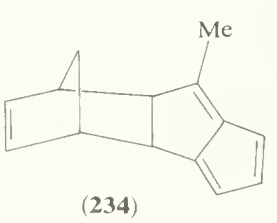




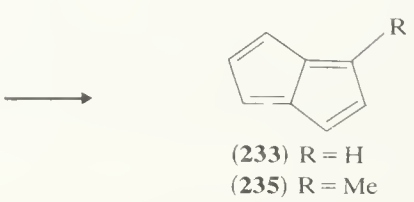
(232)

(187)

best weakly or non-aromatic, and at worst anti-aromatic. Two successful preparations will be mentioned. Thus the flash vacuum thermolysis of the fulvene derivative (**234**) at 600 °C and collection of the products at −196 °C gave evidence for the production of the methylpentalene (**235**) (equation 188).[229] The dimethylpentalene shown in equation (189) is formed at 25 °C from the quaternary methiodide; it is evidently a short-lived species since the dimer (**236**) was the product isolated from this reaction.[228b]

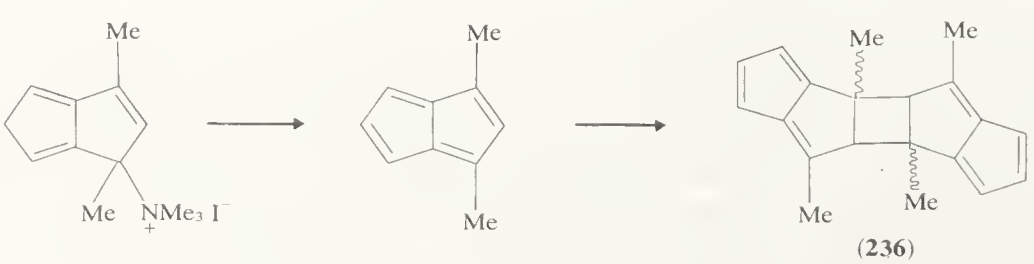


(234)



(233) R = H
(235) R = Me

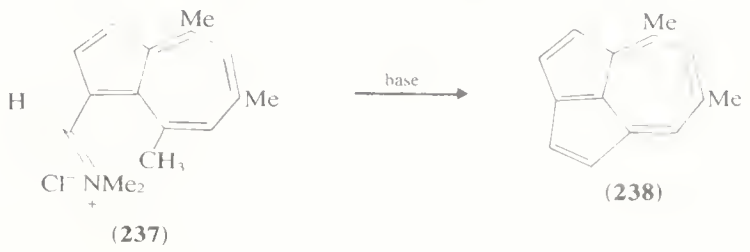
(188)



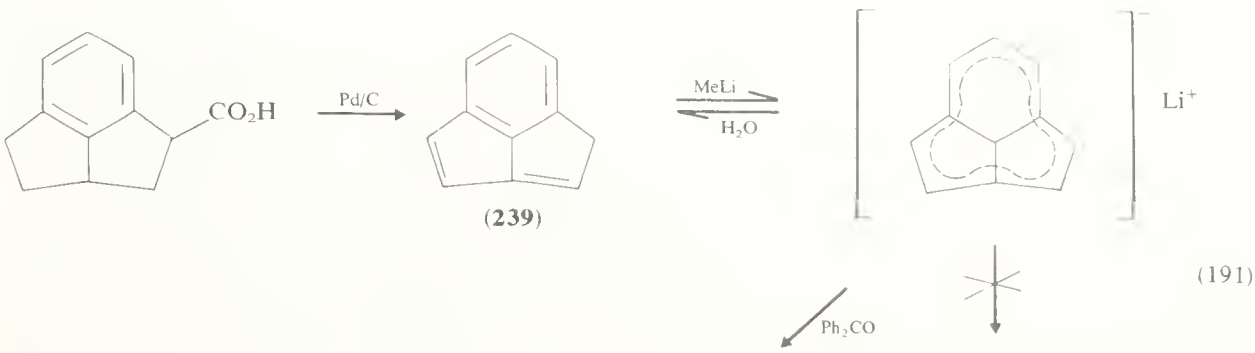
(236)

(189)

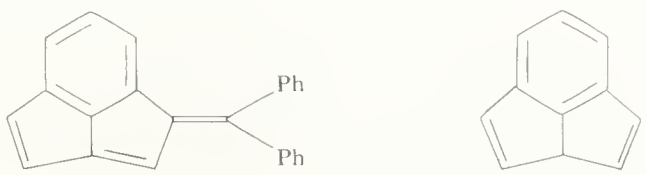
The cyclopent[*c*,*d*]azulene (**238**) has also been prepared by an elegant synthesis (equation 190) using the aldiminium salt (**237**). The tricyclic compound (**239**) is also of considerable interest as the tautomer of the highly acidic fluoradene (**240**). Compound (**239**) was prepared as shown in equation (191) and was deprotonated by methyl-lithium. Reprotonation regenerated the starting material and condensation reactions of the anion, for example with benzophenone, also occur at position-1.



(237) (238) (190)



(239) (191)



(240)

Many other interesting examples of non-benzenoid aromatic reactivity are known and the reader should consult the many excellent accounts that are available.

References

1. W. A. Tilden, 'A Short History of the Progress of Scientific Chemistry', Longmans, London, 1899, p. 136.
2. A. D. Wurtz, 'Dictionnaire de Chimie', Hachette, Paris, 1874, vol. 1, p. 386.
3. 'Handbook for Chemical Society Authors', Chemical Society Special Publications, 1960, No. 14; 'Nomenclature of Organic Chemistry, Sections A, B, and C', 3rd edn., Butterworths, London, 1971.
4. R. A. Friedel and M. Orchin, 'Ultraviolet Spectra of Aromatic Compounds', Wiley, New York, 1951; A. I. Scott, 'Interpretation of the Ultraviolet Spectra of Natural Products', Pergamon, Oxford, 1964.
5. E. P. Clar, 'Aromatische Kohlenwasserstoffe', Springer Verlag, Berlin, 1952.
6. L. J. Bellamy, 'The Infra-red Spectra of Complex Molecules', Chapman and Hall, London, 1975.
7. G. C. Levy and G. L. Nelson, 'Carbon-13 Nuclear Magnetic Resonance for Organic Chemists', Wiley-Interscience, New York, 1972; J. B. Stothers, 'Carbon-13 N.M.R. Spectroscopy', Academic, New York, 1972; L. F. Johnson and W. C. Jankowski, 'Carbon-13 N.M.R. Spectra', Wiley-Interscience, New York, 1972.
8. (a) L. M. Jackman and S. Sternhell, 'Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry', Pergamon, Oxford, 1969; (b) C. J. Pouchert and J. R. Campbell, 'The Aldrich Library of N.M.R. Spectra', Aldrich, Milwaukee, 1974, vol. 4.
9. T. Amemiya and E. Nakamura, *Proc. Eighth World Petroleum Congress*, 1971, **4,** 269; 'Modern Petroleum Technology', 4th edn., ed. G. D. Hobson, Applied Science, Barking, 1973.
10. J. J. McKetta, R. W. Scott, D. E. Lambert, T. C. Ponder, H. L. Hoffman, and J. D. Wall, *Proc. Ninth World Petroleum Congress*, 1975, **5,** 1.
11. M. Berthelot, *Compt. rend.*, 1866, **62,** 905; G. M. Badger, G. E. Lewis, and I. M. Napier, *J. Chem. Soc.*, 1960, 2825.
12. W. Reppe, O. Schlichting, K. Klager, and T. Toepel, *Annalen*, 1948, **560,** 1; W. Reppe and W. J. Sweckendick, *ibid.*, 1948, **560,** 105.
13. F. L. Bowden and A. B. P. Lever, *Organometallic Chem. Rev.* (*A*), 1968, **3,** 227.
14. (a) K. P. C. Vollhardt, *Accounts Chem Res.*, 1977, **10,** 1; (b) R. L. Funk and K. P. C. Vollhardt, *J. Amer. Chem. Soc.*, 1977, **99,** 5483.
15. J. G. Hoggett, R. B. Moodie, J. R. Penton, and K. Schofield, 'Nitration and Aromatic Reactivity', Cambridge University Press, 1971.

16. (a) G. A. Olah, *Accounts Chem. Res.*, 1971, **4,** 240; (b) P. Rys, P. Skrabal, and H. Zollinger, *Angew. Chem. Internat. Edn.*, 1972, **11,** 874.
17. J. H. Ridd, *Accounts Chem. Res.*, 1971, **4,** 248; G. A. Olah, in 'Industrial and Laboratory Nitrations', A.C.S. Symposium Series, No. 22, ed. L. F. Albright and C. Hanson, American Chemical Society, Washington, 1976; L. M. Stock, *Progr. Phys. Org. Chem.*, 1976, **12,** 21.
18. R. Taylor, in 'Comprehensive Chemical Kinetics', ed. C. H. Bamford and C. F. H. Tipper, Elsevier, Amsterdam, 1972, vol. 13, chapter 1; R. Taylor, in 'M.T.P. International Review of Science, Organic Chemistry Series One', Butterworths, London, 1973, vol. 3 (ed. H. Zollinger), chapter 1.
19. R. B. Moodie and K. Schofield, *Accounts Chem. Res.*, 1976, **9,** 287; S. R. Hartshorn, *Chem. Soc. Rev.*, 1974, **3,** 167; T. Banwell, C. S. Morse, P. C. Myhre, and A. Vollmar, *J. Amer. Chem. Soc.*, 1977, **99,** 3042.
20. D. V. Nightingale, *Chem. Rev.*, 1947, **40,** 117.
21. 'Isotope Effects in Chemical Reactions', ed. C. J. Collins and N. S. Bowman, A.C.S. Monograph 167, Van Nostrand Reinhold, New York, 1970; 'Isotopes in Organic Chemistry', ed. E. Buncel and C. C. Lee, Elsevier, Amsterdam, 1976, vol. 2; C. D. Ritchie, 'Physical Organic Chemistry', Dekker, New York, 1975; W. H. Saunders, in 'Techniques of Chemistry', ed. E. S. Lewis, Wiley-Interscience, New York, 1974, part 1, chapter V.
22. (a) G. A. Olah, *J. Amer. Chem. Soc.*, 1965, **87,** 1103; (b) G. A. Olah, R. H. Schlosberg, R. D. Porter, Y. K. Mo, D. P. Kelly, and G. D. Mateescu, *ibid.*, 1972, **94,** 2034.
23. (a) C. Eaborn, *J. Organometallic Chem.*, 1975, **100,** 43; (b) R. W. Bott, C. Eaborn, and P. M. Greasley, *J. Chem. Soc.*, 1964, 4804.
24. (a) E. C. Taylor and A. McKillop, *Accounts Chem. Res.*, 1970, **3,** 338; (b) B. Davies and C. B. Thomas, *J.C.S. Perkin I*, 1975, 65.
25. (a) 'Friedel–Crafts and Related Reactions', ed. G. A. Olah, Wiley-Interscience, New York, 1963–1965; (b) R. Miethchen and C.-F. Kröger, *Z. Chem.*, 1975, **15,** 135.
26. G. A. Russell, *J. Amer. Chem. Soc.*, 1959, **81,** 4834.
27. H. Gilman and R. N. Meals, *J. Org. Chem.*, 1943, **8,** 126.
28. A. Natsubori and R. Nakane, *J. Org. Chem.*, 1970, **35,** 3372.
29. C. C. Lee and D. J. Woodcock, *Canad. J. Chem.*, 1970, **48,** 858.
30. P. C. Myhre, T. Rieger, and J. T. Stone, *J. Org. Chem.*, 1966, **31,** 3425.
31. W. M. Harms and E. J. Eisenbraun, *Org. Prep. Proc. Internat.*, 1971, **3,** 239.
32. C. K. Bradsher, *Chem. Rev.*, 1946, **38,** 447.
33. A. S. Daud-pota and H. Heaney, unpublished observations.
34. G. Chuchani, *J. Chem. Soc.*, 1960, 325.
35. M. Takaku, M. Taniguchi, and Y. Inamoto, *Synth. Comm.*, 1971, **1,** 141.
36. D. Bryce-Smith and N. A. Perkins, *J. Chem. Soc.*, 1962, 5295.
37. T. Nakajima, S. Suga, T. Sugita, and K. Ichikawa, *Tetrahedron*, 1969, **25,** 1807.
38. P. Beak, *Accounts Chem. Res.*, 1976, **9,** 230.
39. R. C. Fort, in 'Carbonium Ions', ed. G. A. Olah and P. v. R. Schleyer, Wiley-Interscience, New York, 1973, vol. IV, p. 1783.
40. D. N. Kevill and F. L. Weitl, *J. Amer. Chem. Soc.*, 1968, **90,** 6416.
41. P. Beak and B. R. Harris, *J. Amer. Chem. Soc.*, 1974, **96,** 6363.
42. M. W. Miller, R. W. Amidon, and P. O. Tawney, *J. Amer. Chem. Soc.*, 1955, **77,** 2845.
43. J. E. T. Corrie, G. W. Kirby, and R. P. Sharma, *J.C.S. Chem. Comm.*, 1975, 915.
44. M. Miocque and J. Vierfond, *Bull. Soc. chim. France*, 1970, 1896, 1901, 1907.
45. N. L. Holy and Y. F. Wang, *J. Amer. Chem. Soc.*, 1977, **99,** 944; A. Ahond, A. Cavé, C. Kan-Fan, and P. Potier, *Bull. Soc. chim. France*, 1970, 2707.
46. F. Effenberger and G. Epple, *Angew. Chem. Internat. Edn.*, 1972, **11,** 299, 300.
47. P. H. Gore, J. A. Hoskins, and S. Thorburn, *J. Chem. Soc.* (*B*), 1970, 1343.
48. L. I. Belenkii, A. P. Yakubov, and Ya. L. Goldfarb, *J. Org. Chem.* (*U.S.S.R.*), 1970, **6,** 2531.
49. G. A. Olah, H. C. Lin, and A. Germain, *Synthesis*, 1974, 895.
50. G. A. Olah and S. J. Kuhn, *J. Amer. Chem. Soc.*, 1960, **82,** 2380.
51. H. H. Bosshard and H. Zollinger, *Helv. Chim. Acta*, 1959, **42,** 1659.
52. J. G. Dingwall, D. H. Reid, and K. Wade, *J. Chem. Soc.* (*C*), 1969, 913.
53. G. J. Martin and S. Poignant, *J.C.S. Perkin II*, 1972, 1964.
54. I. M. Downie, H. Heaney, and G. Kemp, *Tetrahedron Letters*, 1975, 3951.
55. H. Wynberg, *Chem. Rev.*, 1960, **60,** 169.
56. R. O. C. Norman and R. Taylor, 'Electrophilic Substitution in Benzenoid Compounds', Elsevier, Amsterdam, 1965.
57. E. H. Bartlett, C. Eaborn, and D. R. M. Walton, *J. Chem. Soc.* (*C*), 1970, 1717.
58. B. C. Challis and A. J. Lawson, *J. Chem. Soc.* (*B*), 1971, 770; B. C. Challis, R. J. Higgins, and A. J. Lawson, *J.C.S. Perkin II*, 1972, 1831; B. C. Challis and R. J. Higgins, *ibid.*, p. 2365.
59. H. Zollinger, 'Azo and Diazo Chemistry', Interscience, New York, 1961.
60. F. Snykers and H. Zollinger, *Tetrahedron Letters*, 1970, 2759; *Helv. Chim. Acta*, 1970, **53,** 1294.
61. R. Curci and J. O. Edwards, *Org. Peroxides*, 1970, **1,** 213.
62. J. A. Vesely and L. Schmerling, *J. Org. Chem.*, 1970, **35,** 4028.
63. A. J. Davidson and R. O. C. Norman, *J. Chem. Soc.*, 1964, 5404.

64. M. E. Kurz and G. J. Johnson, *J. Org. Chem.*, 1971, **36,** 3184.
65. H. Hart, *Accounts Chem. Res.*, 1971, **4,** 337.
66. S. Hashimoto and W. Koike, *Bull. Chem. Soc. Japan*, 1970, **43,** 293.
67. (a) A. F. Holleman, *Chem. Rev.*, 1925, **1,** 187; (b) C. M. Suter and A. W. Weston, *Org. Reactions*, 1946, **3,** 141; (c) E. E. Gilbert, 'Sulphonation and Related Reactions', Interscience, New York, 1965; (d) H. Cerfontain, 'Mechanistic Aspects in Aromatic Sulphonation and Desulphonation', Interscience, New York, 1968; (e) H. Cerfontain and C. W. F. Kort, *Internat. J. Sulfur Chem.* (*C*), 1971, **6,** 123.
68. A. Koeberg-Telder and H. Cerfontain, *J.C.S. Perkin II*, 1973, 633, and references cited therein.
69. J. K. Bosscher and H. Cerfontain, *J. Chem. Soc.* (*B*), 1968, 1524.
70. A. Koeberg-Telder and H. Cerfontain, *Rec. Trav. chim.*, 1972, **91,** 22.
71. H. Cerfontain, A. Koeberg-Telder, C. Ris, and C. Schenk, *J.C.S. Perkin II*, 1975, 966.
72. V. Grakauskas, *J. Org. Chem.*, 1970, **35,** 723.
73. M. J. Shaw, H. H. Hyman, and R. Filler, *J. Amer. Chem. Soc.*, 1969, **91,** 1563.
74. D. H. R. Barton, A. K. Ganguly, R. H. Hesse, S. N. Loo, and M. M. Pechet, *Chem. Comm.*, 1968, 806; D. H. R. Barton, R. H. Hesse, M. M. Pechet, and H. T. Toh, *J.C.S. Perkin I*, 1974, 732.
75. J. Kollonitsch, L. Barash, and G. A. Doldouras, *J. Amer. Chem. Soc.*, 1970, **92,** 7494.
76. E. Berliner, *J. Chem. Educ.*, 1966, **43,** 124.
77. A. Gastaminza, H. M. Gilow, and J. H. Ridd, *J.C.S. Chem. Comm.*, 1972, 130; H. M. Gilow and J. H. Ridd, *J.C.S. Perkin II*, 1973, 1321.
78. P. B. D. de la Mare and L. Main, *J. Chem. Soc.* (*B*), 1971, 90.
79. W. Gottardi, *Monatsh.*, 1967, **98,** 507.
80. W. Gottardi, *Montash.*, 1968, **99,** 815; 1969, **100,** 42.
81. P. B. D. de la Mare and A. Singh, *J.C.S. Perkin II*, 1972, 1801.
82. V. Caló, F. Ciminale, L. Lopez, and P. E. Todesco, *J. Chem. Soc.* (*C*), 1971, 3652.
83. P. B. D. de la Mare, *Accounts Chem. Res.*, 1974, **7,** 361.
84. E. Baciocchi, A. Ciana, G. Illuminati, and C. Pasini, *J. Amer. Chem. Soc.*, 1965, **87,** 3953.
85. P. C. Myhre, G. S. Owen, and L. L. James, *J. Amer. Chem. Soc.*, 1968, **90,** 2115.
86. P. B. D. de la Mare, A. Singh, E. A. Johnson, R. Koenigsberger, J. S. Lomas, V. Sanchez del Olmo, and A. M. Sexton, *J. Chem. Soc.* (*B*), 1969, 717, and references cited therein.
87. Y. Ogata and K. Nakajima, *Tetrahedron*, 1964, **20,** 2751; Y. Ogata and I. Urasaki, *J. Chem. Soc.* (*C*), 1970, 1689.
88. C. L. Perrin and G. A. Skinner, *J. Amer. Chem. Soc.*, 1971, **93,** 3389.
89. V. Gold and M. Whittaker, *J. Chem. Soc.*, 1951, 1184.
90. A. R. Butler, *J. Chem. Educ.*, 1971, **48,** 508.
91. J. Arotsky, R. Butler, and A. C. Darby, *J. Chem. Soc.* (*C*), 1970, 1480.
92. L. M. Stock, 'Aromatic Substitution Reactions', Prentice-Hall, Englewood Cliffs, New Jersey, 1968, chapters 2 and 3.
93. L. M. Stock and H. C. Brown, *Adv. Phys. Org. Chem.*, 1963, **1,** 35.
94. R. S. Cook, R. Phillips, and J. H. Ridd, *J.C.S. Perkin II*, 1974, 1166.
95. M. Godfrey, *J. Chem. Soc.* (*B*), 1971, 1545.
96. M. L. Poutsma, in 'Free Radicals', ed. J. K. Kochi, Wiley, New York, 1973, vol. 2, chapter 14.
97. G. A. Russell, in 'Free Radicals', ed. J. K. Kochi, Wiley, New York, 1973, vol. 1, chapter 7.
98. A. M. Tarr, J. W. Coomber, and E. Whittle, *Trans. Faraday Soc.*, 1965, **61,** 1182; J. C. Polanyi, *Discuss. Faraday Soc.*, 1967, **44,** 293.
99. R. L. Augustine, 'Catalytic Hydrogenation', Arnold, London, 1965; J. E. Germain, 'Catalytic Conversion of Hydrocarbons', Academic, London, 1969.
100. B. R. James, 'Homogeneous Hydrogenation', Wiley, New York, 1973.
101. E. L. Muetterties and F. J. Hirsekorn, *J. Amer. Chem. Soc.*, 1974, **96,** 4063; F. J. Hirsekorn, M. C. Rakowski, and E. L. Muetterties, *ibid.*, 1975, **97,** 237.
102. T. Kaufmann, C. Kosel, and W. Schoeneck, *Chem. Ber.*, 1963, **96,** 999.
103. (a) A. J. Birch and G. Subba Rao, *Adv. Org. Chem.*, 1972, **8,** 1; (b) H. Smith, 'Organic Reactions in Liquid Ammonia', Wiley, New York, 1963; (c) H. O. House, 'Modern Synthetic Reactions', Benjamin, Menlo Park, California, 1972, chapter 3; (d) R. G. Harvery, *Synthesis*, 1970, 161; (e) E. M. Kaiser, *ibid.*, 1972, 391.
104. H. Normant, *Angew. Chem. Internat. Edn.*, 1967, **6,** 1046.
105. D. F. De Tar and R. A. J. Long, *J. Amer. Chem. Soc.*, 1958, **80,** 4742.
106. J. Hine, *J. Org. Chem.*, 1966, **31,** 1236; O. S. Tee, *J. Amer. Chem. Soc.*, 1969, **91,** 7144; see also R. G. Harvey and K. Urberg, *J. Org. Chem.*, 1968, **33,** 2206.
107. E. Vogel, W. Klug, and A. Breuer, *Org. Synth.*, 1974, **54,** 11.
108. E. Vogel, M. Biskup, A. Vogel, U. Haberland, and J. Eimer, *Angew. Chem. Internat. Edn.*, 1966, **5,** 603.
109. E. Vogel, A. Vogel, H.-K. Kübbeler, and W. Sturm, *Angew. Chem. Internat. Edn.*, 1970, **9,** 514.
110. E. Vogel, U. Haberland, and J. Ick, *Angew. Chem. Internat. Edn.*, 1970, **9,** 517.
111. (a) A. S. Onishchenko, 'Diene Synthesis', Israel Program for Scientific Translations, Jerusalem, 1964; (b) H. Wollweber, 'Diels-Alder-Reaktion', Thieme, Stuttgart, 1972.
112. R. S. H. Liu, *J. Amer. Chem. Soc.*, 1968, **90,** 215.
113. C. G. Krespan, B. C. McKusick, and T. L. Cairns, *J. Amer. Chem. Soc.*, 1960, **82,** 1515.

114. R. C. Cookson and J. Dance, *Tetrahedron Letters*, 1962, 879; C. D. Weis *J. Org. Chem.*, 1963, **28,** 74.
115. E. Ciganek, *Tetrahedron Letters*, 1967, 3321.
116. (a) R. W. Hoffmann, 'Dehydrobenzene and Cycloalkynes', Academic, New York, 1967; (b) H. Heaney, *Fortschr. Chem. Forsch.*, 1970. **16,** 35.
117. N. J. Hales, H. Heaney, and J. H. Hollinshead, *Synthesis*, 1975, 707.
118. H. E. Zimmerman, R. J. Boettcher, N. E. Buehler, G. E. Keck, and M. G. Steinmetz, *J. Amer. Chem. Soc.*, 1976, **98,** 7680.
119. H. Plieninger and W. Lehnert, *Chem. Ber.*, 1967, **100,** 2427.
120. R. C. Cookson and N. S. Wariyar, *J. Chem. Soc.*, 1956, 2303.
121. E. Ciganek, *J. Org. Chem.*, 1969, **34,** 1923.
122. C. W. Rees and R. C. Storr, *J. Chem. Soc.* (*C*), 1969, 760.
123. R. W. Hoffmann, G. Guhn, M. Preiss, and B. Dittrich, *J. Chem. Soc.* (*C*), 1969, 769.
124. W. Kirmse, 'Carbene Chemistry', 2nd edn., Academic, New York, 1971, chapter 10.
125. 'Nitrenes', ed. W. Lwowski, Interscience, New York, 1970.
126. (a) D. Bryce-Smith, *Pure Appl. Chem.*, 1973, **34,** 193; (b) D. Bryce-Smith and A. Gilbert, *Tetrahedron*, 1976, **32,** 1309; (c) *ibid.*, 1977, **33,** 2459.
127. H. J. F. Angus and D. Bryce-Smith, *Proc. Chem. Soc.*, 1959, 326.
128. P. Yates and P. Eaton, *J. Amer. Chem. Soc.*, 1960, **82,** 4436.
129. W. Hartmann, H. G. Heine, and L. Schrader, *Tetrahedron Letters*, 1974, 883.
130. W. Hartmann, H. G. Heine, and L. Schrader, *Tetrahedron Letters*, 1974, 3101.
131. B. E. Job and J. D. Littlehailes, *J. Chem. Soc.* (*C*), 1968, 886.
132. K. E. Wilzbach and L. Kaplan, *J. Amer. Chem. Soc.*, 1966, **88,** 2066; D. Bryce-Smith, A. Gilbert, and B. H. Orger, *Chem. Comm.*, 1966, 512.
133. D. Bryce-Smith, *Chem. Comm.*, 1969, 806.
134. (a) A. Gilbert and M. W. bin Samsudin, *Angew. Chem. Internat. Edn.*, 1975, **14,** 552; (b) A. Gilbert and G. Taylor, *J.C.S. Chem. Comm.*, 1977, 242; (c) H. G. Heine and W. Hartmann, *Angew. Chem. Internat. Edn.*, 1975, **14,** 698.
135. C. S. Angadiyavar, J. Cornelisse, V. Y. Merritt, and R. Srinivasan, *Tetrahedron Letters*, 1973, 4407.
136. R. Srinivasan, *J. Amer. Chem. Soc.*, 1972, **94,** 8117.
137. D. Bryce-Smith, B. E. Foulger, and A. Gilbert, *J.C.S. Chem. Comm.*, 1972, 664.
138. K. E. Wilzbach and L. Kaplan, *J. Amer. Chem. Soc.*, 1971, **93,** 2073; D. Bryce-Smith, B. E. Foulger, A. Gilbert, and P. J. Twitchett, *Chem. Comm.*, 1971, 794; D. Bryce-Smith, A. Gilbert, B. Orger, and H. Tyrrell, *J.C.S. Chem. Comm.*, 1974, 334.
139. D. O. Cowan and R. L. Drisko, 'Elements of Organic Photochemistry', Plenum, New York, 1976, chapter 2.
140. H. Bouas-Laurent, R. Lapouyade, A. Castellan, A. Nourmamode, and E. A. Chandross, *Z. phys. Chem.* (*Wiesbaden*), 1976, **101,** 39.
141. T. W. Mattingly, J. E. Lancaster, and A. Zweig, *Chem. Comm.*, 1971, 595.
142. R. S. Davidson and T. D. Whelan, *J.C.S. Chem. Comm.*, 1977, 361.
143. H. H. Wassermann and P. M. Keehn, *J. Amer. Chem. Soc.*, 1967, **89,** 2770; 1969, **91,** 2374.
144. (a) D. Bryce-Smith and A. Gilbert, in 'M.T.P. International Review of Science, Organic Chemistry Series One', Butterworths, London, 1973, vol. 3 (ed. H. Zollinger), chapter 4; (b) see also A. Gilbert in 'Photochemistry', ed. D. Bryce-Smith, Specialist Periodical Reports, The Chemical Society, London, 1970–1977, vols. 1–8.
145. T. Teitei, D. Wells, and W. H. F. Sasse, *Austral. J. Chem.*, 1975, **28,** 571.
146. S. Farid, S. E. Hartman, J. C. Doty, and J. L. R. Williams, *J. Amer. Chem. Soc.*, 1975, **97,** 3697.
147. R. M. Bowman, T. R. Chamberlain, C.-W. Huang, and J. J. McCullough, *J. Amer. Chem. Soc.*, 1974, **96,** 692.
148. N. C. Yang, C. V. Neywick, and K. Srinivasachar, *Tetrahedron Letters*, 1975, 4313.
149. T. J. Katz, E. J. Wang, and N. Acton, *J. Amer. Chem. Soc.*, 1971, **93,** 3782.
150. J. A. Barltrop and A. C. Day, *J.C.S. Chem. Comm.*, 1975, 177; J. A. Barltrop, R. Carder, A. C. Day, J. R. Harding, and C. Samuel, *ibid.*, p. 729.
151. E. E. van Tamelen and S. P. Pappas, *J. Amer. Chem. Soc.*, 1962, **84,** 3789; I. E. Den Besten, L. Kaplan, and K. E. Wilzbach, *ibid.*, 1968, **90,** 5868.
152. W. L. Mandella and R. W. Franck, *J. Amer. Chem. Soc.*, 1973, **95,** 971.
153. Ref. 103(c), chapters 5 and 7.
154. E. J. Corey and J. W. Suggs, *Tetrahedron Letters*, 1975, 2647.
155. D. H. R. Barton and T. Cohen, in 'Festschrift A. Stoll', Birkhauser, Basel, 1957, pp. 117–143; D. H. R. Barton, *Proc. Chem. Soc.*, 1963, 293; 'Oxidative Coupling of Phenols', ed. W. I. Taylor and A. R. Battersby, Arnold, London, 1967; T. Kametani and K. Fukumoto, *Synthesis*, 1972, 657.
156. M. A. Schwartz, R. A. Holton, and S. W. Scott, *J. Amer. Chem. Soc.*, 1969, **91,** 2800.
157. M. N. Afzal, A. D. Allbutt, A. Jordaan, and G. W. Kirby, *Chem. Comm.*, 1969, 996.
158. M. A. Schwartz, B. F. Rose, and B. Vishnuvajjala, *J. Amer. Chem. Soc.*, 1973, **95,** 612.
159. S. M. Kupchan and A. J. Liepa, *J. Amer. Chem. Soc.*, 1973, **95,** 4062.
160. R. A. G. Marshall and R. Naylor, *J.C.S. Perkin II*, 1974, 1242.
161. D. W. Jones and R. L. Wife, *J.C.S. Perkin I*, 1974, 1.
162. W. R. Adams, in 'Oxidation', ed. R. L. Augustine and D. J. Trecker, Dekker, New York, 1971, vol. 2, chapter 2.

163. H. H. Wassermann and P. M. Keehn, *J. Amer. Chem. Soc.*, 1966, **88,** 4522.
164. L. L. Miller, F. R. Stermitz, and J. R. Falck, *J. Amer. Chem. Soc.*, 1973, **95,** 2651.
165. S. M. Kupchan, A. J. Liepa, V. Kameswaran, and R. F. Bryan, *J. Amer. Chem. Soc.*, 1973, **95,** 6861.
166. A. S. Kende and L. S. Liebeskind, *J. Amer. Chem. Soc.*, 1976, **98,** 267.
167. D. H. Hey, *Adv. Free-Radical Chem.*, 1966, **2,** 47.
168. R. A. Abramovitch, *Adv. Free-Radical Chem.*, 1966, **2,** 87.
169. C. Rüchardt and E. Merz, *Tetrahedron Letters*, 1964, 2431.
170. J. I. G. Cadogan, *J. Chem. Soc.*, 1962, 4257.
171. J. I. G. Cadogan, *Accounts Chem. Res.*, 1971, **4,** 186.
172. H. Zollinger, *Accounts Chem. Res.*, 1973, **6,** 335.
173. D. H. Hey, *Quart. Rev.*, 1971, **25,** 483.
174. D. F. DeTar and C.-C. Chu, *J. Amer. Chem. Soc.*, 1960, **82,** 4969.
175. F. F. Gadallah, A. A. Cantu, and R. M. Elofson, *J. Org. Chem.*, 1973, **38,** 2386.
176. P. E. Fanta, *Synthesis*, 1974, 9, and other reviews cited therein.
177. A. J. Copson, H. Heaney, A. A. Logun, and R. P. Sharma, *J.C.S. Chem. Comm.*, 1972, 315.
178. G. Smolinsky, *J. Amer. Chem. Soc.*, 1961, **83,** 2489.
179. G. Kemp, Ph.D. Thesis, Loughborough University of Technology, 1976.
180. T. Cohen and I. Cristea, *J. Amer. Chem. Soc.*, 1976, **98,** 748, and references cited therein.
181. A. Cairncross and W. A. Sheppard, *J. Amer. Chem. Soc.*, 1968, **90,** 2186.
182. G. M. Whitesides, W. F. Fischer, J. S. Filippo, R. W. Bashe, and H. O. House, *J. Amer. Chem. Soc.*, 1969, **91,** 4871.
183. A. I. Meyers and E. D. Mihelich, *J. Amer. Chem. Soc.*, 1975, **97,** 7383.
184. F. E. Ziegler, K. W. Fowler, and S. Kanfer, *J. Amer. Chem. Soc.*, 1976, **98,** 8282.
185. M. P. Cava and M. J. Mitchell, 'Cyclobutadiene and Related Compounds', Academic, New York, 1967.
186. J. C. Salfeld and E. Baume, *Tetrahedron Letters*, 1966, 3365.
187. C. Bjorklund, M. Nilsson, and D. Wennerström, *Acta Chem. Scand.*, 1970, **24,** 3599.
188. M. Nilsson, *Acta Chem. Scand.*, 1966, **20,** 423; C. Bjorklund and M. Nilsson, *ibid.*, 1968, **22,** 2585.
189. D. V. Banthorpe, *Topics Carbocyclic Chem.*, 1969, **1,** 1.
190. E. V. Blackburn and C. J. Timmons, *Quart. Rev.*, 1969, **23,** 482.
191. L. R. Hughes and R. A. Raphael, *Tetrahedron Letters*, 1976, 1543.
192. R. S. Cahn, C. Ingold, and V. Prelog, *Angew. Chem. Internat. Edn.*, 1966, **5,** 385, and references 4 and 5 cited therein.
193. T. D. Doyle, W. R. Benson, and N. Filipescu, *J. Amer. Chem. Soc.*, 1976, **98,** 3262.
194. R. H. Martin, *Angew. Chem. Internat. Edn.*, 1974, **13,** 649; R. H. Martin and M. Baes, *Tetrahedron*, 1975, **31,** 2135.
195. M. S. Newman and D. Lednicer, *J. Amer. Chem. Soc.*, 1956, **78,** 4765.
196. A. H. A. Tinnemans and W. H. Laarhoven, *J. Amer. Chem. Soc.*, 1974, **96,** 4611.
197. F. Mikeš, G. Boshart, and E. Gil-Av, *J.C.S. Chem. Comm.*, 1976, 99.
198. H. J. Lindner, *Tetrahedron*, 1975, **31,** 281.
199. P. J. Jessup and J. A. Reiss, *Tetrahedron Letters*, 1975, 1453.
200. B. Thulin and O. Wennerström, *Acta Chem. Scand. (B)*, 1976, **30,** 688.
201. R. E. Buntrock and E. C. Taylor, *Chem. Rev.*, 1968, **68,** 209.
202. I. Puskas and E. K. Fields, *J. Org. Chem.*, 1968, **33,** 4237.
203. D. H. R. Barton, P. G. Sammes, and G. G. Weingarton, *J. Chem. Soc. (C)*, 1971, 729.
204. H. A. Staab, H. Mack, and E. Wehinger, *Tetrahedron Letters*, 1968, 1465.
205. H. A. Staab, A. Nissen and J. Ipaktschi, *Angew. Chem. Internat. Edn.*, 1968, **7,** 226.
206. B. Bossenbroek and H. Shechter, *J. Amer. Chem. Soc.*, 1967, **89,** 7111.
207. A. D. Wolf, V. V. Kane, R. H. Levin, and M. Jones, *J. Amer. Chem. Soc.*, 1973, **95,** 1680; see also N. L. Allinger and T. J. Walter, *ibid.*, 1972, **94,** 9267.
208. V. V. Kane, A. D. Wolf, and M. Jones, *J. Amer. Chem. Soc.*, 1974, **96,** 2643.
209. N. L. Allinger, T. J. Walter, and M. G. Newton, *J. Amer. Chem. Soc.*, 1974, **96,** 4588.
210. S. Hirano, H. Hara, T. Hiyama, S. Fujita, and H. Nozaki, *Tetrahedron*, 1975, **31,** 2219.
211. J. W. van Straten, W. H. de Wolf, and F. Bickelhaupt, *Tetrahedron Letters*, 1977, 4667.
212. B. H. Smith, 'Bridged Aromatic Compounds', Academic, New York, 1964; D. J. Cram and J. M. Cram, *Accounts Chem. Res.*, 1971, **4,** 204; F. Vögtle and P. Neumann, *Synthesis*, 1973, 85; F. Vögtle and P. Neumann, *Forschr. Chem. Forsch.*, 1974, **48,** 67.
213. H. E. Winberg and F. S. Fawcett, *Org. Synth. Coll. Vol.* 5, 1973, 883.
214. M. L. Kaplan and E. A. Truesdale, *Tetrahedron Letters*, 1976, 3665.
215. T. Sato and K. Nishiyama, *J. Org. Chem.*, 1972, **37,** 3254.
216. R. H. Mitchell and V. Boekelheide, *J. Amer. Chem. Soc.*, 1974, **96,** 1547.
217. E. L. Eliel, 'Stereochemistry of Carbon Compounds', McGraw-Hill, New York, 1962; K. Mislow, 'Introduction to Stereochemistry', Benjamin, New York, 1965.
218. R. Rossi and P. Diversi, *Synthesis*, 1973, 25.
219. R. E. Pincock and K. R. Wilson, *J. Amer. Chem. Soc.*, 1971, **93,** 1291.
220. D. M. Hall, *Progr. Stereochem.*, 1969, **4,** 1.
221. A. G. Pinkus, J. I. Riggs, and S. M. Broughton, *J. Amer. Chem. Soc.*, 1968, **90,** 5043.
222. H. Kessler, *Angew. Chem. Internat. Edn.*, 1970, **9,** 219; M. Oki, *ibid.*, 1976, **15,** 87.

223. T. H. Siddall and W. E. Stewart, *J. Org. Chem.*, 1969, **34,** 233.
224. J. W. Rakshys, S. V. McKinley, and H. H. Freedman, *J. Amer. Chem. Soc.*, 1970, **92,** 3518.
225. H. Lankamp, W. Th. Nauta, and C. MacLean, *Tetrahedron Letters*, 1968, 249.
226. W. D. Ollis, J. F. Stoddart, and I. O. Sutherland, *Tetrahedron*, 1974, **30,** 1903.
227. 'Non-Benzenoid Aromatic Compounds', ed. D. Ginsberg, Interscience, New York, 1959.
228. (a) K. Hafner, in 'The Chemistry of Nonbenzenoid Aromatic Compounds', ed. M. Oki, Butterworths, London, 1971; (b) K. Hafner, in '23rd International Congress of Pure and Applied Chemistry', Butterworths, London, 1971, vol. 2.
229. R. Bloch, R. A. Marty, and P. de Mayo, *J. Amer. Chem. Soc.*, 1971, **93,** 3071.

2.6

Annulenes and Related Systems

P. J. GARRATT
University College London

2.6.1 INTRODUCTION 361
2.6.2 SYNTHETIC METHODS 365
2.6.2.1 Oxidative coupling of terminal acetylenes (Sondheimer method) 365
2.6.2.2 Photoirradiation of polycyclic valence tautomers 366
2.6.2.3 Norcaradiene–cycloheptatriene valence tautomerism (Vogel method) 368
2.6.2.4 Miscellaneous methods 369
2.6.3 PROPERTIES OF THE $4n+2$ ANNULENES 370
2.6.4 PROPERTIES OF THE $4n$ ANNULENES 379
2.6.5 DEHYDROANNULENES 384
2.6.6 ANNELATED ANNULENES 386
2.6.7 AROMATIC AND ANTI-AROMATIC MONOCYCLIC IONS 390
2.6.8 AROMATIC AND ANTI-AROMATIC POLYCYCLIC IONS 404
2.6.9 HOMOAROMATIC SYSTEMS 406

2.6.1 INTRODUCTION

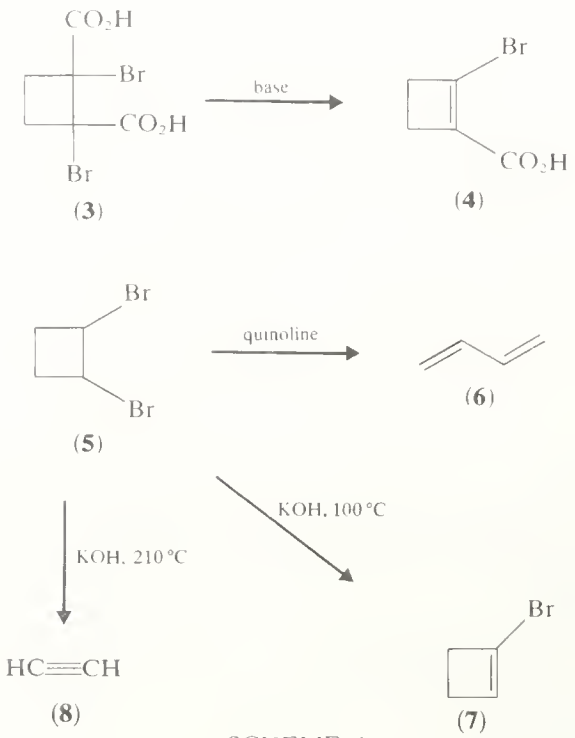
The monocyclic conjugated systems of the general formula $(CH)_{2m}$ have been called annulenes,[1] the number of carbon atoms in the ring being denoted by a prefixed number in brackets. In this system of nomenclature, benzene is [6]annulene. The annulenes can be grouped into two series, as discussed in Section 2.4.2: (i) those in which m is odd having $4n+2$ π-electrons, and (ii) those in which m is even having $4n$ π-electrons.[2] Following the general adoption of the Kekulé structure for benzene ($m=3$), chemists turned their attention to the two adjacent members of the series, cyclobutadiene (**1**) with $m=2$ and cyclo-octatetraene (**2**) with $m=4$.

(**1**)

(**2**)

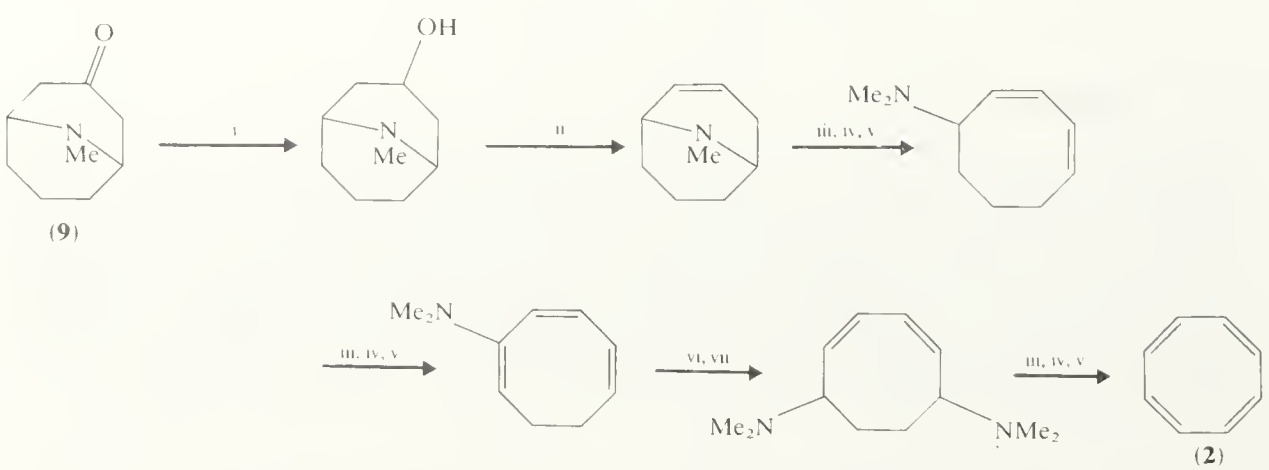
Numerous compounds were obtained in the last century which were thought to contain a cyclobutadiene moiety, but all of the assumed structures were later shown to be incorrect.[3] Deliberate attempts to prepare cyclobutadiene (**1**) were also made (equation 1

and Scheme 1). Perkin treated 1,2-dibromocyclobutane-1,2-dicarboxylic acid (**3**) with various bases, but obtained only 2-bromocyclobutenecarboxylic acid (**4**), and Willstätter and Schnädel treated 1,2-dibromocyclobutane (**5**) with base only to obtain butadiene (**6**) or 1-bromocyclobutene (**7**). However, compound (**5**) gave acetylene (**8**) on treatment with powdered KOH at 210 °C.



SCHEME 1

Willstätter also investigated the synthesis of cyclo-octatetraene (**2**). In this case he had more success and its preparation from pseudopelletierine (**9**) was described in 1911 (Scheme 2).[4] The synthesis involved an extensive series of Hoffmann eliminations and

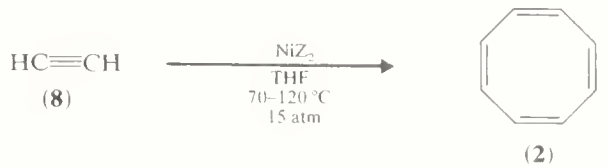


i, Na, EtOH; ii, H_2SO_4; iii, MeI; iv, Ag_2O; v, Δ; vi, Br_2; vii, Me_2NH.

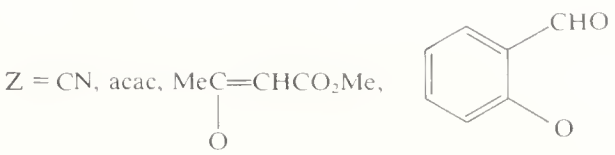
SCHEME 2

only a small amount of (**2**) was obtained. Nevertheless, there was sufficient of the pale yellow oil for it to be characterized and its olefinic, rather than benzenoid, properties demonstrated.[5] Although doubt was subsequently cast on this synthesis, it was completely vindicated by later repetition. The development of the chemistry of cyclo-octatetraene

had to await the one-step synthesis discovered by Reppe,[6] which involves the nickel (II) catalysed tetramerization of acetylene in THF at 70–120 °C under pressure (equation 2).



(2)



The reaction can also be applied to the synthesis of substituted cyclo-octatetraenes and has served as the basis of the enormous growth of cyclo-octatetraene chemistry since 1948. The description of the use of the nickel catalyst was also a stimulus to the revival of interest in transition metals as reagents in organic syntheses.[7] Other methods for preparing cyclo-octatetraene and its derivatives have subsequently been reported.[5]

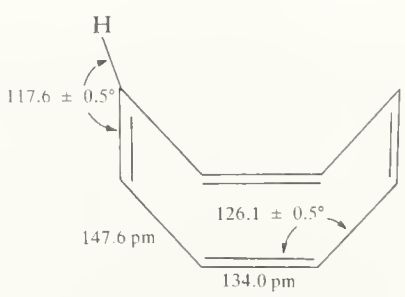
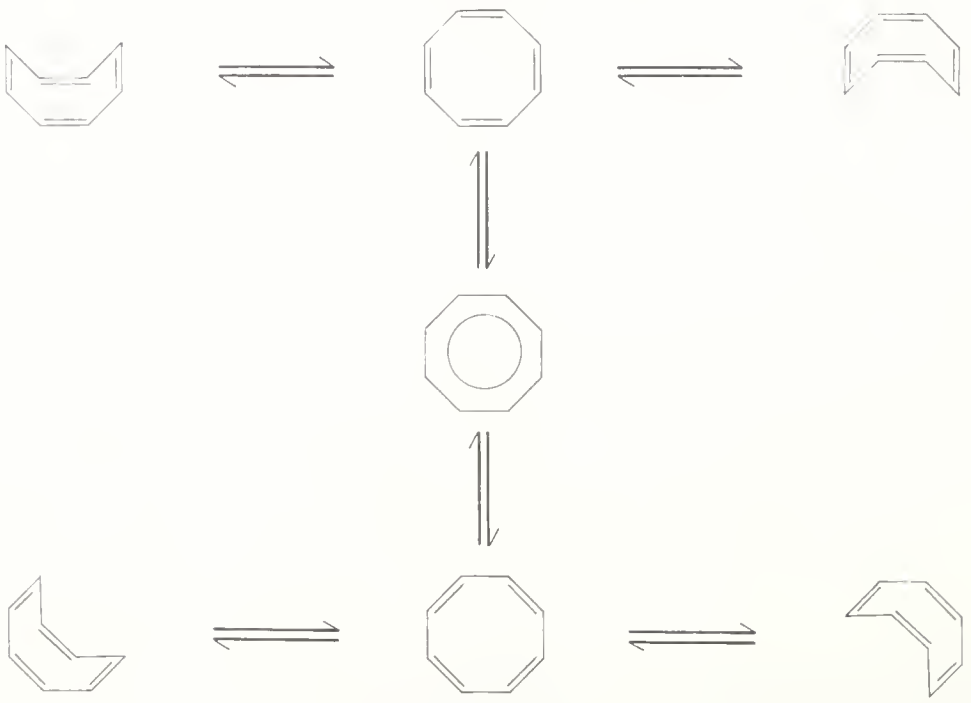


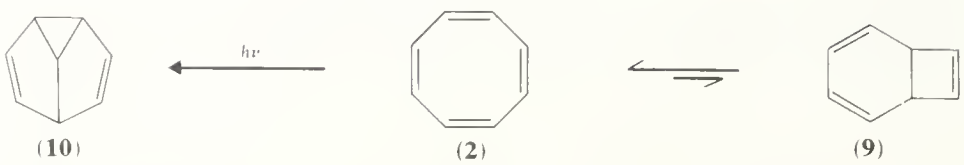
Figure 1

Cyclo-octatetraene (**2**) is a non-planar molecule having the $\mathbf{D}_{2d}$ tub-like conformation shown in Figure 1. The molecule has alternate double and single bonds and the structural parameters shown have been obtained by a variety of techniques. Besides the normal molecular vibrations, cyclo-octatetraene also undergoes slow fluxional changes which can be discerned on the ^{1}H n.m.r. timescale (10^{-2}–10^{-4} s). Both inversion and bond shift occur, as shown in Scheme 3. Inversion may be considered to proceed through a planar, bond-localized structure, whereas bond shift requires the intervention of a planar, delocalized structure. Bond shift (bs) has a higher activation energy than inversion (inv) ($\Delta G^{\neq}_{\text{inv}} = 39{\cdot}7$ kJ mol^{-1}, $\Delta G^{\neq}_{\text{bs}} = 55{\cdot}6$ kJ mol^{-1}) and the difference (15·9 kJ mol^{-1}) can be considered to arise from the *destabilization* introduced by delocalization.

Cyclo-octatetraene is also in equilibrium with a small amount of its valence tautomer, bicyclo [4,2,0] octa-2,4,7-triene (**9**),[8] and a number of its reactions proceed through this form (equation 3). Thus cyclo-octatetraene undergoes Diels–Alder reactions to give compounds derived from addition across the diene grouping of (**9**). Vogel and his co-workers[9] have prepared (**9**) and have shown that it is about 29 kJ mol^{-1} less stable than (**2**). Photoirradiation of (**2**) gave semibullvalene (**10**) in low yield (equation 3).

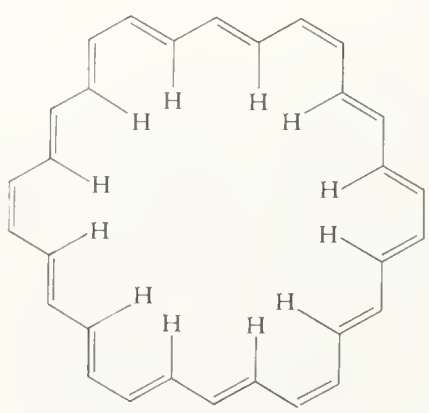


SCHEME 3

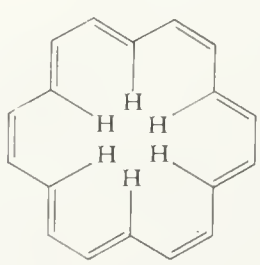


(10) (2) (9) (3)

The properties of benzene and cyclo-octatetraene are strikingly different and appear to substantiate the predictions of the Hückel theory. However, the difference in properties could arise because of the bond angle strain in cyclo-octatetraene which, if planar, would have bond angles of 135°. Thus the synthesis of larger members of the annulene series was of interest because bond angle strain can be relieved by introducing *trans* double bonds, although some hydrogen atoms now have to be inside the ring. Mislow[10] suggested that [30]annulene (**11**) would be the smallest planar macrocyclic system in which bond angle strain and non-bonded interactions would be sufficiently reduced to allow synthesis. However, other authors considered that [18]annulene (**12**) should be capable of existence



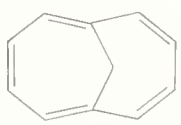
(11)



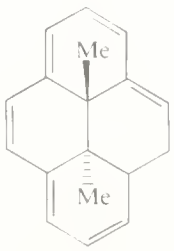
(12)

in a planar form. The latter was the first macrocyclic annulene to be prepared by Sondheimer and his co-workers[1] and is a brick-red, crystalline solid which sustains a diamagnetic ring current and can be acetylated and nitrated under specific conditions. The synthesis and properties of (**12**) provided strong support for Hückel's predictions, and led to a vigorous, continuing activity in this area.

Vogel and Roth[11] subsequently prepared 1,6-methano[10]annulene (**13**), a system in which a one-carbon bridge replaces two hydrogens of the annulene. This compound is diatropic and undergoes substitutions. Boekelheide and Philips[12] prepared 15,16-dimethyl-15,16-dihydropyrene (**14**) which has a peripheral 14π-electron system and is aromatic. Both (**13**) and (**14**) are rigid systems (the geometry being constrained by the σ-bond framework) whereas (**12**) is able to adopt the minimum energy conformation. A large number of macrocyclic and bridged annulenes have been prepared and the general methods of synthesis will be outlined in the next Section.



(**13**)

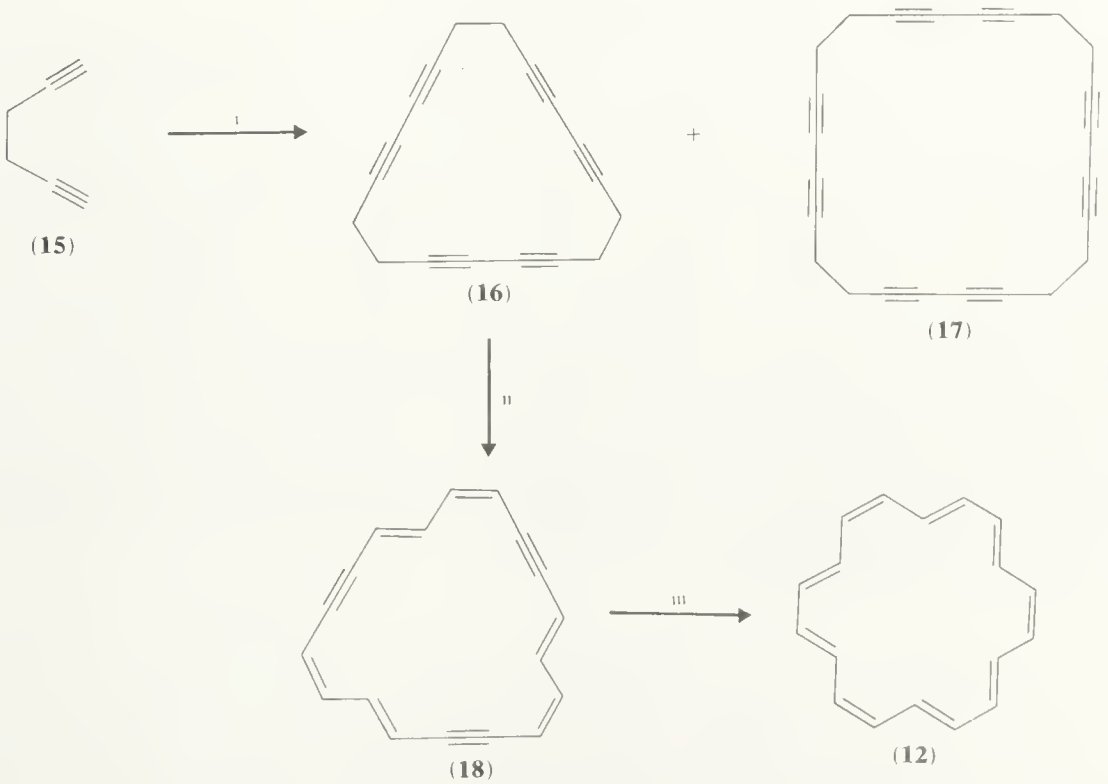


(**14**)

2.6.2 SYNTHETIC METHODS[13]

2.6.2.1 Oxidative coupling of terminal acetylenes (Sondheimer method)

The synthesis of [18]annulene (**12**) is outlined in Scheme 4.[14] Hexa-1,5-diyne (**15**) was coupled under Eglington conditions (cupric acetate in pyridine) to give a mixture of (**16**), (**17**), larger ring systems, and linear compounds. The macrocyclic polynes were separated by chromatography and the hexayne (**16**) was rearranged in the presence of KOBu^t to give 1,7,13-trisdehydro[18]annulene (**18**) which on partial hydrogenation gave (**12**).

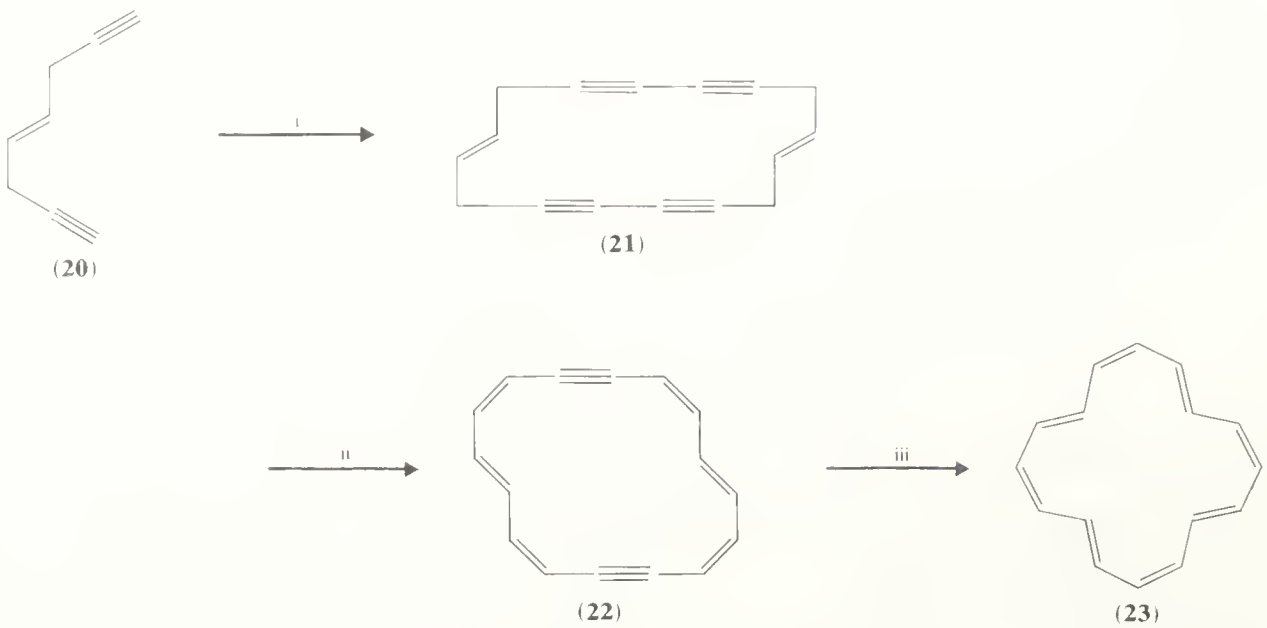


(**15**) (**16**) (**17**) (**18**) (**12**)

i, $Cu(OAc)_2$, py; ii, $KOBu^t$, Bu^tOH, C_6H_6, 30 min, 55 °C; iii, H_2, Pd/C, C_6H_6.

SCHEME 4

This is a general method and, by the choice of the appropriate precursor, annulenes with from 14 to 30 carbon atoms have been prepared.[15] Variation of the oxidative coupling step is possible. For example, octa-3-ene-1,7-diyne (**20**) was coupled with copper(II) chloride and oxygen (Glaser conditions) to give mainly (**21**), which can be rearranged to (**22**) followed by partial hydrogenation to [16]annulene (**23**) (Scheme 5).



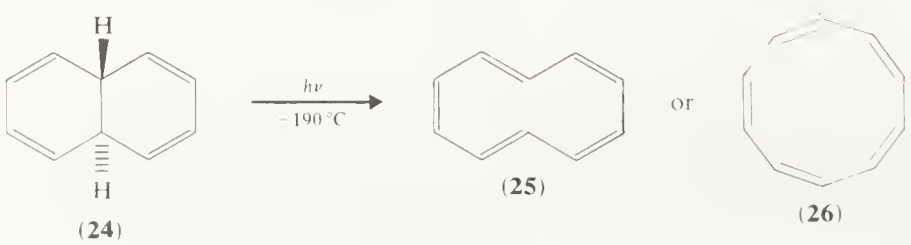
(**20**) (**21**) (**22**) (**23**)

i, O_2, $CuCl_2$, NH_4Cl, C_6H_6; ii, $KOBu^t$; iii, H_2, Pd/C, C_6H_6.

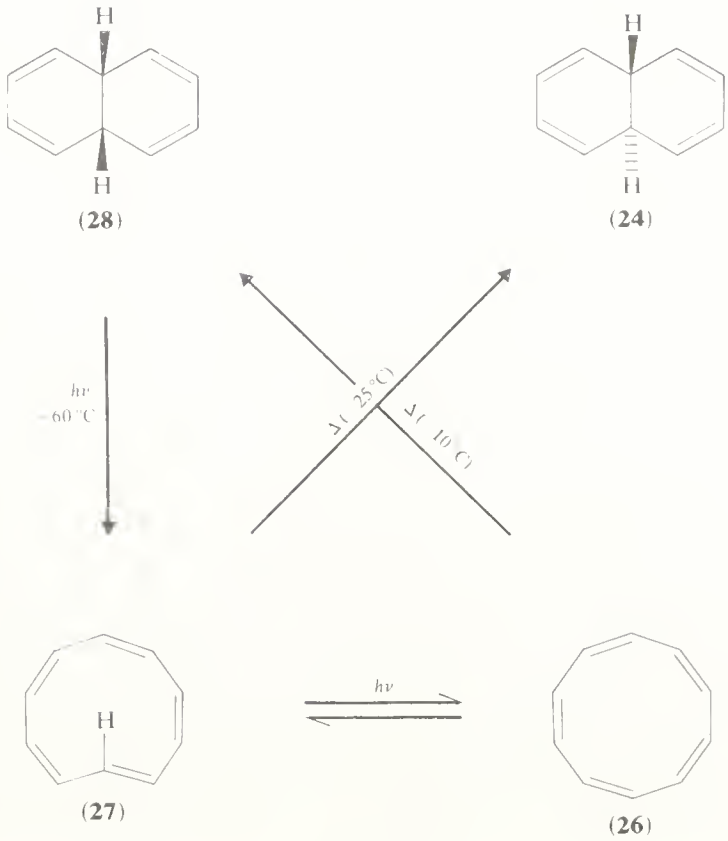
SCHEME 5

2.6.2.2 Photoirradiation of polycyclic valence tautomers

Photochemical ring opening of a polycyclic valence tautomer has been used as the last step in the synthesis of annulenes. The method is particularly suitable for labile molecules because the annulence can be formed at low temperature without any reagent present.[16] The photochemical route was used by van Tamelen and Burkoth[17] in an attempt to prepare [10]annulene. When *trans*-9,10-dihydronaphthalene (**24**) is irradiated, the di-*trans* (**25**) or all-*cis* (**26**) isomers of [10]annulene should be formed (equation 4). Some evidence for the formation of [10]annulene was provided by this investigation—particularly in the formation of cyclodecane by hydrogenation. However, the method was later more extensively investigated by Masamune and his co-workers,[18] who succeeded in isolating the all-*cis* (**26**) and mono-*trans* (**27**) isomers of [10]annulene by the series of reactions shown in Scheme 6. Irradiation of (**28**) at −50 to −60 °C gave a mixture of the [10]annulenes (**26**) and (**27**) together with polycyclic valence tautomers. The annulenes were purified by low-temperature chromatography. The two isomers are thermally unstable, being converted into the respective 9,10-dihydronaphthalene stereoisomers allowed by the Woodward–Hoffmann rules.

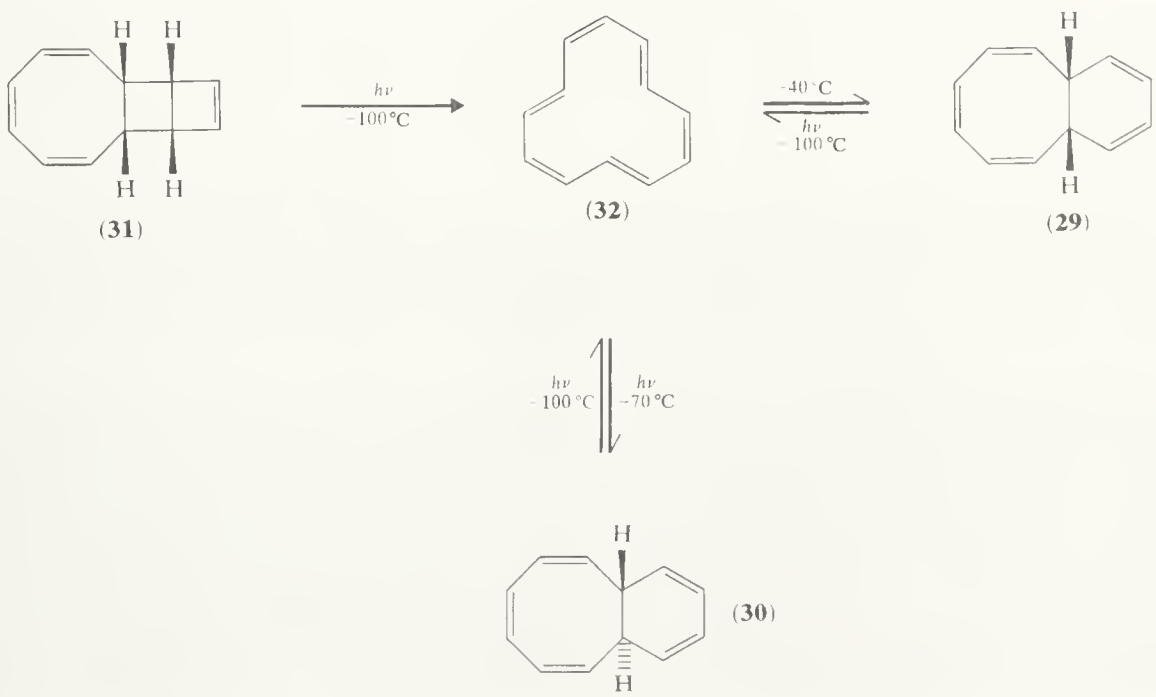


(**24**) (**25**) (**26**) (4)

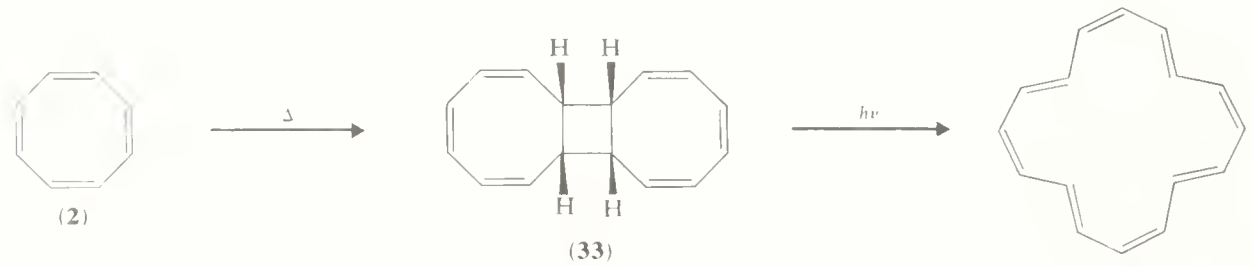


SCHEME 6

[12]Annulene (**32**) was prepared (Scheme 7) by the low-temperature photoirradiation of *cis*- (**29**) or *trans*-bicyclo[6,4,0]dodecapentaene (**30**), or from the tricyclic compound (**31**) prepared from cyclo-octatetraene (**2**).[19a] [12]Annulene (**32**) rearranges at −40 °C into (**29**). Cyclo-octatetraene can also be converted *via* its all-*cis* dimer (**33**) into [16]annulene (**23**).[19b] This route (Scheme 8) is superior to that employed by Sondheimer.



SCHEME 7

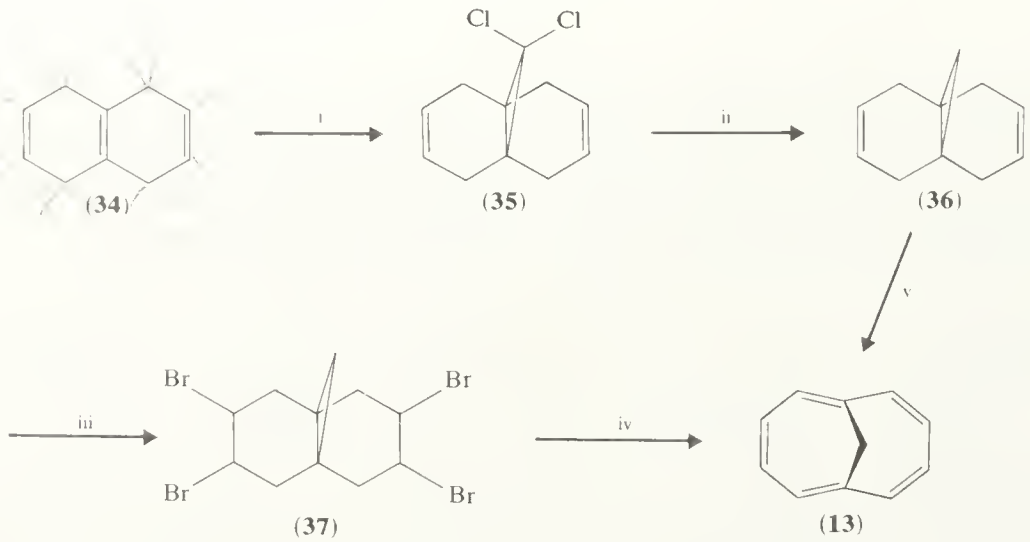


(2) (33) (23)

SCHEME 8

2.6.2.3 Norcaradiene–cycloheptatriene valence tautomerism (Vogel method)[20]

Vogel and his co-workers have prepared numerous bridged [10]- and [14]-annulenes utilizing the norcaradiene–cycloheptatriene valence tautomerization as the final step in the reaction sequence. 1,6-Methano[10]annulene (**13**) was prepared by the route outlined in Scheme 9.[21] Isotetralin (**34**), prepared by Birch reduction of naphthalene, was treated with chloroform and potassium t-butoxide to give the dichlorocarbene adduct (**35**), which was then dechlorinated with sodium in liquid ammonia to yield (**36**). Bromination of (**36**) gave the tetrabromide (**37**) which on dehydrobromination with alcoholic potassium hydroxide gave (**13**), presumably *via* its norcaradiene tautomer. The bromination–dehydrobromination step is profitably replaced by direct oxidation of (**36**) to (**13**) with dichlorodicyanoquinone (DDQ). 1,6-Oxido- and 1,6-imino-[10]annulene can be prepared by variants of this route.

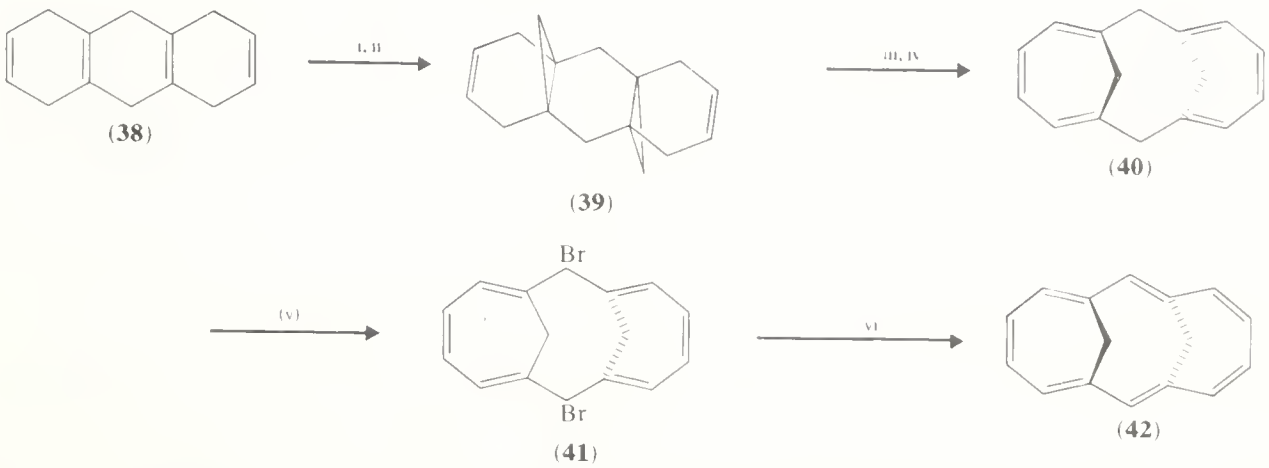


(34) (35) (36) (37) (13)

i, $KOBu^t$, $CHCl_3$; ii, Na, liq. NH_3; iii, Br_2, CH_2Cl_2; iv, KOH, MeOH; v, DDQ.

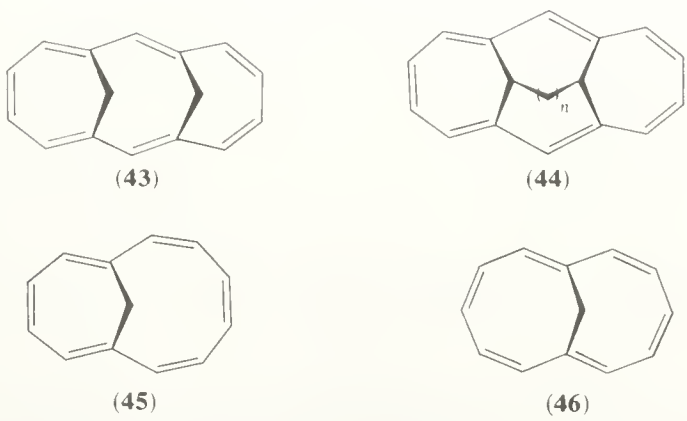
SCHEME 9

anti-1,6:8,13-Bismethano[14]annulene (**42**) was prepared in a similar manner from hexahydroanthracene (**38**), as shown in Scheme 10. The biscarbene adduct (**39**) was converted into (**40**) by bromination–dehydrobromination and (**40**) was then brominated with *N*-bromosuccinimide (NBS) to afford (**41**). Debromination of (**41**) with sodium iodide in acetone gave (**42**). The same reaction sequence was not successful in the synthesis of *syn*-1,6:8,13-bismethano[14]annulene (**43**), but propano[14]annulene (**44**,n = 1) and a number of related systems were prepared by suitable modifications of the method. The method was extended to the synthesis of the $4n$ 12π-electron systems 1,6- (**45**) and 1,7-methano[12]annulenes (**46**) by carbene addition to (**36**) followed by ring expansion and dehydrogenation.[22]



i, Cl_3CCO_2Na, Δ; ii, Li, Bu^{t}OH, THF; iii, Br_2, CH_2CL_2; iv, KOH, MeOH; v, NBS; vi, NaI, Ph_3P CHSCH PPh_3;

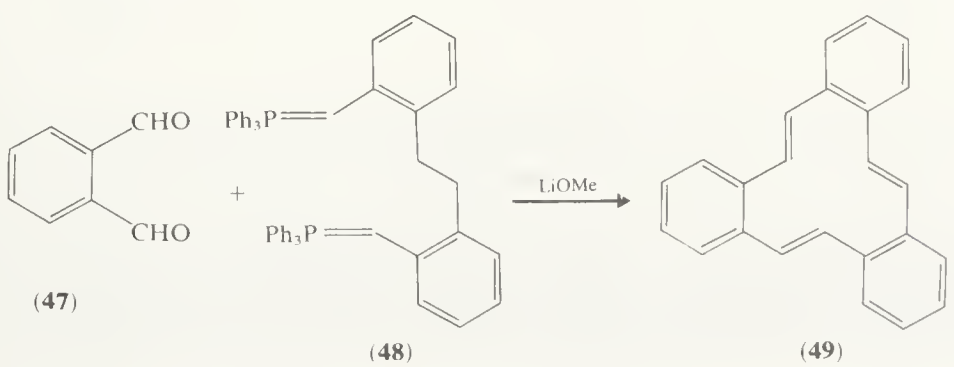
SCHEME 10



In principle, Vogel's method is capable of extension to all the linear, methano-bridged annulenes, but the synthesis of the larger members is restricted by the difficulty of preparing the aromatic precursors and by the proliferation of stereoisomeric carbene adducts. However, this problem has recently been circumvented by the development of a new synthetic approach outlined in the next section.

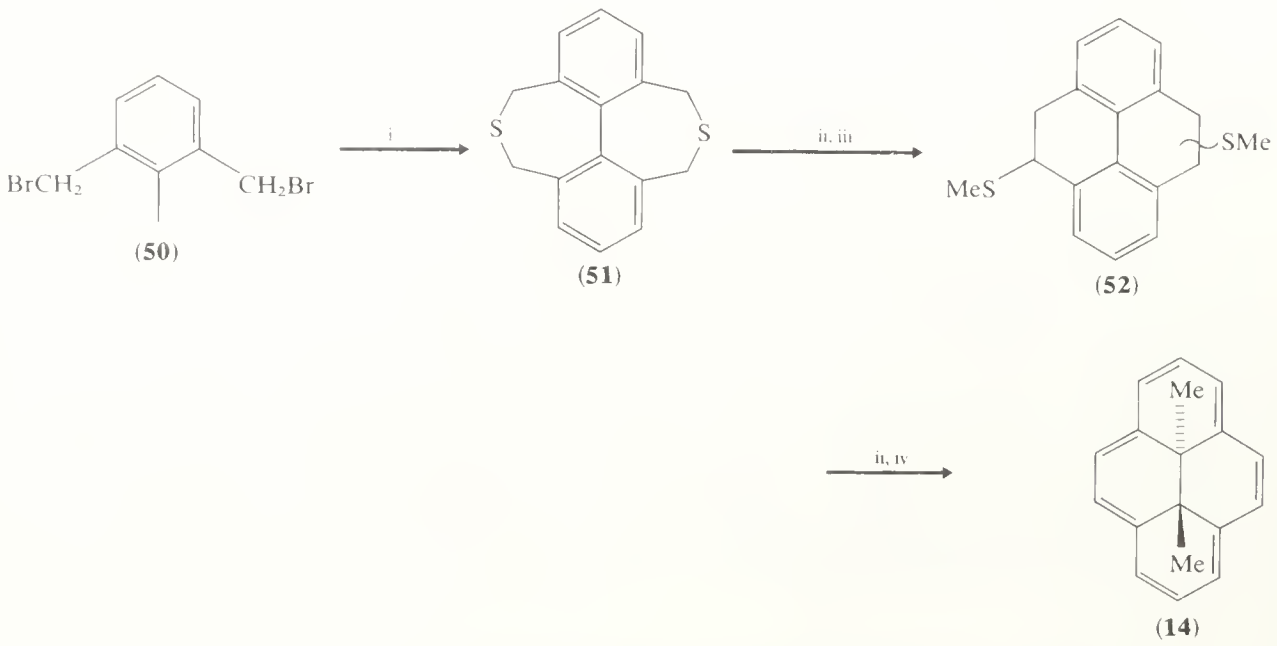
2.6.2.4 Miscellaneous methods

A variety of other methods have been used to prepare specific annulenes. The bis-Wittig reaction[23] has been used extensively to prepare benzannelated systems, as illustrated for 1,2:5,6:9,10-tribenzo[12]annulene (**49**), prepared[24] from *o*-phthalaldehyde (**47**) and the bis-ylide (**48**) (equation 5). Methods involving the extrusion of sulphur in the



(5)

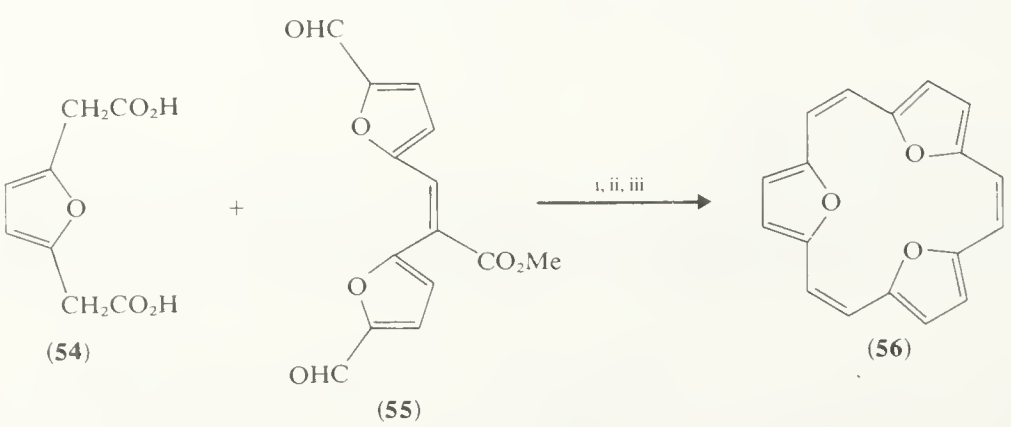
formation of the final carbon–carbon bond have also been extensively used, and the necessary cyclic sulphides can be prepared in high yield. This is the preferred method for the synthesis of 15,16-dimethyl-15,16-dihydropyrene (**14**).[25] The dibromide (**50**) is treated with sodium sulphide to give the cyclic dithioether (**51**), which, on methylation and subsequent elimination, gives the disulphide (**52**). Further methylation and elimination affords (**14**) (Scheme 11).



i, Na_2S, EtOH; ii, $(MeO)_2\overset{+}{C}H\ BF_4^-$, CH_2Cl_2; iii, NaH, THF; iv, $KOBu^t$, Bu^tOH, Δ.

SCHEME 11

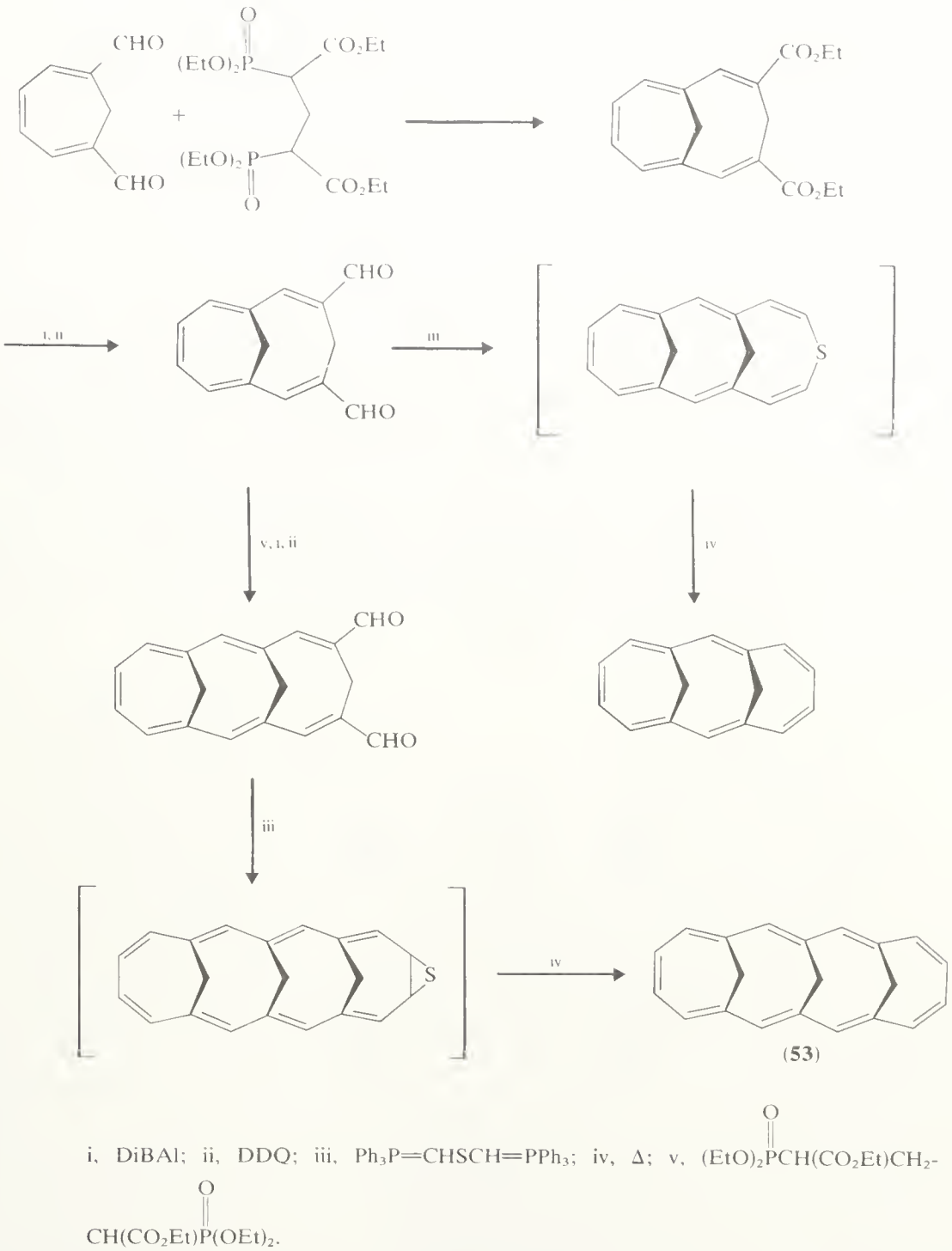
A number of 1,4:7,10:13,16-tribridged [18]annulenes have been prepared using a Perkin condensation between a 2,5-disubstituted five-membered heterocycle and the appropriate bisaldehyde.[26] Thus treatment of 2,3-bis(methoxycarbonyl)furan (**53**) with the bisaldehyde (**54**), followed by decarboxylation, gave [18]annulene trioxide (**55**) (Scheme 12).



i, Ac_2O; ii, CH_2N_2; iii, H_3O^+, Δ.

SCHEME 12

Vogel and his co-workers[22] have used a combination of the Wittig–Horner and sulphur extrusion reactions to prepare a series of *syn*-methano-bridged annulenes, including the trimethano-bridged [18]annulene (**56**) as shown in Scheme 13. It involves the preparation of an homologous series of dialdehydes using a bifunctional Wittig–Horner reagent. These



i, DiBAl; ii, DDQ; iii, $Ph_3P{=}CHSCH{=}PPh_3$; iv, Δ; v, $(EtO)_2\overset{O}{\overset{\|}{P}}CH(CO_2Et)CH_2$-$CH(CO_2Et)\overset{O}{\overset{\|}{P}}(OEt)_2$.

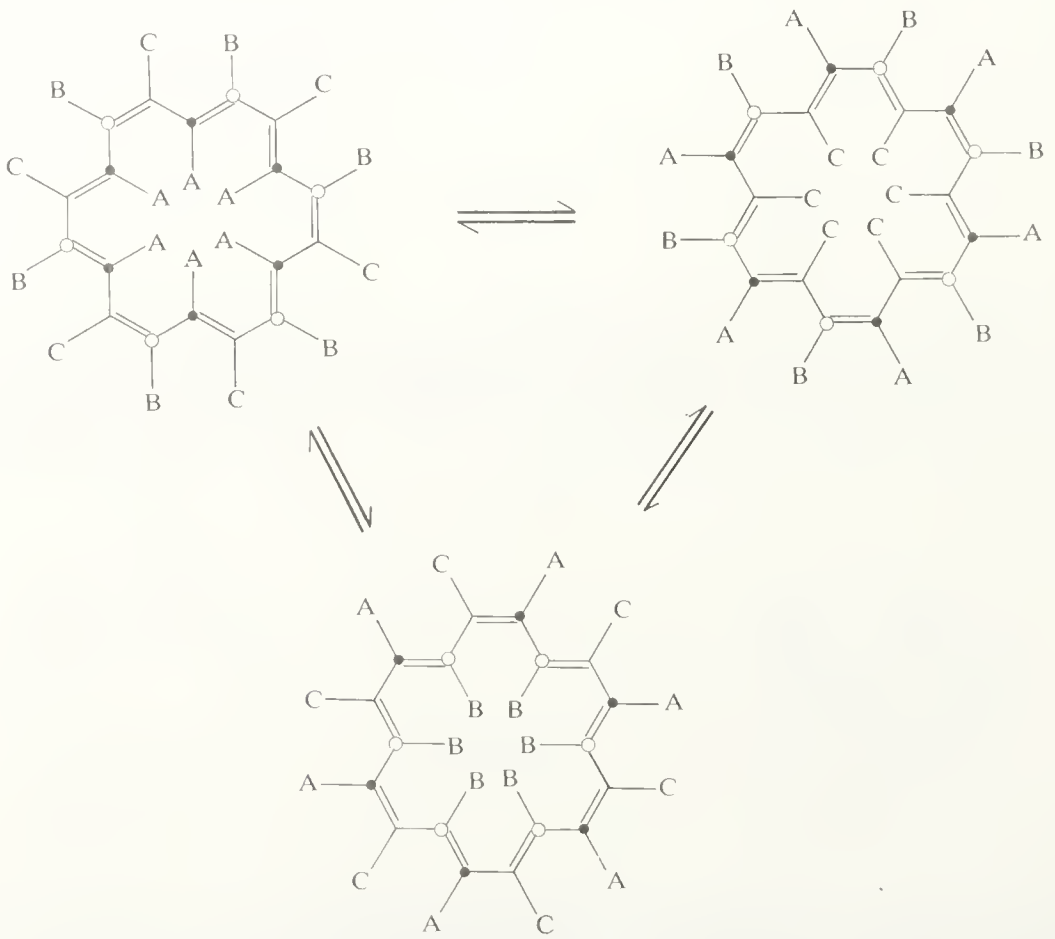
SCHEME 13

dialdehydes are then converted *via* a bis-Wittig reaction with the ylide derived from α,α'-dichlorodimethyl sulphide into bis-vinyl sulphides which are converted finally into the methanoannulenes by sulphur extrusion. Other methods have been used to transform the dialdehydes into the corresponding methanoannulenes. For example, the dialdehydes are transformed into the bismethylene derivatives which are then converted into annulenes by extended Diels–Alder reactions.

A number of methods specific to the formation of particular annulenes will be described later. Methods leading to dehydroannulenes will be discussed in Section 2.6.5.

2.6.3 PROPERTIES OF THE $4n+2$ ANNULENES

The properties of benzene, the archetypal aromatic system, have been described in detail in Chapter 2.5. How do the properties of the large $4n+2$ π-electron annulenes relate to those of benzene? [18]Annulene (**12**) was the first macrocyclic annulene to be prepared. It is stable in the crystalline state but decomposes in solution at room temperature, presumably as a result of oxidation. It has an extensive electronic spectrum with the main maximum at 369 nm (ε 303 000).[13] The ^{1}H n.m.r. spectrum is temperature dependent: at −70 °C, the spectrum shows two signals, a multiplet at δ 9.28 (12H) and a triplet at δ −2.99 (6H), which broaden on warming, coalesce, and eventually at 110 °C give a sharp singlet at δ 5.45.[27] The low-temperature spectrum is that expected for (**12**) with twelve outer, deshielded protons and six inner, shielded protons. The change in the spectrum at higher temperatures indicates that exchange of protons between inner and outer positions is occurring fast on the n.m.r. timescale. This behaviour may be interpreted in terms of inversion of the three equivalent structures in Scheme 14. Fluxional behaviour has been found to be a general property of the macrocyclic annulenes. The chemical shifts of the inner and outer protons in the low-temperature spectrum of [18]annulene indicate that it is a diatropic molecule. The broad-band decoupled ^{13}C n.m.r. spectrum is also temperature dependent; it shows two signals at δ 128 and 121 at −70 °C and one at δ 126 at 60 °C.[14] This behaviour arises because of exchange of carbon atoms between the two possible sites (see Scheme 14).



SCHEME 14

A three-dimensional X-ray crystallographic analysis of [18]annulene showed that it was a near-planar molecule with non-alternate bonds of two types, six '*cisoid*' (141.9 pm) and twelve '*transoid*' (138.2 pm) (Figure 2).[28] A number of estimates of the delocalization energy have been made; the most recent from the thermochemical decomposition of (**12**) to benzene and dihydrobenzocyclo-octene[29] is 155±25 kJ mol^{-1}.

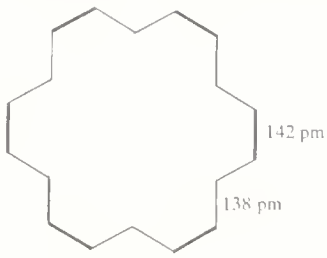
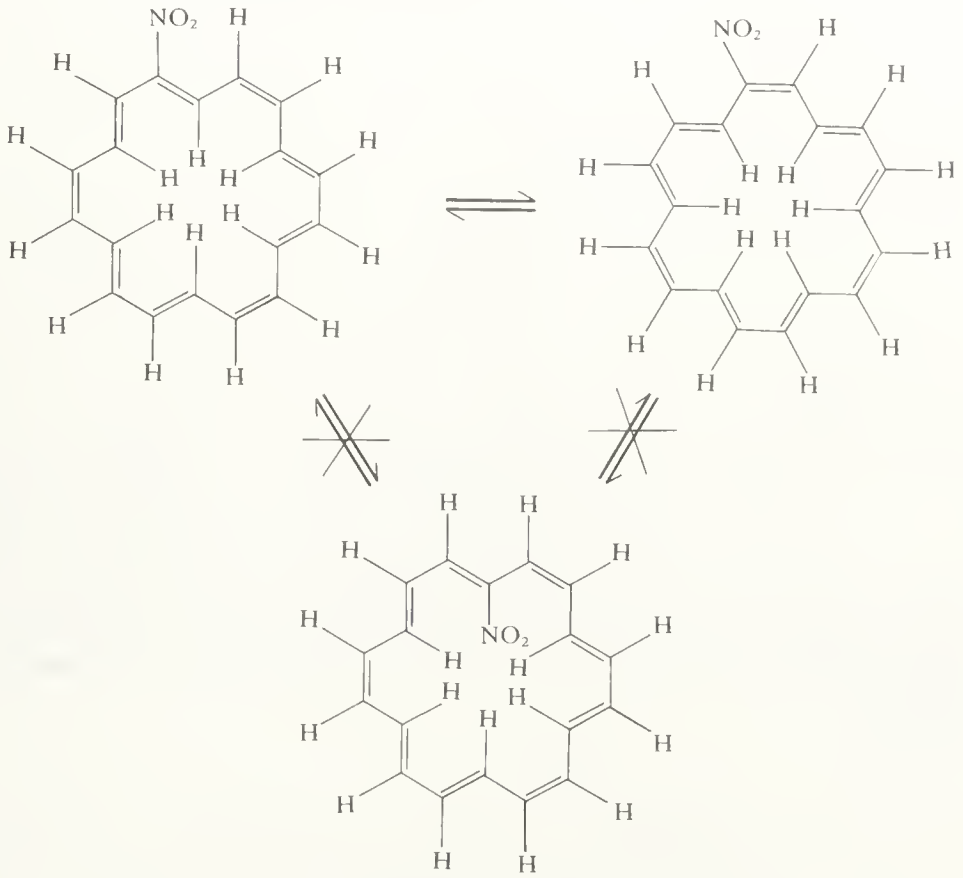


Figure 2

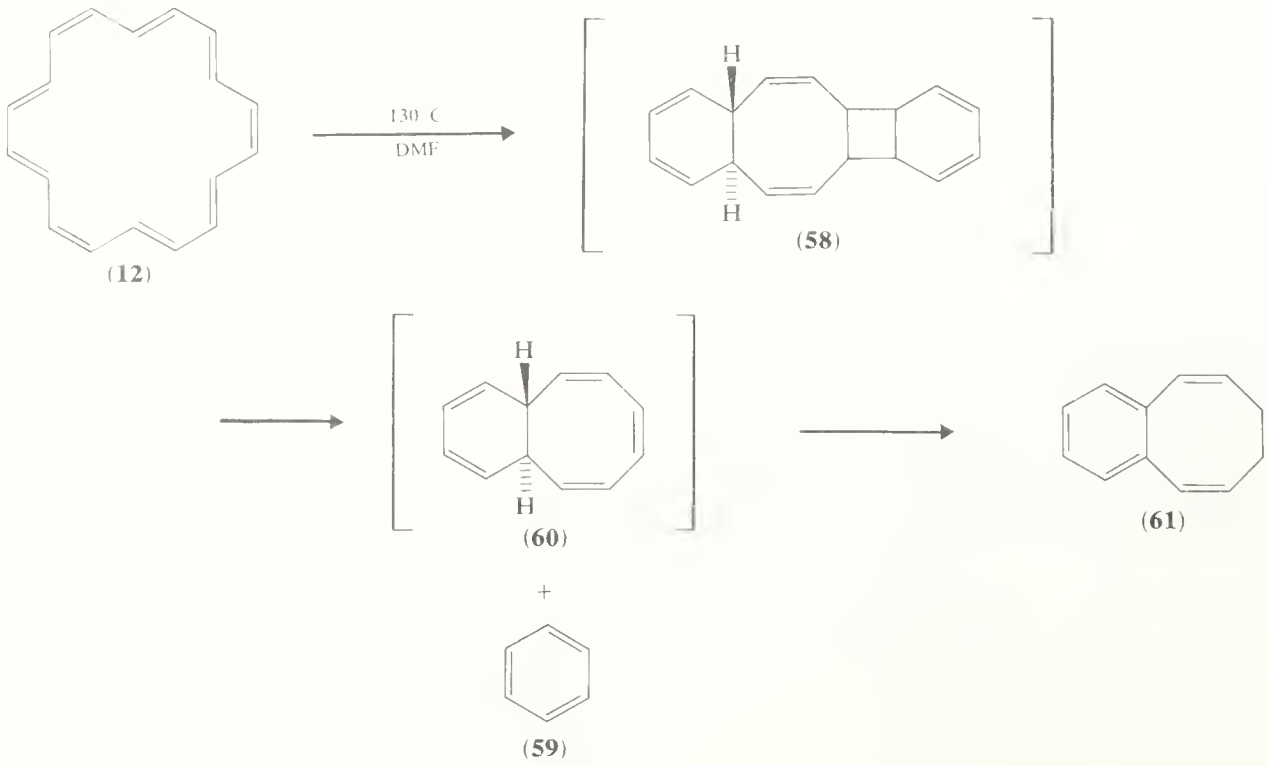
[18]Annulene (**12**) can be acetylated, nitrated, formylated, and brominated to give acetyl- (**57a**), nitro- (**57b**), formyl- (**57c**), and bromo-[18]annulene (**57d**), respectively.[15] Whether or not these reactions proceed by electrophilic substitution mechanisms is not known. The substituent is fixed in an outer position; this is clearly revealed in the temperature-dependent ^{1}H n.m.r. spectra since the five associated hydrogens also remain permanently in an outer position (Scheme 15).



SCHEME 15

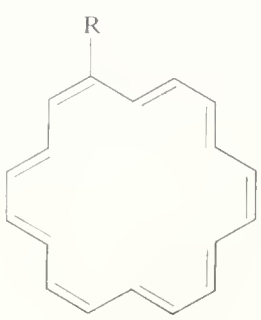
[18]Annulene (**12**) decomposes at 130 °C in DMF to give benzene (**59**) and dihydrobenzocyclo-octene (**61**).[30] This reaction appears to proceed by conversion of (**12**) to a mixture of valence tautomers (*e.g.* **58**); these cleave thermally to give benzene and *trans*-bicyclo[6,4,0]dodeca-2,4,6,9,11-pentaene (**60**), which undergoes two 1,5-hydrogen shifts to give (**61**) (Scheme 16).

The bridged [18]annulene (**63**) has been obtained[31] by photoirradiation of the cyclophane (**62**) prepared *via* the sulphide route. The inner protons resonate at δ −2.58 and −2.86 in the ^{1}H n.m.r. spectrum, indicating that compound (**63**) is strongly diatropic. However, it is less diatropic than the related bridged [18]annulene (**64**) in which the inner protons resonate at δ −6.44, −6.82 and −7.88. The difference in diatropicity could arise from the difference in perimeter geometry, the 'inversion' in the ring of (**63**) producing a local ring current opposite in sense to the main ring current.

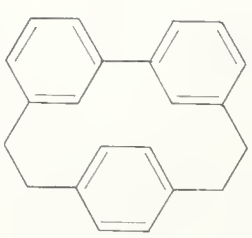


(12) (58) (60) (61) (59)

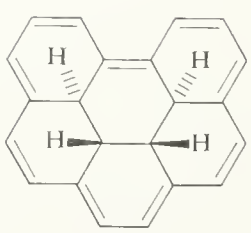
SCHEME 16



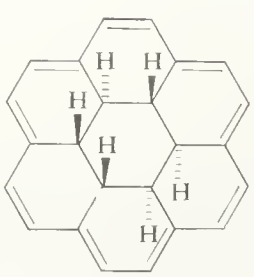
(**57a**) CH_3CO
(**57b**) NO_2
(**57c**) CHO
(**57d**) Br



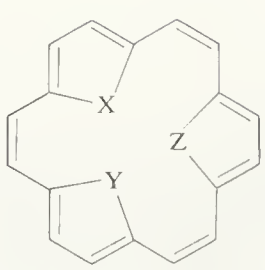
(**62**)



(**63**)



(**64**)



(**65a**) X = Y = O, Z = S
(**65b**) X = O, Y = Z = S
(**65c**) X = Y = Z = S

The ^{1}H n.m.r. spectrum of [18]annulene trioxide (**56**) shows only low-field signals (*ca.* δ 8.7) and the molecule is clearly diatropic. When the oxygen atoms are progressively replaced by sulphur atoms, the series of compounds (**65a–c**) show changes in their ^{1}H n.m.r. spectra consistent with the monosulphide bisoxide (**65a**) being diatropic and the bis-sulphide monoxide (**65b**) and trisulphide (**65c**) being atropic. The decrease in cyclic

delocalization may arise from (i) the steric bulk of the sulphur atoms and (ii) the preference of thiophen to maintain its own conjugative delocalization.

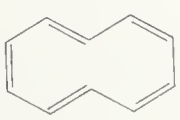
Unlike [18]annulene (**12**), all-*cis*- (**26**) and mono-*trans*-[10]annulenes (**27**) do not exhibit any aromatic properties and are only stable at low temperature.[17] The isomers do not interconvert thermally; however, interconversion does occur photochemically.

(**26**)

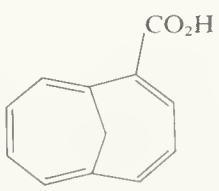
(**27**)

The ^{1}H n.m.r. spectrum of (**26**) shows a singlet at δ 5.47 and the broad-band decoupled ^{13}C n.m.r. spectrum also shows a single peak at 130.4 p.p.m.; both spectra are temperature independent. The electronic spectrum exhibits low intensity maxima at 256 (ε *ca.* 2000) and 265 nm. The molecule rearranges thermally at −14 °C into *cis*-9,10-dihydronaphthalene (**28**). The ^{1}H n.m.r. spectrum of (**27**) is temperature dependent with two signals at −100 °C and a singlet at δ 5.86 at −40 °C, indicating that the *trans* double bond is interchanging its position around the ring. The electronic spectrum shows extensive tailing into the high-wavelength region with maxima at 257 (ε 29 000) and 265 (ε 20 000) nm. Compound (**27**) rearranges to *trans*-9,10-dihydronaphthalene (**24**) at −40 °C (Scheme 5). Compounds (**26**) and (**27**) are non-planar molecules.

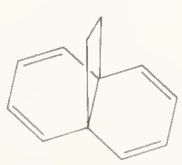
Replacing the two interacting hydrogens in the unknown di-*trans*-[10]annulene (**66**) gives 1,6-methano[10]annulene (**13**) in which the transannular interactions are removed. The ^{1}H n.m.r. spectrum of (**13**) shows an AA′BB′ system for the ring protons at low field [δ 7.27 (4H) and 6.95 (4H)] and a singlet for the methylene bridge protons at high field [δ −0.52]. This indicates that (**13**) is a diatropic molecule, a conclusion confirmed by its high diamagnetic exaltation ($\Lambda = 36.8$).[32] The broad-band decoupled ^{13}C n.m.r. spectrum shows four lines, the three types of ring carbon being at low field [C-1, δ 114.6; C-2, 128.7; C-3, 126.1] with the methylene bridge carbon at higher field (δ 34.8). The electronic spectrum shows a maximum at 256 nm (ε 68 000). An X-ray crystallographic analysis of 1,6-methano[10]annulene-2-carboxylic acid (**67**) shows that the perimeter of the 10-membered ring is like a flattened bowl with bond lengths in the range 138–142 pm.[33]



(**66**)



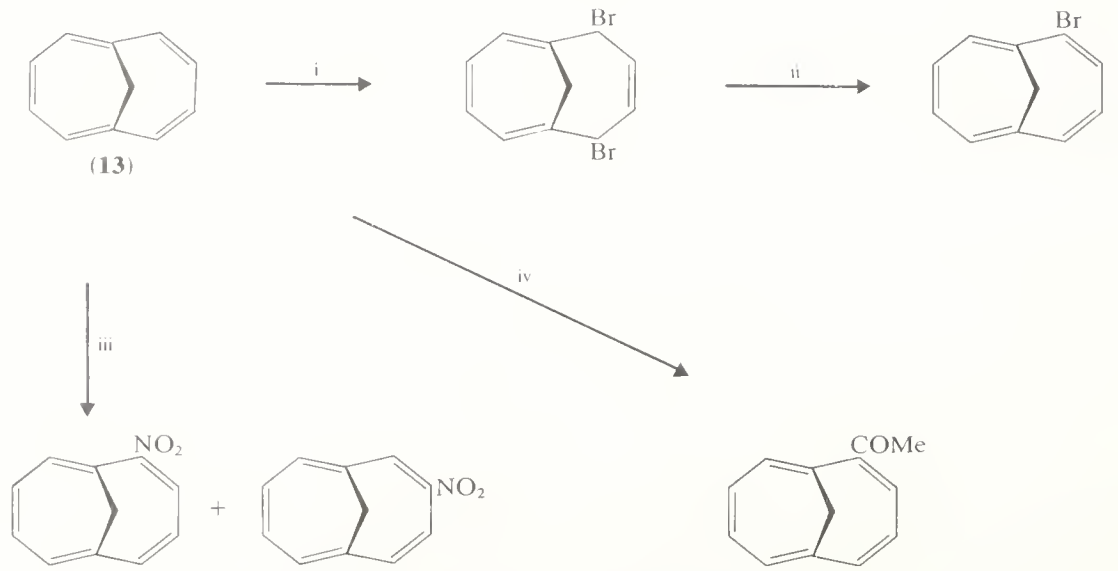
(**67**)



(**68**)

1,6-Methano[10]annulene (**13**) can be acetylated, nitrated, and brominated; bromination occurs by an addition–elimination mechanism (Scheme 17).[20]

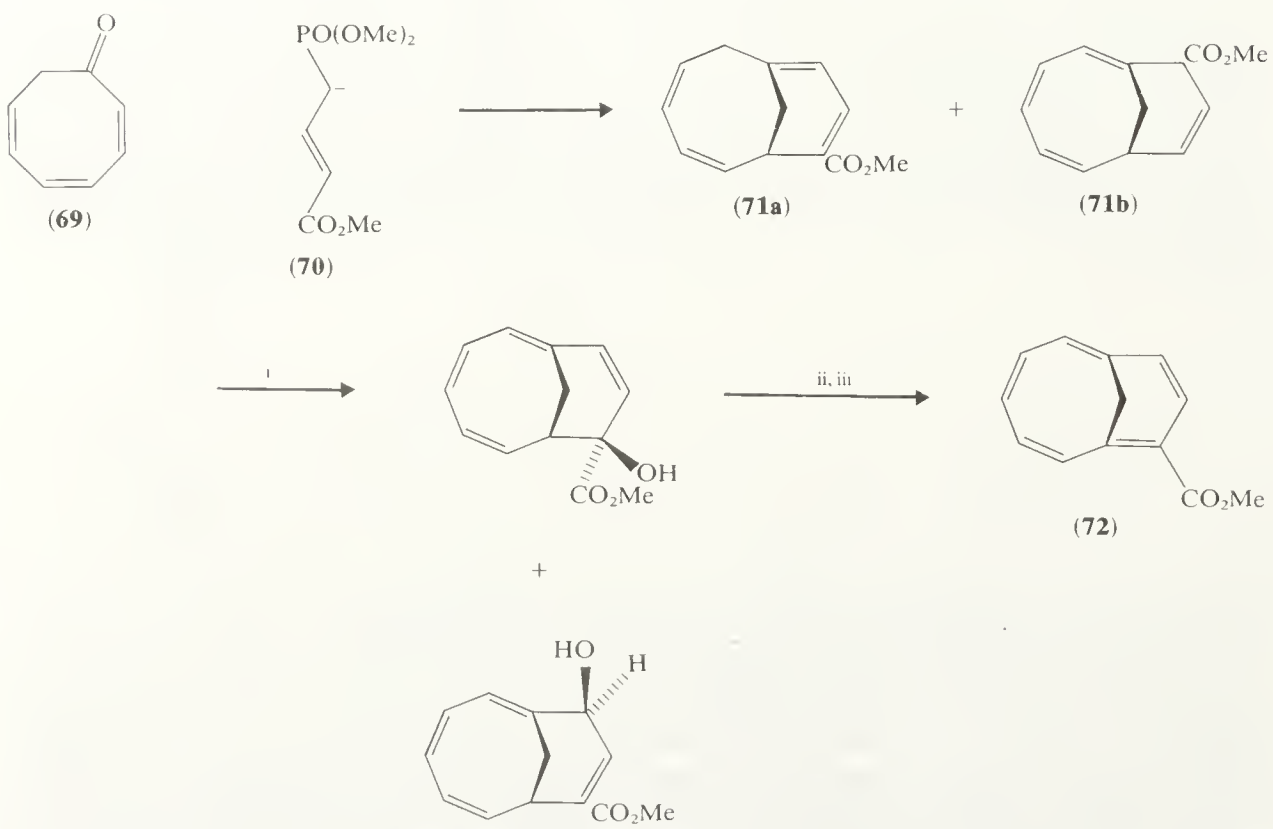
The substitution of two inner protons by a one-carbon bridge clearly removes the non-bonded interactions without sufficiently distorting the molecular framework such that delocalization of the 10 π-electrons cannot occur. Introduction of a two-carbon bridge, which could lead to 1,6-ethano[10]annulene, does in fact give the dihydronaphthalene valence tautomer (**68**).[34] The preference for (**68**) rather than the [10]annulene tautomer may result from the increased strain introduced by the two-carbon bridge in the open structure, but the different electronic structures of cyclopropane and cyclobutane are probably also contributing factors.



i, Br_2, $CHCl_3$, 0 °C; ii, 0 °C; iii, $Cu(NO_3)_2$, HOAc; iv, Ac_2O, $SnCl_4$.

SCHEME 17

A second bridged [10]annulene, 1,5-methano[10]annulene (**73**), has recently been prepared in an impure form by Masamune and his co-workers.[35] A number of derivatives have been well characterized and the method of preparation is outlined in Scheme 18. The crucial step in the synthesis is the addition of the phosphonate (**70**) to cyclo-octatrienone (**69**) to give the strained dihydro[10]annulenes (**71**). Methyl 1,5-methano[10]-annulene-8-carboxylate (**72**) shows signals for the ring protons at δ 8.78, 8.14, and 7.50,

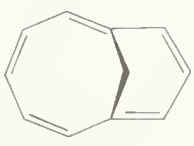


i, $LiNPr^i_2$, $^3O_2$; ii, *p*-$NO_2C_6H_4COCl$; iii, 150 °C.

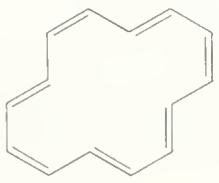
SCHEME 18

with the methylene bridge protons at δ −0.34 and −1.27 in its ^{1}H n.m.r. spectrum. The parent system (**73**) has the methylene bridge protons at δ −0.45 and −0.96 in the ^{1}H n.m.r. spectrum. Clearly these are diatropic systems. The broad-band decoupled ^{13}C n.m.r. spectrum of (**72**) shows the methylene carbon at δ 35.3 and the ring carbons in the range δ 126.9–158.5. Both the ^{1}H and ^{13}C n.m.r. spectra are temperature independent down to −90 °C, and if bond switching is occurring then it must be very rapid. The electronic spectrum shows maxima at 266 (ε 16 000), 295 (25 000), 364 (9000), and 480 (600) nm, the bands being shifted to longer wavelength than in 1,6-methano[10]annulenes, reminiscent of the difference between azulene and naphthalene.

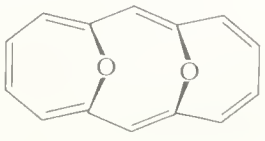
[14]Annulene (**74**) was prepared by Sondheimer and his co-workers from tetradeca-4,10-diene-1,7,13-triyne by a sequence of coupling, prototropic rearrangement, and partial hydrogenation. The compound exists as a mixture of two configurational isomers. The crystalline component was shown by X-ray crystallographic analysis to have the configuration (**74**). The molecule is significantly non-planar with C—C bond lengths in the range 135–147 pm.[36] The ^{1}H n.m.r. spectrum of isomer (**74**) is temperature dependent. The two signals [δ 7.6 (10H) and δ 0.0 (4H)] at −60 °C coalesce to give a singlet (δ 5.58) at room temperature. The other isomer gave two signals at much lower temperature. [14]Annulene is less stable than [18]annulene and no substitution products have been obtained.[15]



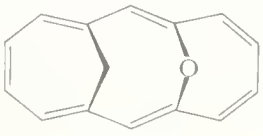
(**73**)



(**74**)



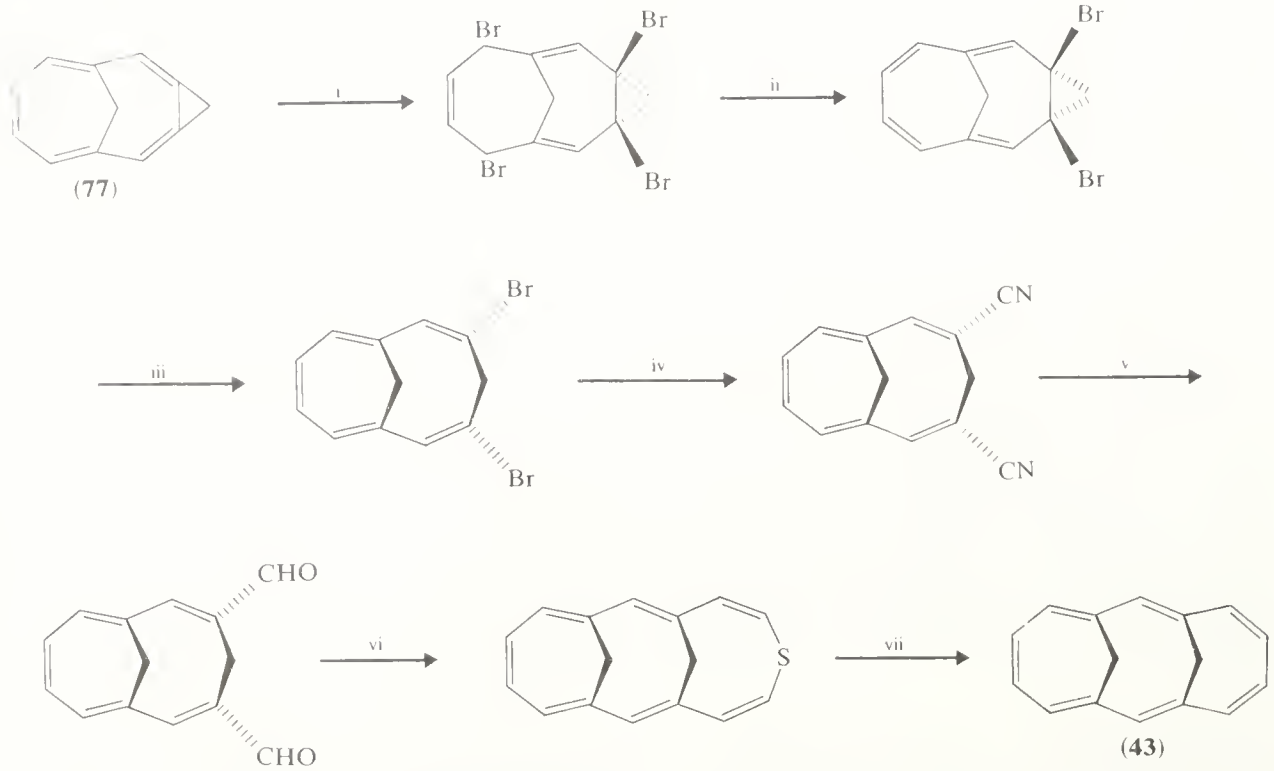
(**75**)



(**76**)

A variety of 1,6:8,13-bridged [14]annulenes have been prepared with both carbon and heteroatom bridges. *syn*-1,6:8,13-Bisoxido[14]annulene (**75**) is a red crystalline, thermally stable compound, which is diatropic by the ^{1}H n.m.r. criterion. An X-ray crystallographic analysis shows that it has a reasonably planar periphery with bonds of similar length (139 pm). *syn*-1,6-Methano-8,13-oxido[14]annulene (**76**) is also a diatropic system. *anti*-1,6:8,13-Bismethano[14]annulene (**42**) is, by contrast, a highly reactive yellow, atropic polyolefin. The methylene bridges presumably distort the σ-framework so that interaction of the π-bonds is prevented. Although *syn*-1,6:8,13-bismethano[14]annulene (**43**) could not be prepared by the norcaradiene–cycloheptatriene route, it has recently been obtained from 1,6-methano[10]annuleno[*b*]cyclopropene (**77**) by the reaction sequence outlined in Scheme 19,[37] and also by the sequence in Scheme 12. The ring protons resonate at δ 7.9–7.4 and the methylene protons at δ 0.9 and −1.2 in the ^{1}H n.m.r. spectrum, indicating that (**43**) is diatropic. Despite the hydrogen–hydrogen interaction between the *syn*-mythylene groups, the molecule can attain sufficient planarity for delocalization to occur. A series of compounds with a bridge between the *syn*-methylene groups had been prepared earlier using the standard method, and an analysis of their ^{1}H n.m.r. spectra showed that there is no significant reduction in delocalization around the periphery of (**44**) with increasing value of n up to $n = 3$.[38]

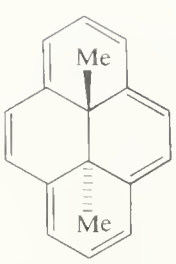
trans-15,16-Dimethyl-15,16-dihydropyrene (**14**) has a 14π-electron periphery and is diatropic. The methyl groups resonate at δ −4.25 in the ^{1}H n.m.r. spectrum and the molecule exhibits a high diamagnetic exaltation ($\Lambda = 81$). Compound (**14**) readily undergoes electrophilic substitution and the 2-acetyl (**78a**), 2-nitro (**78b**), and 2,7-dibromo (**78c**) derivatives have all been prepared. On photoirradiation, compound (**14**) ring opens to give the metacyclophane (**79**), which is thermally reconverted into (**14**). The parent *trans*-15,16-dihydropyrene (**80**) has been prepared and it is also diatropic; it is readily oxidized to pyrene. *cis*-15,16-Dimethyl-15,16-dihydropyrene (**81**) is less diatropic than (**14**) with the methyl groups resonating at δ −2.06. Introduction of different groups at the 15,16-positions has made it possible to map the magnetic field inside the ring.[39]



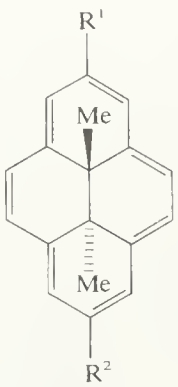
(77) (43)

i, Br_2; ii, KI, Me_2CO; iii, C_6H_6, Δ; iv, CuCN, DMF; v, Bu^i_2AlH; vi, $(Ph_3P{=}CH)_2S$; vii, Ph_3P.

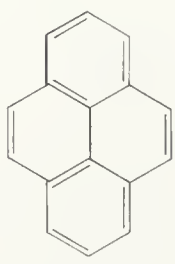
SCHEME 19



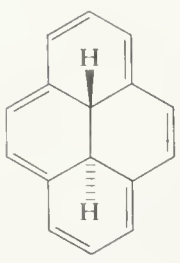
(14)



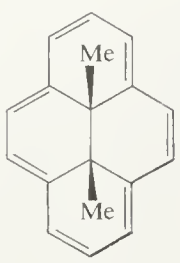
(78a) $R^1 = COMe$, $R^2 = H$
(78b) $R^1 = NO_2$, $R^2 = H$
(78c) $R^1 = R^2 = Br$



(79)

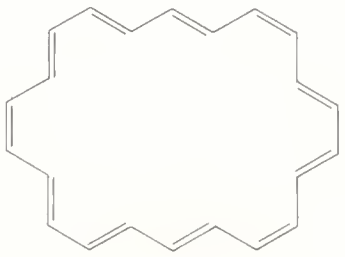


(80)



(81)

[22]Annulene (**82**), prepared by Sondheimer's method,[40] is a dark purple, unstable crystalline compound. The ^{1}H n.m.r. spectrum is temperature dependent; the two bands at δ 9.65–9.3 and −0.4 to −1.2 at −90 °C coalesce to give one band at δ 5.65 at 65 °C. The complexity of the low-field band at −90 °C indicates that [22]annulene (**82**) is a mixture of isomers. The electronic spectrum has a maximum at 400 nm (ε 141 000).



(**82**)

The $4n+2$ annulenes with from 14 to 22 carbon atoms are all diatropic systems but, unlike benzene, they are fluxional molecules which undergo conformational changes with low inversion barriers (see Table 1). No thermodynamic properties have been measured except for [18]annulene, for which the latest estimate of the resonance energy gives a REPE one-third that of benzene. [10]Annulene is clearly not an aromatic system, both the all-*cis* (**26**) and mono-*trans* (**27**) forms adopting non-planar conformations. Bridging in the annulenes leads to more stable structures. The resulting molecules have fewer non-bonded interactions, but these are no longer macrocyclic systems.

TABLE 1

Inversion Barriers to Proton Exchange in the Annulenes

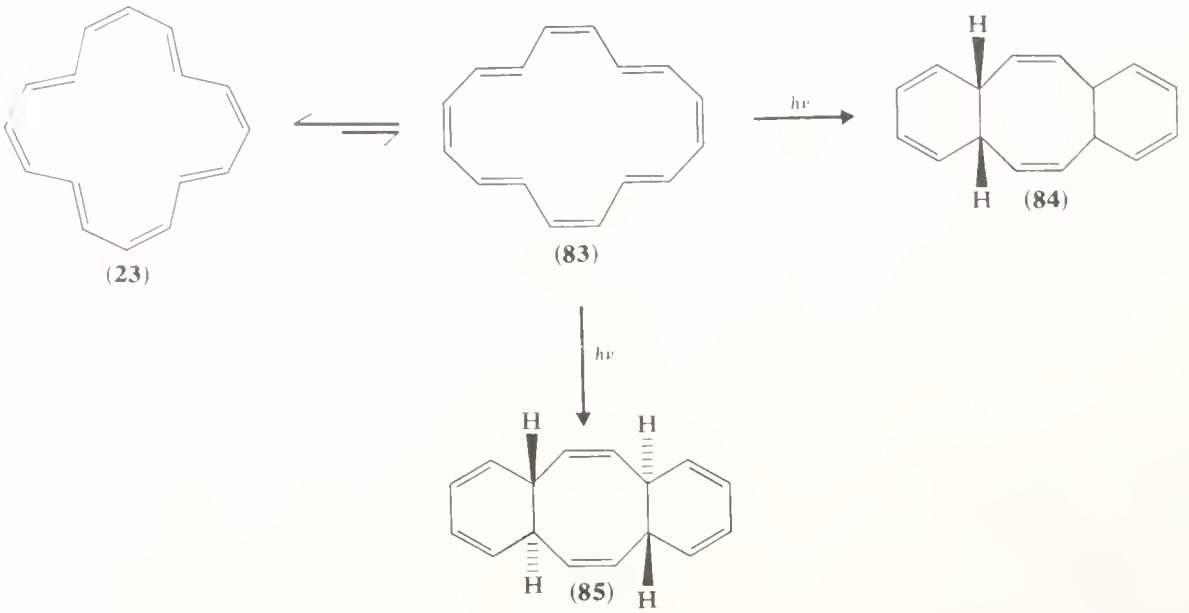
Annulenes	$\Delta G^{\neq}$ (kJ mol^{-1})	*Ref*
[12]	23·0	a
[14]	42·43, 45·2	a, b
[16]	36·2, 36·0	a, b
[18]	61·50, 56·1	a, b
[20]	41·0	c
[22]	53·6	b
[24]	46·0	b

[a]. J. F. M. Oth, *Pure Appl. Chem.*, 1971, **25**, 573. [b] I. C. Calder and P. J. Garratt, *J. Chem. Soc.* (*B*), 1967, 660. [c] B. W. Metcalf and F. Sondheimer, *J. Amer. Chem. Soc.*, 1971, **93**, 6675.

2.6.4 PROPERTIES OF THE 4*n* ANNULENES

[16]Annulene (**23**) occupies a similar position in the hierarchy of the $4n$ annulenes to that of [18]annulene (**12**) in the $4n+2$ annulene series. It is a crystalline, stable compound with an extensive electronic spectrum and a main absorption maximum at 284 nm (ε 77 000). The ^{1}H n.m.r. spectrum is temperature dependent; at −110 °C the spectrum shows two bands [δ 10.43 (4H) and δ 5.4 (12H)] which coalesce on warming the sample to give a singlet (δ 6.71) at 30 °C. Clearly, similar processes are occurring to those described for the $4n+2$ annulenes and lead to exchange of inner and outer protons. However, the outer protons are at high field and the inner protons at low field in the low-temperature spectrum. Thus [16]annulene is a paratropic system. This is confirmed by the diamagnetic exaltation ($\Lambda = -5$).[32] An X-ray crystallographic analysis shows that (**23**) has alternate double and single bonds and is non-planar, although the deviation from planarity is

small.[41] It exists as a mixture of configurational isomers, the predominant isomer (**23**) being in equilibrium with (**83**) (equation 6). On thermolysis, [16]annulene reacts *via* the isomer (**83**) to give the *cis-transoid-cis* tricyclic tautomer (**84**). On photoirradiation, it gives the *trans-transoid-trans* tautomer (**85**), again probably *via* (**83**).[42]



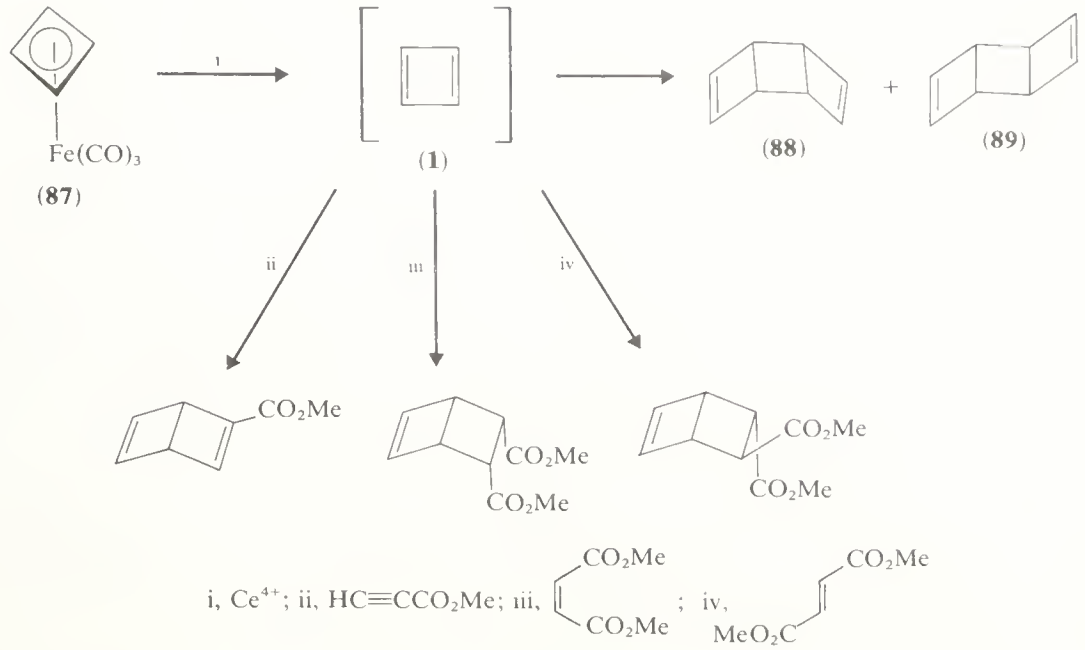
(23) (83) (84) (85) (6)

Cyclobutadiene (**1**) has provided a challenge to synthetic and theoretical chemists for over 100 years. Virtually all possible states (or non-states!) have been predicted for cyclobutadiene; its transformation into two molecules of acetylene has been categorically advanced, and later, just as categorically denied; tetrahedrane (**86**) has been suggested as a more stable alternative and the rectangular and square-planar forms have both been put forward for the ground-state configuration. Simple Hückel theory predicts it has zero resonance energy, although later calculations have suggested that the resonance energy is negative and hence it is anti-aromatic.

(**86**)

The first convincing evidence for the intervention of cyclobutadiene in a reaction was provided by Petit and his co-workers from a study of the oxidation of the cyclobutadiene–iron tricarbonyl complex (**87**).[43] On oxidation, (**87**) gave a mixture of *syn*- (**88**) and *anti*-(**89**)tricyclo[4,2,0,$0^{2,5}$]octadienes (**89**) and, in the presence of dienophiles, adducts of cyclobutadiene were formed (Scheme 20). The adducts with dimethyl fumarate and dimethyl maleate were formed stereospecifically and (**1**) behaved as a diene. It was shown clearly that the reactions were not occurring *via* (**87**) or a derived organometallic system, but that 'free' cyclobutadiene was involved.

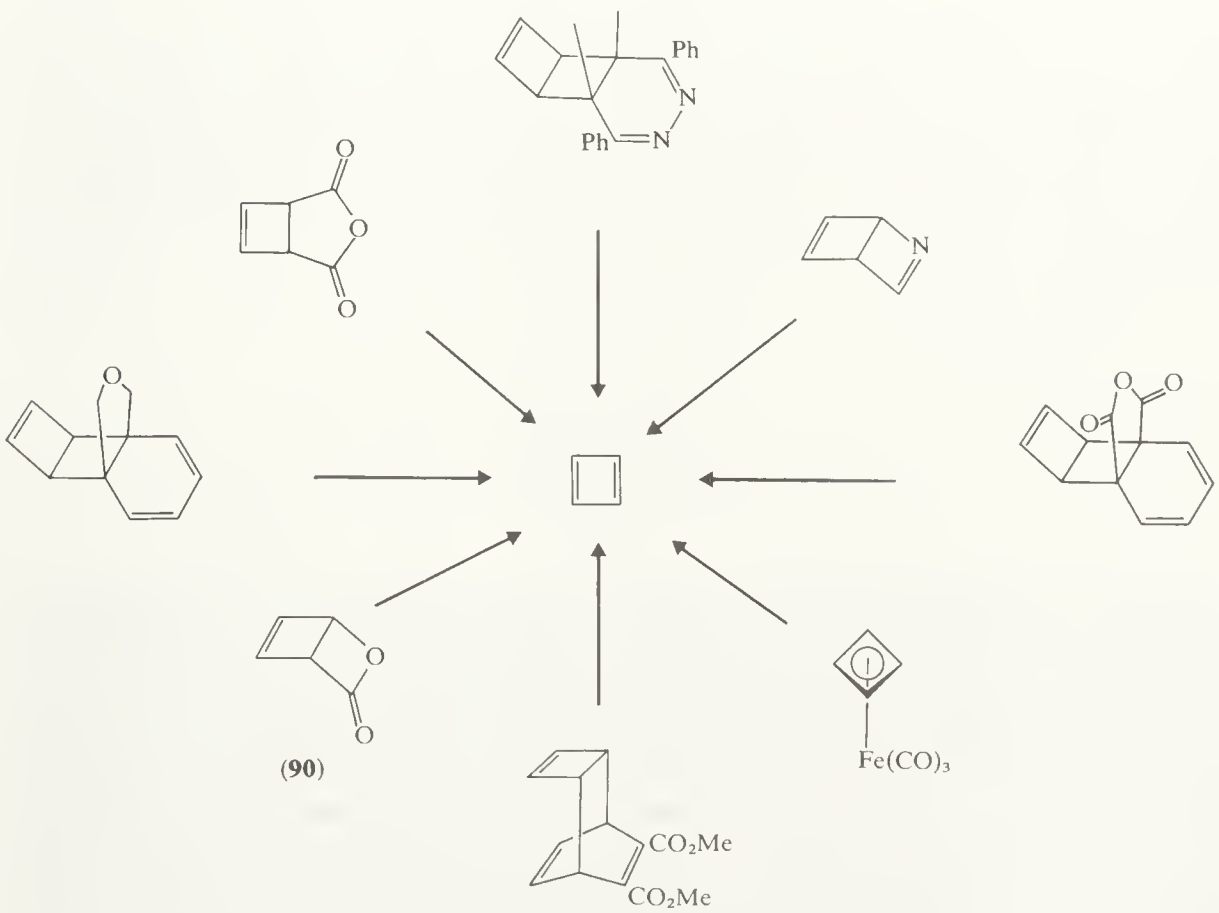
Cyclobutadiene has recently been observed spectroscopically as a discrete entity by photochemical formation in a matrix at low temperature (*ca.* 8–20 K). Lin and Krantz[44] and Chapman and co-workers[45] reported that photoirradiation of photo-α-pyrone (**90**) in an argon matrix gives a compound with a simple i.r. spectrum which was attributed by them to cyclobutadiene. Controversy regarding the origin of this and other subsequent spectra has recently been resolved by Maier and his co-workers,[46] who showed that some of the bands were due to charge transfer complexes formed between (**1**) and the other photofragment, and that (**1**) only has i.r. bands at 1240 and 570 cm^{-1}. The electronic



SCHEME 20

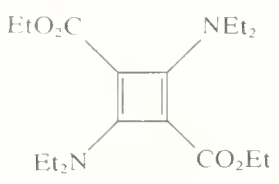
spectrum shows end absorption beginning at 290 nm,[46] other previously observed absorption bands again being due to charge-transfer species.

A number of alternative precursors (Scheme 21) have now been irradiated[47] in matrixes at low temperatures to give cyclobutadiene. On allowing the matrix to thaw, (**1**) dimerizes to give exclusively the *syn*-dimer (**88**) and, in the presence of dienophiles, adducts are obtained.

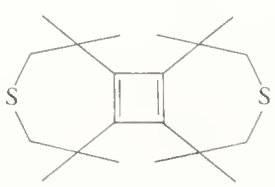


SCHEME 21

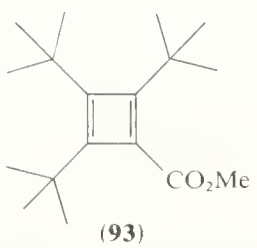
A variety of substituted cyclobutadienes have been prepared which are more stable than the parent system. The first types of cyclobutadienes to be isolated were stabilized by a push–pull conjugation, bearing electron-withdrawing and electron-donating substituents, *e.g.* (**91**).[48] The first isolated cyclobutadiene which was stabilized only by steric protection was the tricyclic system (**92**), prepared by Kimling and Krebs.[49] This is a stable compound which has been shown by X-ray crystallographic analysis to have a rectangular structure.[50] The PE spectrum indicates that the sulphur atoms do not interact with the cyclobutadiene system.[51] Methyl tri-t-butylcyclobutadienecarboxylate (**93**) has also been examined by X-ray crystallography and this molecule is also rectangular with two long (151, 155 pm) and two short (141, 138 pm) bonds.[52] The ^{1}H n.m.r. spectrum of tri-t-butylcyclobutadiene (**94**) shows signals at δ 5.35 (1H), 1.14 (9H), and 1.05 (18H). The signal at δ 5.35, attributable to the ring proton, resonates at higher field than expected for an olefinic proton, indicating that (**94**) is paratropic.[53]



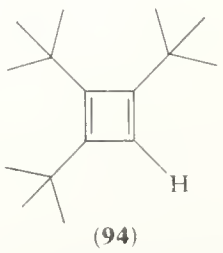
(**91**)



(**92**)

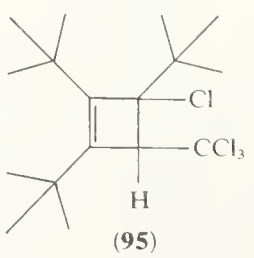


(**93**)



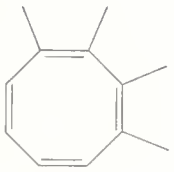
(**94**)

Although the substituted cyclobutadienes so far investigated appear to have rectangular ground states, at least in the crystalline form, the i.r. spectrum suggests that cyclobutadiene (**1**), as produced by matrix photoirradiation, is a square molecule. Two explanations have been advanced for this observation: (i) Dewar and Kollmar[54] have suggested that cyclobutadiene prepared in this way is in a nexcited triplet state which is prevented by a low activation barrier from transforming to the rectangular ground state, while (ii) Borden[55] has suggested that, contrary to all previous predictions, cyclobutadiene can have a square, or effectively square, ground-state geometry. Maier and Sauer[56] have observed that tri-t-butylcyclobutadiene (**94**), for which a rectangular structure has been assumed, undergoes triplet-type reactions: treatment of (**94**) with carbon tetrachloride giving the adduct (**95**). It seems possible, in the case of cyclobutadiene, that the reactivity expressed may depend more on the requirement of the reagent than on the electronic state of cyclobutadiene.

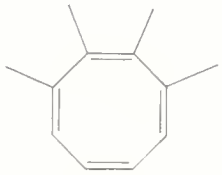


(**95**)

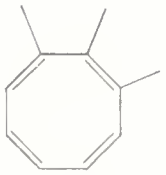
The synthesis and some of the properties of cyclo-octatetraene (**2**) were discussed previously. It was shown to behave like a polyolefin. Paquette and his co-workers[57] have dramatically illustrated the difference between cyclo-octatetraene and benzene by the isolation of a tetramethylcyclo-octatetraene as two constitutional isomers, 1,2,3,4-tetramethylcyclo-octatetraene (**96**) and 1,2,3,8-tetramethylcyclo-octatetraene (**97**). Further, enantiomers of 1,2,3-trimethylcyclo-octatetraene (**98**) have been obtained (dextrorotatory, $[\alpha]_D^{25} + 20.2°$), which racemize by a first-order process.[58] Clearly the bond shift and ring inversion behaviour described for cyclo-octatetraene in Scheme 2 is inhibited by the presence of three adjacent methyl groups which further destabilize the planar form. A minimum value of 113 kJ mol^{-1} for the bond shift process, and a value of 132.5 kJ mol^{-1} for ring inversion, were found.



(96)

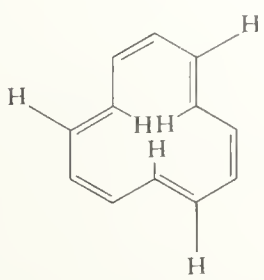


(97)

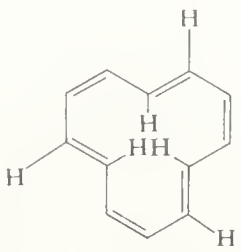


(98)

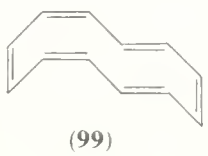
[12]Annulene (**32**) is thermally unstable and rearranges to *syn*-tricyclo[8,2,0,$0^{2,3}$]dodecatetraene (**29**) at −40 °C (Scheme 7). The ^{1}H n.m.r. spectrum is temperature dependent with two bands (δ 6·88 and 5·97) of equal intensity at −80.2 ·C becoming two bands (δ 7.83 and 5.88) in the ratio 1:3 at −170 °C. At the low temperature three protons are in an outer position (together with six other outer protons) and three are in an inner position, whereas at the higher temperature these six protons are exchanged between inner and outer positions. These exchanging protons are those on the *trans* double bonds in (**32**), which is in equilibrium with (**32a**). The chemical shift data suggest that (**32**) is slightly paratropic. On photoirradiation at −70 °C, (**32**) reverts to *trans*-tricyclo[8,2,0,$0^{2,3}$]-dodecatetraene (**30**), probably *via* the di-*trans* isomer (**99**).



(32)

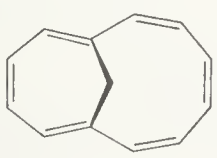


(32a)

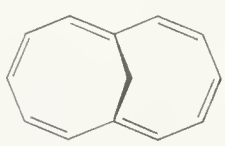


(99)

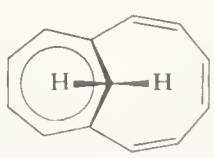
Two bridged [12]annulenes, 1,6-methano[12]annulene (**100**) and 1,7-methano[12]-annulene (**101**), have recently been prepared[22] from (**36**) (Scheme 9) by ring expansion of one or both of the cyclohexene rings, respectively. The ^{1}H n.m.r. spectrum of (**101**) shows two multiplets at δ 5.5 and 5.2 for the ring protons and a singlet at δ 6.06 for the methylene protons. Compound (**100**) has two signals for the bridge protons in the ^{1}H n.m.r. spectrum (δ 7·0 and 2·89). The high-field signal for the proton over the cyclo-heptatriene ring suggests that a homobenzene structure (**102**) may be important in this system.



(100)



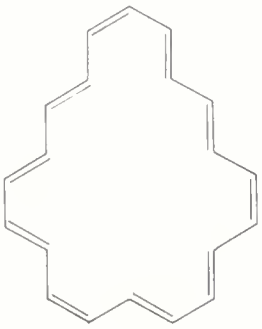
(101)



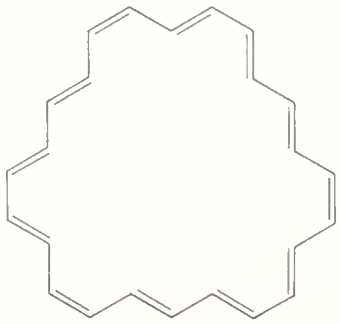
(102)

[20]Annulene (**103**) was obtained as brown-red needles by Sondheimer's method. The electronic spectrum shows a maximum at 323 nm (ε 146 000) and the ^{1}H n.m.r. spectrum is temperature dependent, consisting of two broad multiplets (δ 13.9–10.9 and δ 6.6–4.1) at −105 °C, which coalesce to give a singlet (δ 7.18) at 25 °C. It is paratropic and probably exists as a mixture of configurational isomers.

[24]Annulene (**104**) was obtained as deep purple crystals by prototropic rearrangement of (**17**) followed by partial hydrogenation (Scheme 3). The electronic spectrum shows a maximum at 364 nm (ε 201 000), and the ^{1}H n.m.r. spectrum is again temperature dependent, consisting of two multiplets (δ 12.9–11.2 and 4.73) at −80 °C which coalesce to give a singlet (δ 7.25) at 30 °C. It is paratropic and probably exists as a stereoisomeric mixture.



(**103**)



(**104**)

Except for [8]- and [10]-annulene, the series of annulenes with 4 to 24 carbon atoms show the predicted alternation of properties, the $4n+2$ members being diatropic, and the $4n$ members paratropic (Table 2). Although large annulenes have been prepared (*e.g.* [30]annulene), little information about their spectral behaviour is available. As regards the chemical properties of the two series, the difference between them is not large, although [18]annulene, unlike the other monocyclic annulenes, does undergo electrophilic

TABLE 2

The ^{1}H N.M.R. Spectral Characteristics of the Annulenes

Compound	*Type*
Cyclobutadiene	Paratropic (?)
Benzene	Diatropic
Cyclo-octatetraene	Atropic
[10]Annulene	Atropic
[12]Annulene	Paratropic
[14]Annulene	Diatropic
[16]Annulene	Paratropic
[18]Annulene	Diatropic
[20]Annulene	Paratropic
[22]Annulene	Diatropic
[24]Annulene	Paratropic

substitutions. Although the electronic spectra of the two series are similar, the $4n+2$ compounds show a bathochromic shift when compared with their $4n$ near neighbours (Figure 3). The extinction coefficients increase with ring size, but, again, the $4n+2$ members have more intense bands than the corresponding $4n$ compounds.

The bridged annulenes show the same alternation in properties as the monocyclic annulenes. In their case, however, the medium ring compounds also conform to the Hückel predictions, the non-bonded interactions having been removed.

2.6.5 DEHYDROANNULENES

The Sondheimer annulene synthesis involves the preparation of conjugated monocyclic systems containing triple bonds. These compounds have been termed dehydroannulenes,[1] and the number of triple bonds, if more than one, has been designated by the appropriate prefix bis, tris, tetrakis, and so on.[13] Using this nomenclature, compound (**105**) is 1,8-bisdehydro[14]annulene and compound (**18**) is 1,7,13-trisdehydro[18]annulene. The triple bond contributes only two π-electrons to the ring π-system, with the remaining two π-electrons occupying an orthogonal orbital. Thus the dehydroannulenes will be of the same Hückel type as the corresponding annulenes.

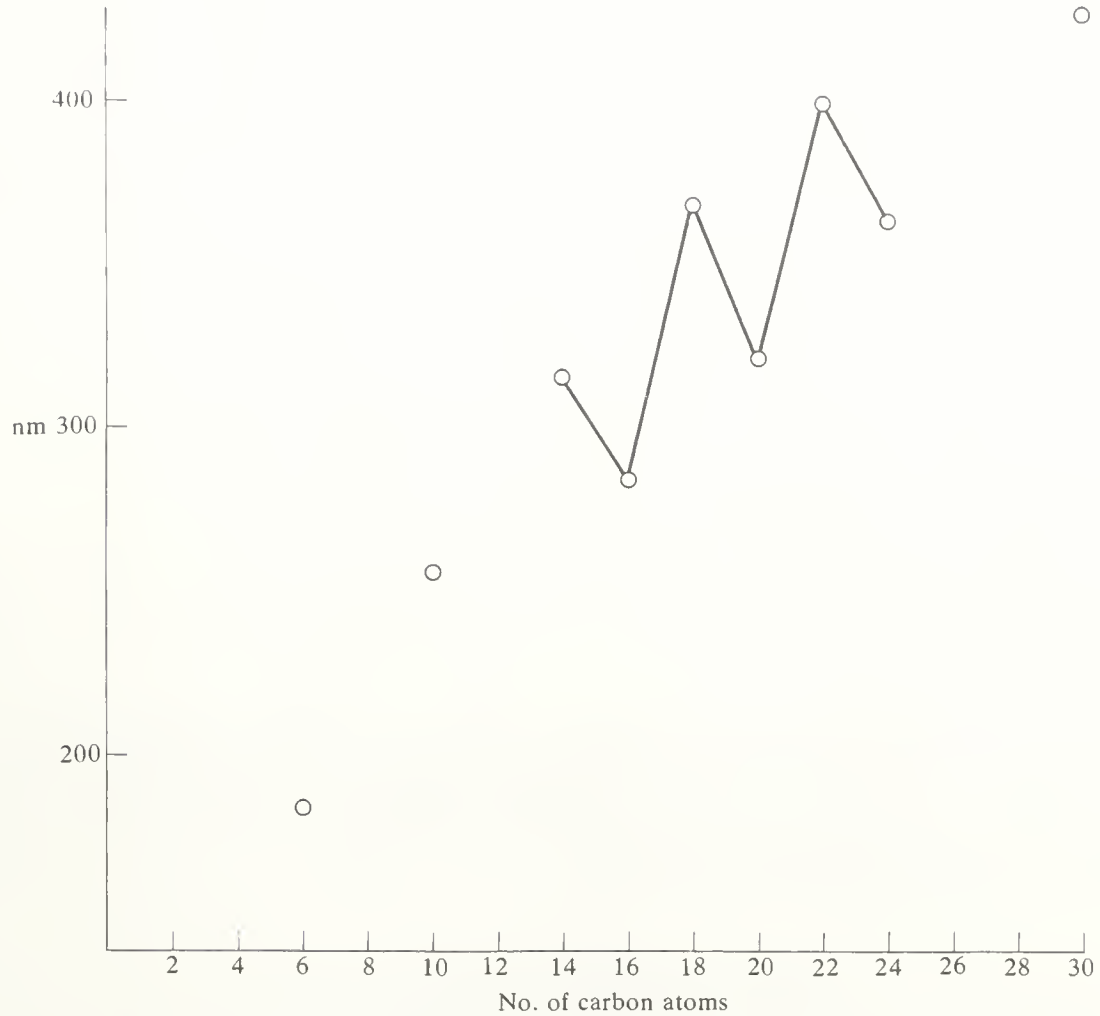
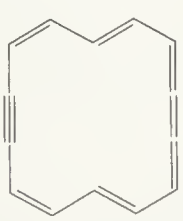
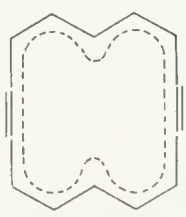


Figure 3 Plot of position of maximum absorption in the electronic spectrum against ring size for the annulenes

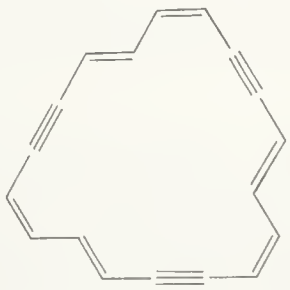
The dehydroannulenes have very similar magnetic properties to the annulenes but, because of the triple bond, the σ-framework is more rigid. Consequently, the fluxional behaviour is damped and non-averaged ^{1}H n.m.r. spectra are often obtained at room temperature for the $4n+2$ dehydroannulenes. The rigidity also leads to an increase in diatropicity in the $4n+2$ series and to paratropicity in the $4n$ series. The classical chemical behaviour of the $4n+2$ dehydroannulenes approximates more closely to that of benzene. For example, 1,8-bisdehydro[14]annulene (**105**) can be readily nitrated, acetylated, and sulphonated under conditions[15] which decompose [14]annulene. The X-ray crystallographic analysis of (**105**) indicates that it is centrosymmetric and best represented by (**105a**), with a triple bond length of 120.8 pm and the remaining bonds in the range 137.8–140.3 pm.[59]



(**105**)

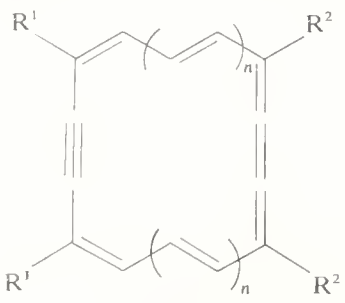


(**105a**)

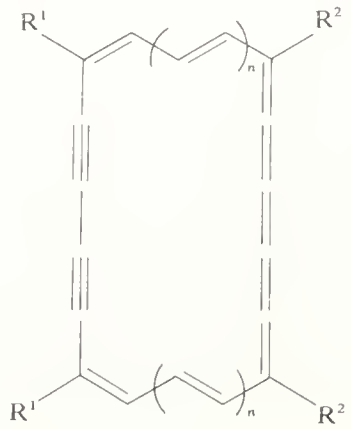


(**18**)

Nakagawa and his co-workers[60] have recently devised a general synthesis of dehydroannulenes which proceeds in high overall yield. Bisdehydroannulenes (**106,** $n = 0$–4) containing 14, 18, 22, 26, and 30 carbon atoms have been prepared which have the same general structure but vary in the number of double bonds separating the triple bonds. A variety of substituents — other than hydrogen — can be used, both with $R^1 = R^2$ and $R^1 \neq R^2$. The tetrakisdehydroannulenes (**107,** $n = 1, 2$) can be made in a similar manner



(**106**)



(**107**)

and these, and on the basis of spectral data, are clearly symmetrical delocalized systems. This was confirmed for (**107,** $n = 1$) by preparing it in two ways with $R^1 = Ph$, $R^2 = Bu^t$ and $R^1 = Bu^t$, $R^2 = Ph$ and showing that the resulting compounds are identical. The ^1H n.m.r. spectra of all of these compounds show that they are diatropic, but that the diatropicity decreases with increasing ring size (Table 3).

TABLE 3

^1H N.M.R. Spectral Data for some Tetra-t-butyltetrakisdehydroannulenes[a]

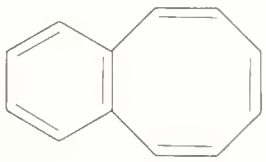
Tetrakisdehydroannulene	*Chemical shift (δ)* *Inner protons*	*Outer protons*	*Δδ = (outer − inner)*
[14]	−4.44	9.32	13.76
[18]	−3.42	9.87	13.29
[22]	−0.83	9.16	9.99
[26]	1.95	8.23	6.28
[30]	3.5	7.5	4.0

[a] M. Nakagawa, *Pure Appl. Chem.*, 1975, **44,** 885.

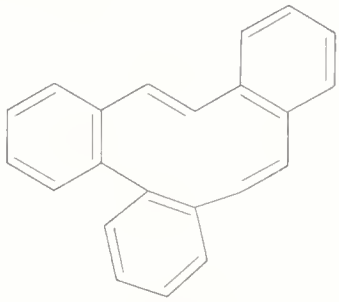
The electronic spectra also show a regular bathochromic shift as the series is ascended and the absorption bands become broader with less fine structure. The loss of fine structure may be due to the increased flexibility of the large molecules. All of the compounds are coloured, ranging from deep green to black violet, and the absorption extends out beyond 1000 nm in the case of the bisdehydro-[26]- and -[30]-annulenes. The stability also decreases with increasing ring size, a factor which probably reflects the increase in bond localization.

2.6.6 ANNELATED ANNULENES

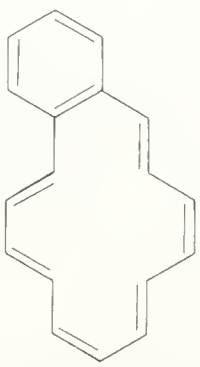
A large number of benzannelated annulenes, *e.g.* (**108**),[5] (**109**),[61] (**49**),[62] (**110**),[63] (**111**),[64] (**112**),[65] and (**113**),[66] and annelated dehydroannulenes, *e.g.* (**114**),[67a] (**115**),[67b] and (**116**),[68] have been prepared in both the $4n$ and $4n+2$ π-electron series and, in all cases, the diatropicity or paratropicity of the macrocyclic ring is decreased.



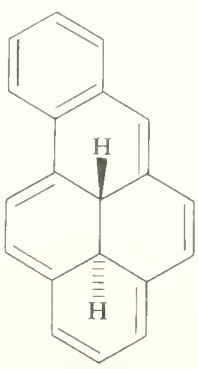
(108)



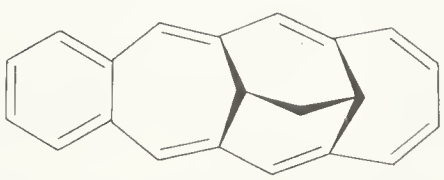
(109)



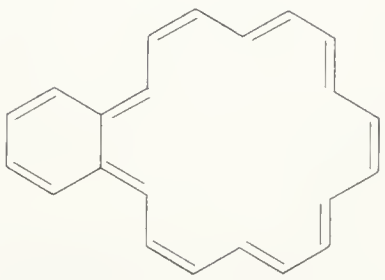
(110)



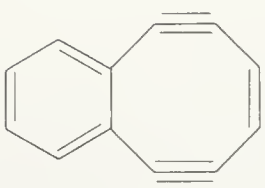
(111)



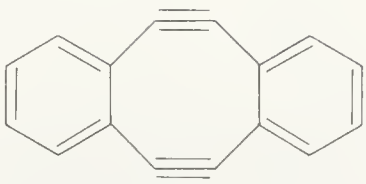
(112)



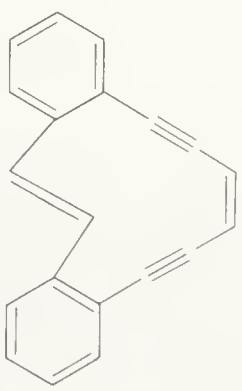
(113)



(114)



(115)



(116)

Gunther and co-workers[69] have calculated that the ratio of the π-bond orders of the six-membered ring of benzannelated annulenes can be used to predict the ground-state electronic properties of the [*n*]annulenes, and they have substantiated this view by analysing the ^{1}H n.m.r. spectra of a number of benzannelated annulenes. For delocalized $(4n+2)$ annulenes the ratio (Q) of P_{23}/P_{24} (taking the annelation position as 1,6) is >1.10 and for delocalized $4n$ annulenes it is <1.04, whereas for localized systems of either type the value lies between 1.04 and 1.10. Thus the benzotropylium cation has a Q-value of 1.223, benzocyclo-octatetraene of 1.072, the benzocyclo-octatetraenyl dianion of 1.584, and compound (**115**) of 0.96.

The diatropicity of (**117**) is less than that of the parent 1,8-bisdehydro[14]annulene (**105**) or of the mononaphtho derivative (*vide infra*). The dibenzo derivative is very unstable. A series of naphtho- and partially reduced naphthobisdehydro-[14]annulenes have been prepared and the ^{1}H n.m.r. spectra are tabulated in Table 4.[60] Whereas

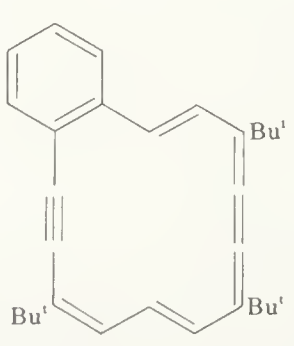
Table 4

^{1}H N.M.R. Chemical Shifts of the Inner and Outer Macrocyclic Ring Protons in Compounds (**118**), (**119**), and (**120**)

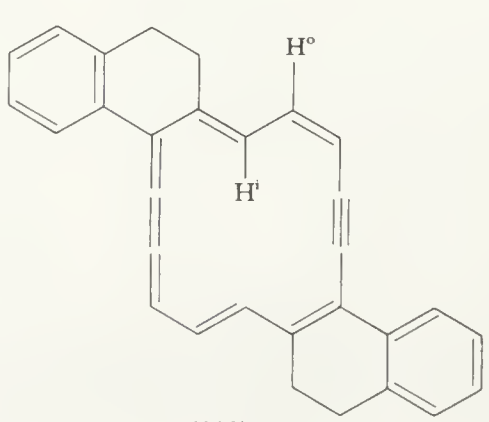
Chemical shift (δ)					
Compound (**118**)		*Compound* (**119**)		*Compound* (**120**)	
H^o	9.52	H^o	9.80	H^o	10.22
H^i	−3.47	$H^{o'}$	9.17	H^i	−3.45
		H^i	−1.22		
		$H^{i'}$	−1.53		
$\Delta\delta(H^o-H^i)$	12.99	$\Delta\delta(H^o-H^i)$	10.86	$\Delta\delta(H^o-H^i)$	13.67

annelation by one naphthalene ring (**119**) reduces the diatropicity of the macrocycle, fusion of two naphthalene rings, as in (**120**), *increases* the diatropicity over that of the bisdehydronaphthalene analogue (**118**). This may be accounted for by a comparison of the Kekulé structures, since in (**120**) the two structures (**120a**) and (**120b**) are equivalent, whereas in (**119**) they (**119a** and **119b**) are not. In (**119**) there is competition between naphthalene and a macrocyclic phenanthrene structure, whereas in (**120**) two phenanthrene-type structures are attained and this molecule is probably best represented by (**120c**).

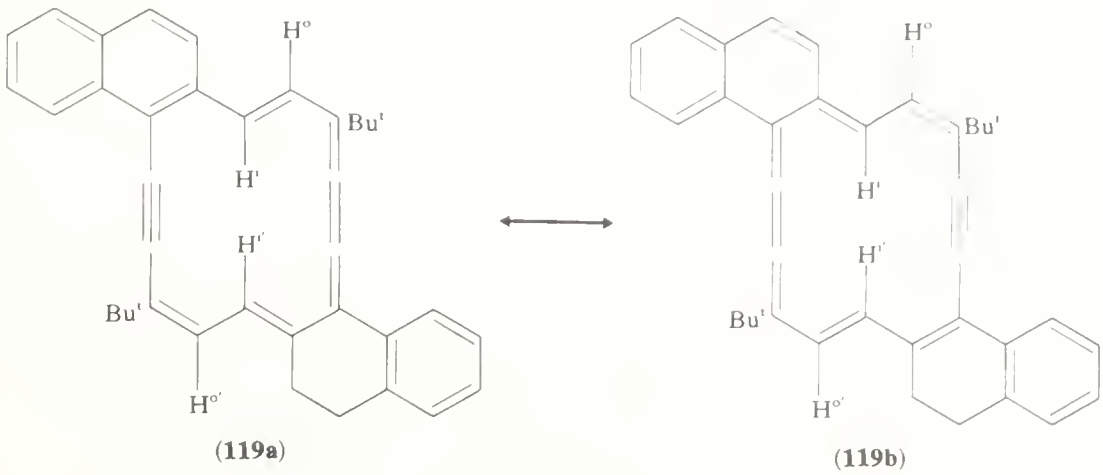
In the preceding discussion, benzene has been annelated on to a macrocyclic ring to form an analogue of naphthalene. Related systems can be conceived in which both rings are macrocyclic. Such systems have recently been prepared, linked both by a single or a number of common C—C bonds. Up to the present time, all of the systems have been dehydroannulenes and the two synthetic routes devised both involve oxidative acetylene



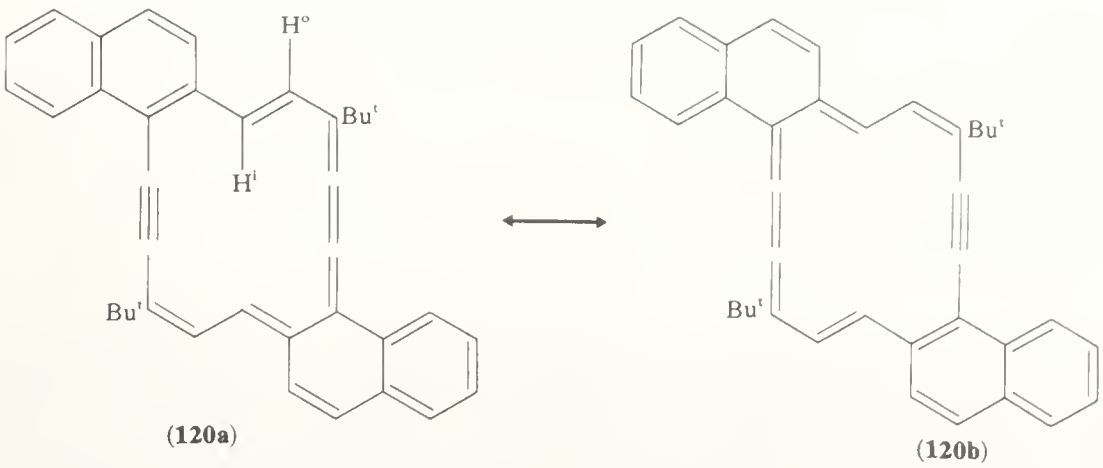
(**117**)



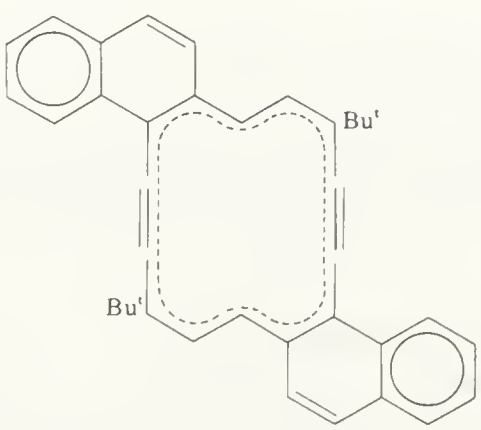
(**118**)



(119a) **(119b)**

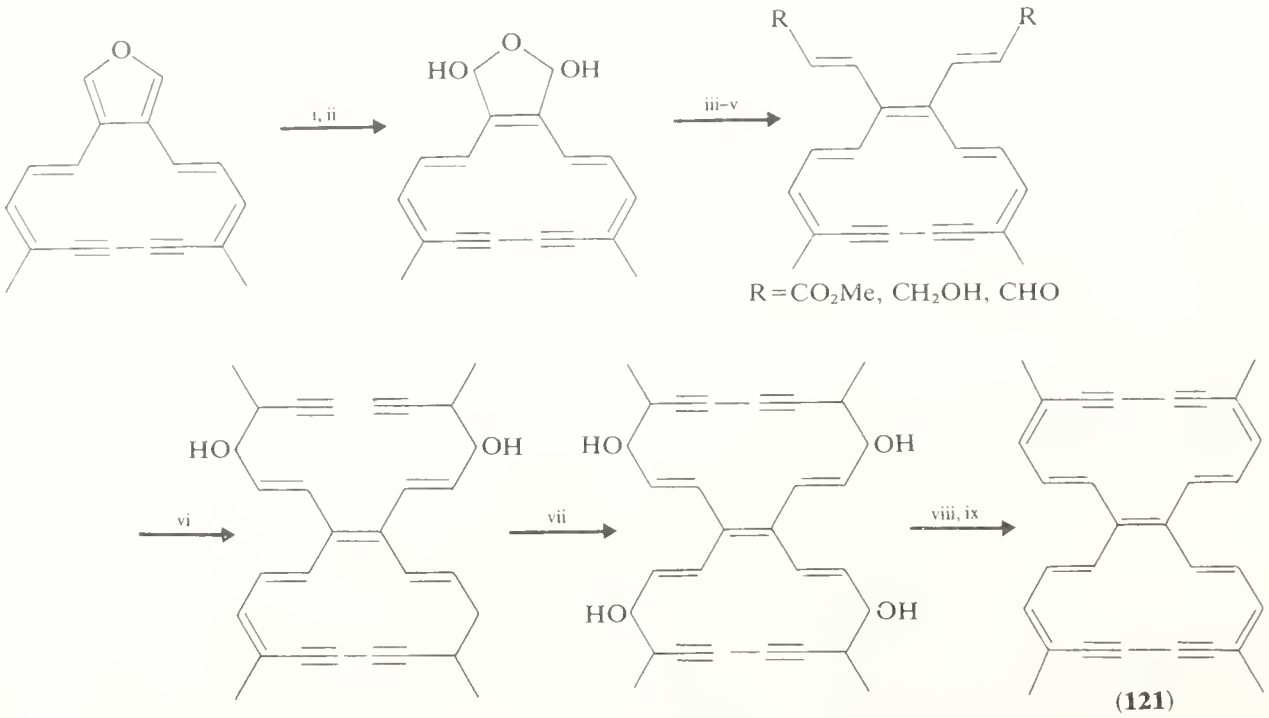


(120a) **(120b)**



(120c)

coupling. Cresp and Sondheimer[70] have explored the method shown in Scheme 22, in which one ring is added to a preformed ring, to prepare 5,10,18,23-tetramethyl-6,8,19,21-tetrakisdehydro[14]annuleno[14]annulene (**121**), and Nakagawa and his co-workers[71] have used the method shown in Scheme 23, in which a bridge is made across a macrocyclic ring, to prepare 5,10,18,23-tetra-t-butyl-6,8,19,21,27,29-hexakisdehydro-[12,12,4][18]annuleno[18]annulene (**122**). The bicyclo nomenclature, [12,12,4], used for (**122**) allows the number of common atoms at the ring junction to be specified.



i, $Pb(OAc)_4$, HOAc; ii, $(CO_2H)_2$; iii, $Ph_3\overset{+}{P}\overset{-}{C}HCO_2Me$; iv, Bu^i_2AlH; v, MnO_2; vi, $BrMgCH(Me)C{\equiv}CH$; vii, $Cu(OAc)_2$, DMF; viii, MsCl; ix, DBN.

SCHEME 22

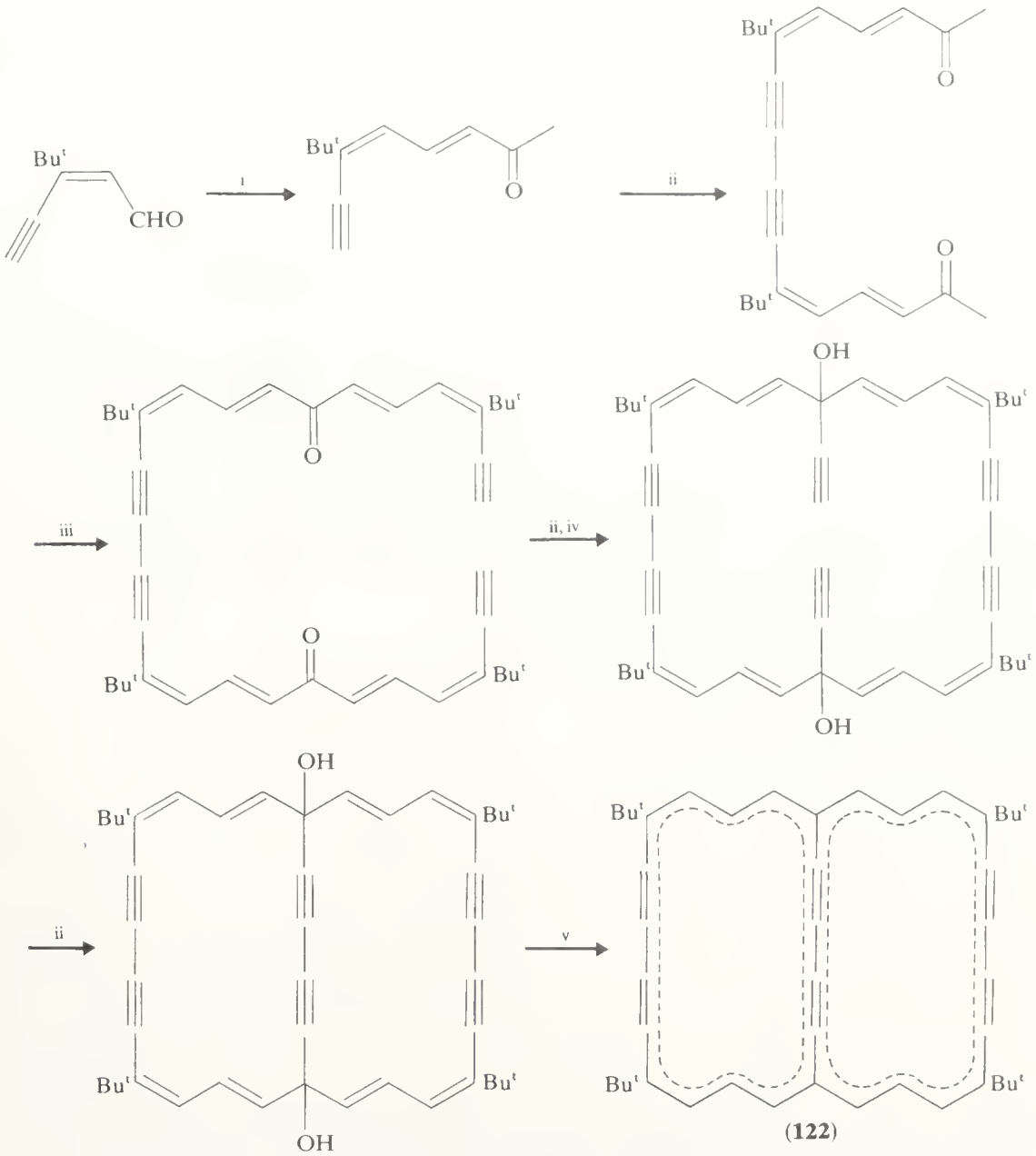
In the series (**121**), (**123**), and (**124**), the [14]annulene rings are all diatropic, and judged by the ^{1}H n.m.r. chemical shifts of the methyl groups, which are remote from the annelating ring, the diatropicity decreases with the decreasing size of the other ring, *i.e.* (**124**) > (**123**) > (**121**). Examination of the inner protons of the 14-membered ring show that in the case of (**123**) the 16-membered rings make a paratropic contribution, the inner protons being at higher fields than in (**121**) and (**124**) in which the annelating ring makes a diatropic contribution.

The ^{1}H n.m.r. spectrum of (**122**) can also best be accounted for on the basis of two annelated 18-membered rings rather than a peripheral 26 π-electron system. Likewise, two annelated 14-membered rings rather than a 22 π-electron system account for the ^{1}H n.m.r. spectral properties of (**125**). The electronic spectrum of both (**122**) and (**125**) show intense bands at long wavelength: (**125**), 553 nm (ε 39 900) and (**122**), 641 nm (ε 88 900). The chemistry of these macrocyclic analogues of naphthalene has so far been little investigated.

2.6.7 AROMATIC AND ANTI-AROMATIC MONOCYCLIC IONS

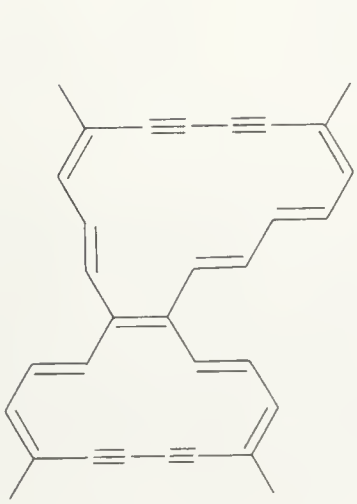
One of the early successes of the Hückel theory was the explanation of the stability of the cyclopentadienyl anion (**126**) and the prediction of the stability of the cycloheptatrienyl cation (**127**), both systems having $4n+2$ π-electrons. As for the neutral species, Hückel theory predicts that ions with $4n+2$ π-electrons will have closed electronic shells whereas those with $4n$ electrons will have open shells and will exist in triplet ground states. The monocyclic ions with $n = 0$–4 are shown in Table 5, the systems — or derivatives thereof — in heavy type having been prepared.[72]

The simplest 2π-electron system, the cyclopropenium ion (**128**), was prepared in 1967 by two research groups by the reaction sequences shown in Scheme 24.[73,74] Cyclopropenium hexachloroantimonate is stable at room temperature in the absence of moisture but is rapidly decomposed by water. The i.r. spectrum shows only four bands, as

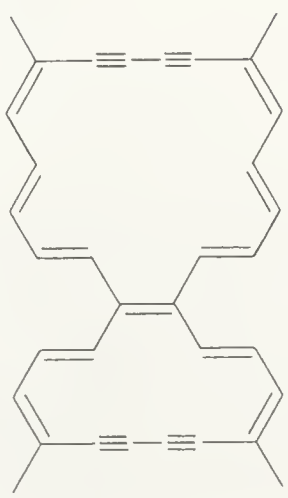


i, Me_2CO, NaOH, H_2O, EtOH; ii, $Cu(OAc)_2$, py; iii, $CH{\equiv}CCBu^t{=}CHCHO$, NaOEt; iv, $LiC{\equiv}CH$; v, $SnCl_2$, Et_2O, HCl.

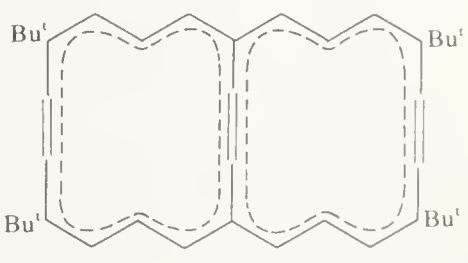
SCHEME 23



(123)



(124)



(125)

(126) **(127)**

TABLE 5
Monocyclic Aromatic and Anti-aromatic Ions

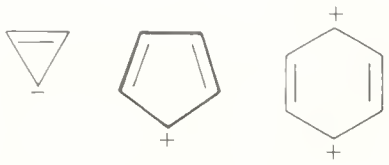
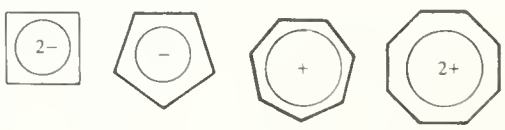
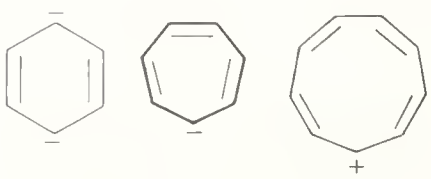
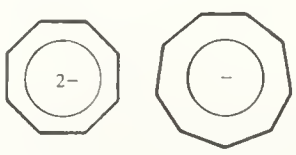
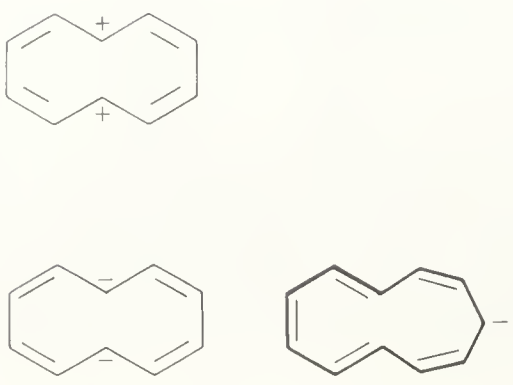
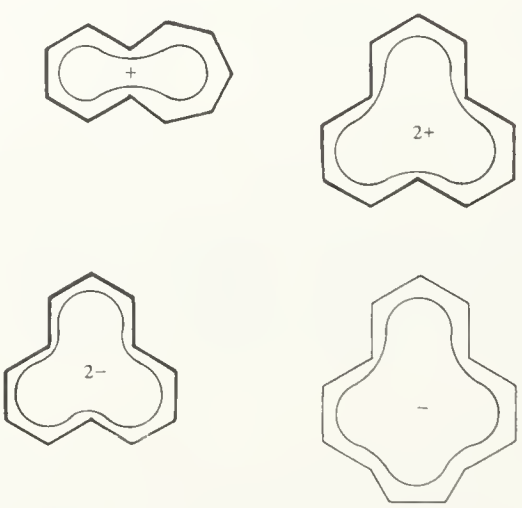
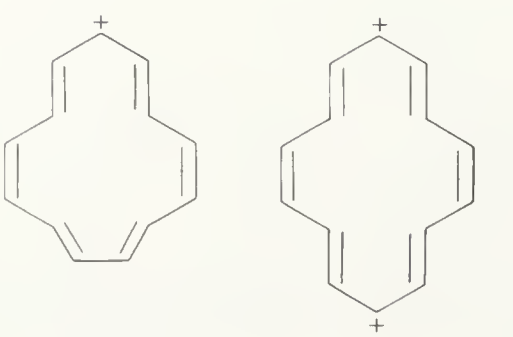
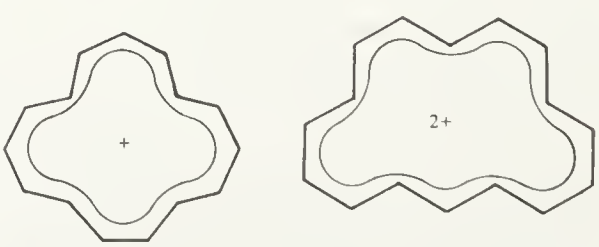
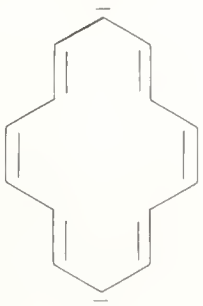
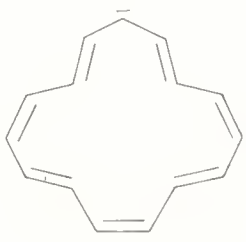
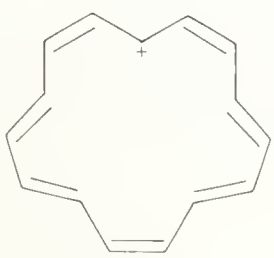
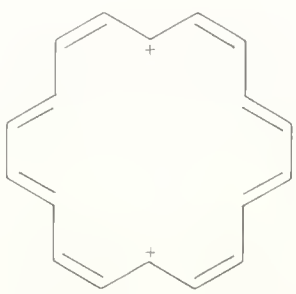
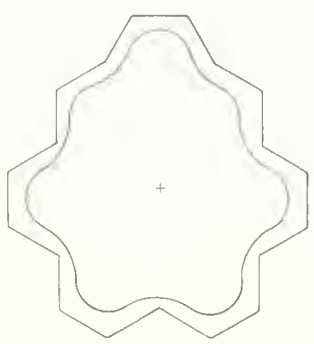
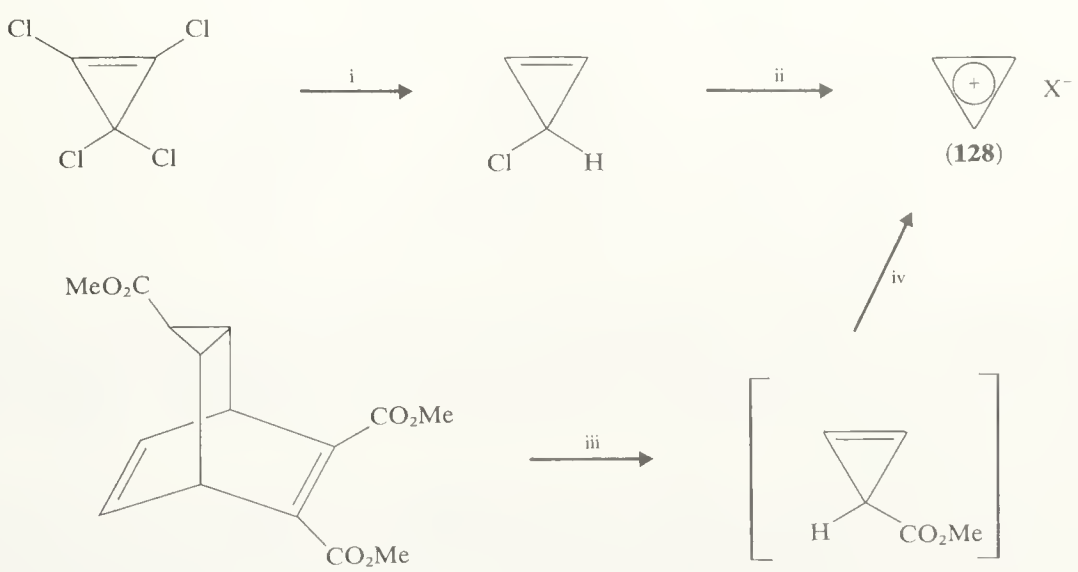
Value of n	*4n Systems*	*4n + 2 Systems*
$n = 0$		
$n = 1$		
$n = 2$		
$n = 3$		
		

TABLE 5 (*continued*)

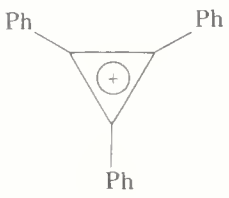
Value of n	*4n Systems*	*4n + 2 Systems*	
			
$n = 4$			



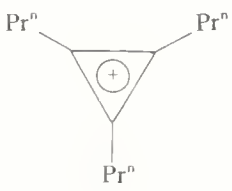
i, Bu^n_3SnH; ii, $SbCl_5$, CH_2Cl_2; iii, Δ; iv, FSO_3H.

SCHEME 24

expected for a molecule with $\mathbf{D}_{3h}$ symmetry, and the ^1H n.m.r. spectrum shows only a singlet at δ 11.1. The ^{13}C–H coupling constant (265 Hz) indicates that this bond has considerable *s*-character. A model can be constructed for the cation with, for each carbon atom, an *sp* orbital to hydrogen, two sp^3 orbitals for the bent cyclopropenyl bonds, and a *p* orbital for the π-system. The first cyclopropenium cation to be prepared was the triphenyl derivative (**129**) by Breslow in 1957.[75] A large number of substituted cations have subsequently been synthesized. These systems are often extremely stable, the tri-n-propylcyclopropenium ion (**130**) having a pK_{R^+} value of 7.2, and (**129**) and (**128**) values of 3.1 and −7.4, respectively. The sequence shows a decline in stability.

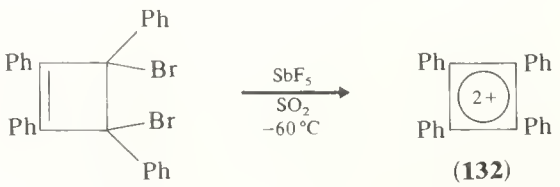


(**129**)

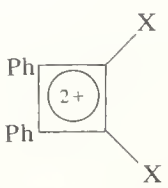


(**130**)

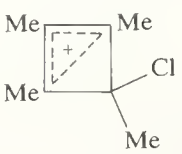
The parent cyclobutadienyl dication has not been prepared but a number of substituted derivatives have recently been synthesized using strongly acidic media.[76] Thus treatment of the dibromide (**131**) with antimony pentafluoride in SO_2 at −60 °C gave a solution of the tetraphenylcyclobutadienyl dication (**132**) (equation 7). The diphenyldifluoro (**133a**) and diphenyl (**133b**) dications were prepared in a similar manner. The tetramethyl dication (**135**) was prepared from the corresponding cyclobutene dichloride *via* the intervening homocyclopropenium ion (**134**), which loses chloride ion slowly to give (**135**) at −75 °C. The broad-band decoupled ^{13}C n.m.r. spectra of all of these ions have chemical shifts in accord with their being delocalized, double-charged species, and evidence has been adduced to show that the products are dications and not rapidly equilibrating monocations.



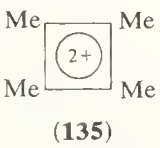
(**131**) (**132**) (7)



(**133a**) X = F
(**133b**) X = H



(**134**)

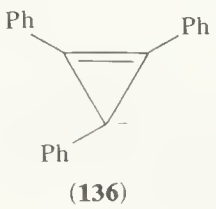


(**135**)

The cyclopropenyl anion is unknown but evidence has been obtained to show that the triphenyl derivative (**136**) is an anti-aromatic system, which is destabilized in comparison with either the triphenylcyclopropanyl or allyl anion. Thus triphenylcyclopropene has a pK of *ca.* 51 (as estimated by linear scan voltammetry), indicating the low acidity of the cyclopropenyl hydrogen.[77]

The cyclopentadienyl cation (**138**) has been prepared by treatment of 5-bromo- or 5-chloro-cyclopentadiene (**137**) with SbF_5 at 78 K.[78] The e.s.r. spectrum shows that (**138**) is a ground-state triplet and the spectral parameters are in accord with (**138**) being a planar pentagon. The pentachlorocyclopentadienyl cation (**139a**) is also a ground-state triplet, whereas the pentaphenyl derivative (**139b**) has the triplet state about 5.4 kJ mol^{-1} above the ground state. Clearly the larger system more successfully distorts to remove the triplet degeneracy.

The cyclobutadienyl dianion (**140**), a potential 6π-electron system, has not been



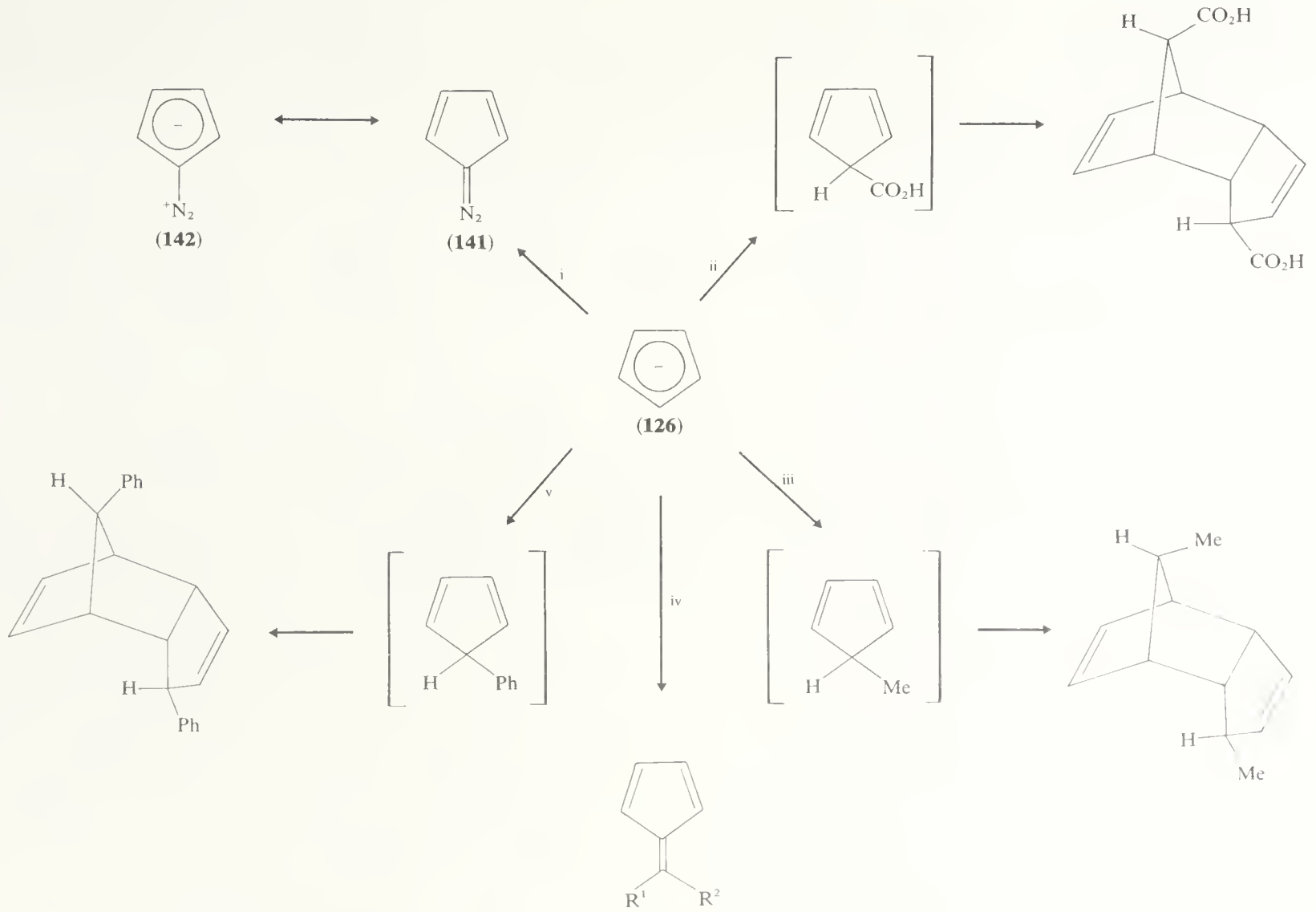
(**136**)

(**137**) X = Br, Cl

(**138**)

(**139a**) R = Cl
(**139b**) R = Ph

(**140**)



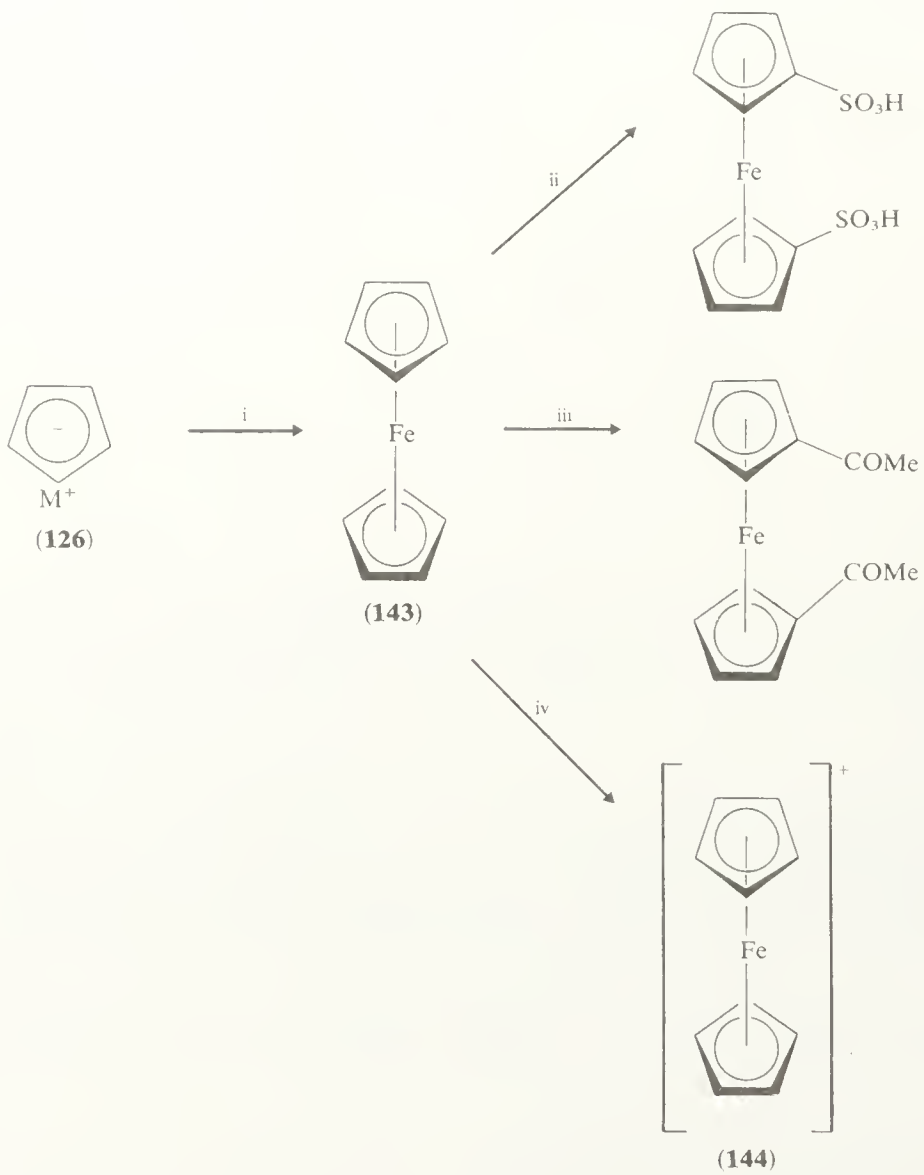
i, *p*-$MeC_6H_4SO_2N_3$, Et_2O; ii, CO_2; iii, MeI; iv, R^1R^2CO; v, PhBr.

SCHEME 25

isolated but evidence for its existence has been obtained by treating 3,4-dichlorocyclobutene with sodium naphthalide and quenching the product with MeOD to give 3,4-dideuteriocyclobutene.[79]

The cyclopentadienyl anion (**126**), the first aromatic ion to be recognized, was prepared by Thiele in 1901 by treatment of cyclopentadiene with a dispersion of potassium in benzene. The i.r. and Raman spectra are simple, in accord with $\mathbf{D}_{5h}$ symmetry. The ^{1}H n.m.r. spectrum shows a single resonance at δ 5.57. The cyclopentadienyl anion reacts with electrophiles, is carboxylated with CO_2, and is alkylated or arylated by the appropriate halide. In all cases the dimeric dicyclopentadienes are formed (Scheme 25). Lithium cyclopentadienide was found by Doering and DePuy to react with *p*-toluenesulphonylhydrazide to give the ylide diazacyclopentadiene (**141**), which is stabilized by a contribution from the dipolar form (**142**). A variety of related ylides have subsequently been prepared.

The cyclopentadienyl anion reacts with transition metals to form organometallic 'sandwich' molecules, the so-called metallocenes. The first compound of the type to be discovered was ferrocene (**143**), prepared by treatment of (**126**) with iron(II) chloride (Scheme 26). An extensive chemistry of metallocenes has subsequently been developed.[80]

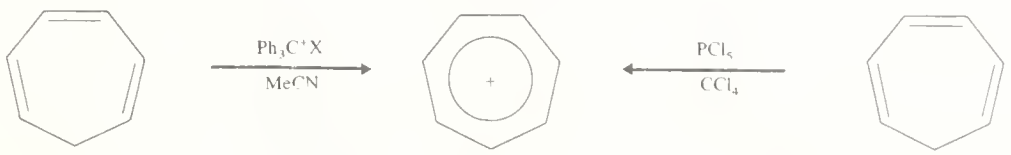


i, $FeCl_2$, THF, N_2; ii, H_2SO_4, HOAc; iii, Ac_2O, $AlCl_3$; iv, HNO_3.

SCHEME 26

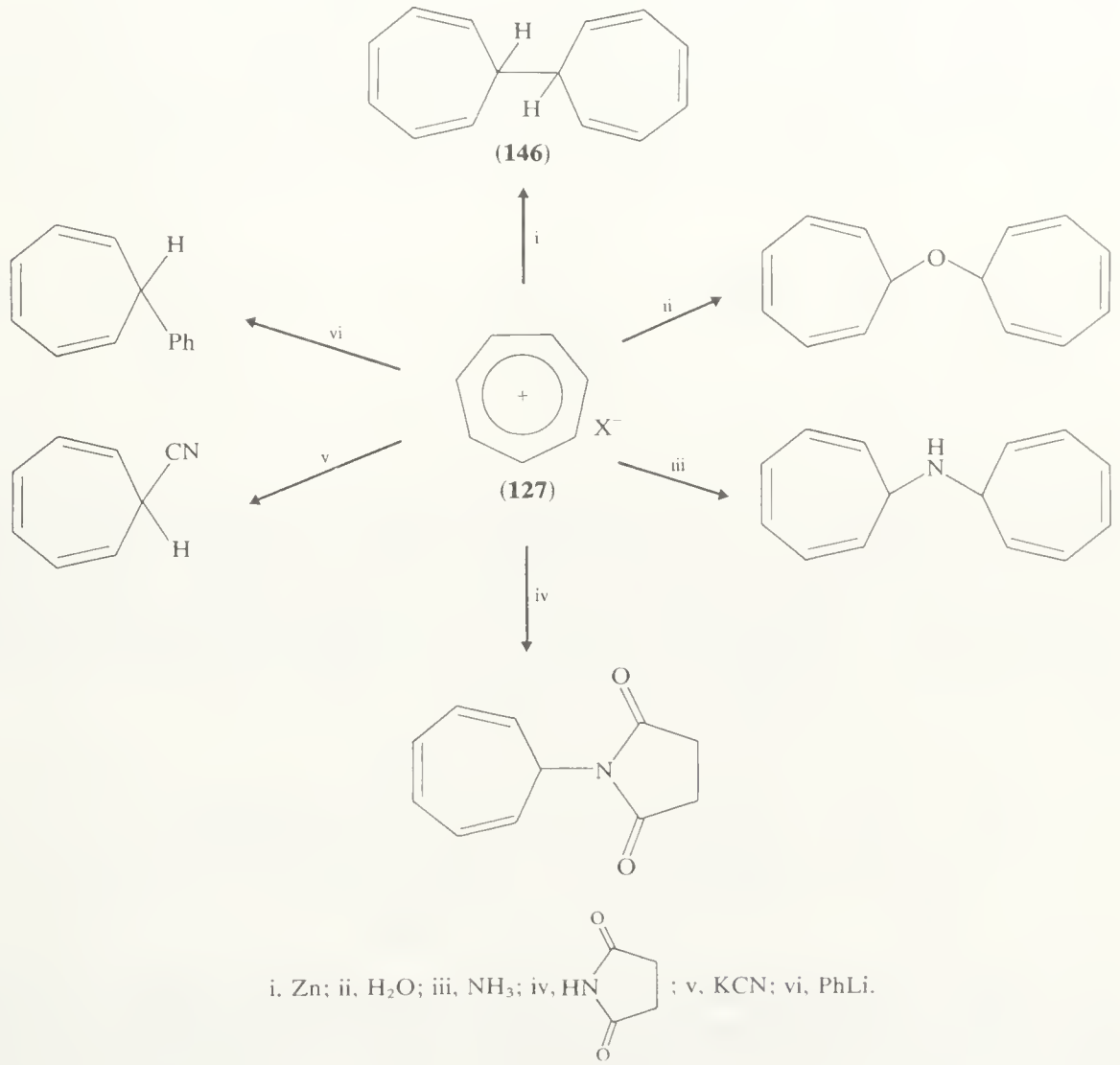
Ferrocene reacts as an aromatic system, undergoing acylation and sulphonation of the five-membered rings. However, reaction with nitric acid causes oxidation of the iron(II) to iron(III) to give the ferricenium ion (**144**).

The cycloheptatrienyl (tropylium) cation (**127**) was first prepared by Doering and Knox by distillation of the product obtained from bromination of cycloheptatriene (**145**). This experiment had been carried out in the nineteenth century by Merling but, not unexpectedly, he failed to identify the product. The preferred methods of synthesis of (**127**) involve either (i) reaction of cycloheptatriene with the trityl cation (Dauben) or (ii) treatment of cycloheptatriene with PCl_5 (Conrow) (equation 8).



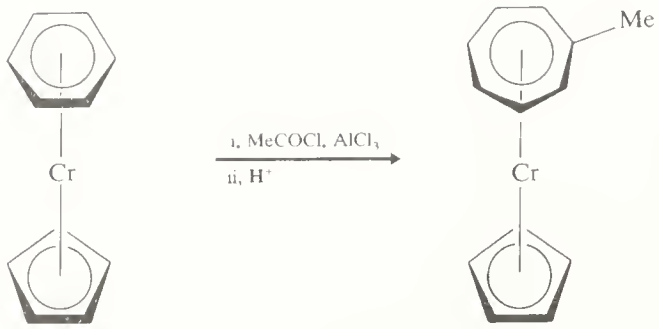
(**145**) (**127**) (**145**) (8)

The tropylium cation has the i.r. and Raman spectra expected for a planar $\mathbf{D}_{7h}$ system, with no coincidences of i.r. and Raman lines. The ^{1}H n.m.r. spectrum shows a singlet at δ 9.28 and the electronic spectrum shows a maximum at 275 nm. The cation has a pK_a of 4.01 and is thus of comparable acidity to acetic acid. The tropylium cation reacts with nucleophiles to give a variety of addition products (Scheme 27). It is reduced by zinc to



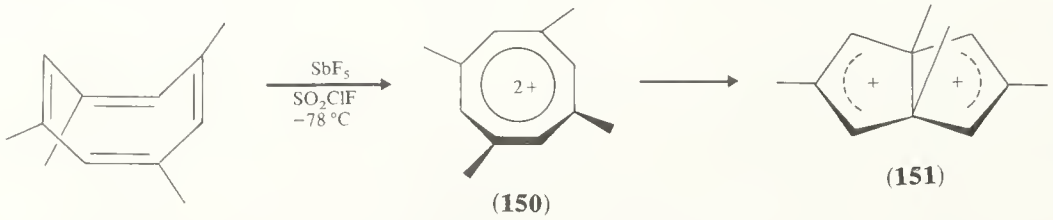
SCHEME 27

ditropyl (**146**) and oxidized by chromic acid or silver oxide to benzaldehyde. Metallocenes can be formed which contain the tropylium ion; thus treatment of the complex (**147**) with acetyl chloride and $AlCl_3$ followed by acidification gives the chromium sandwich (**148**) (equation 9).



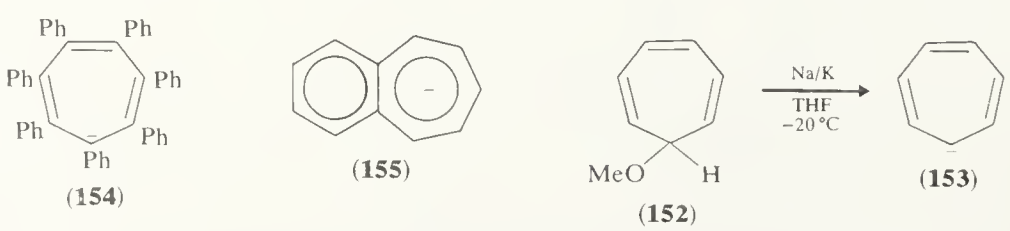
(147) (148) (9)

In principle, cyclo-octatetraene (**2**) can be converted into a $4n+2$ π-electron system by the addition or removal of two electrons. The cyclo-octatetraenyl dication has 6 π-electrons in three bonding orbitals and the cyclo-octatetraenyl dianion has 10 π-electrons in three bonding and two non-bonding orbitals. Cyclo-octatetraene (**2**) forms the homotropylium cation rather than the cyclo-octatetraenyl dication. However, treatment of 1,3,5,7-tetramethylcyclo-octatetraene (**149**) with SbF_5 in SO_2ClF at $-78\,°C$ gives the dication (**150**) (equation 10).[81] The ^1H n.m.r. spectrum shows signals at δ 4.27 and 10.80 for the methyl and ring protons, respectively. In the broad-band decoupled ^{13}C n.m.r. spectrum, the carbon atoms of the ring are at δ 182.7 ($C—CH_3$) and 170.0 ($C—H$). On warming to $-20\,°C$ the dication rearranged to the bicyclic dication (**151**) (equation 10).



(149) (150) (151) (10)

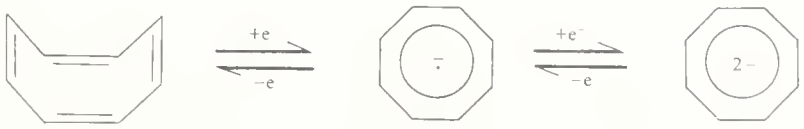
The cycloheptatrienyl anion (**153**), an 8π-electron system, was prepared by Dauben and Rifi[82] by treatment of 7-methoxycycloheptatriene (**152**) with sodium potassium alloy in THF at $-20\,°C$ (equation 11). The anion (**153**) is unstable and appears to have a triplet ground state. The heptaphenyl derivative (**154**) is more stable and has a unsymmetrical singlet ground state.[83] The benzocycloheptatrienyl anion (**155**) is paratropic and considerable delocalization of charge into the benzene ring occurs.[84] The cyclononatetraenyl cation — also an 8π-electron system — has not been observed.



(154) (155) (152) (153) (11)

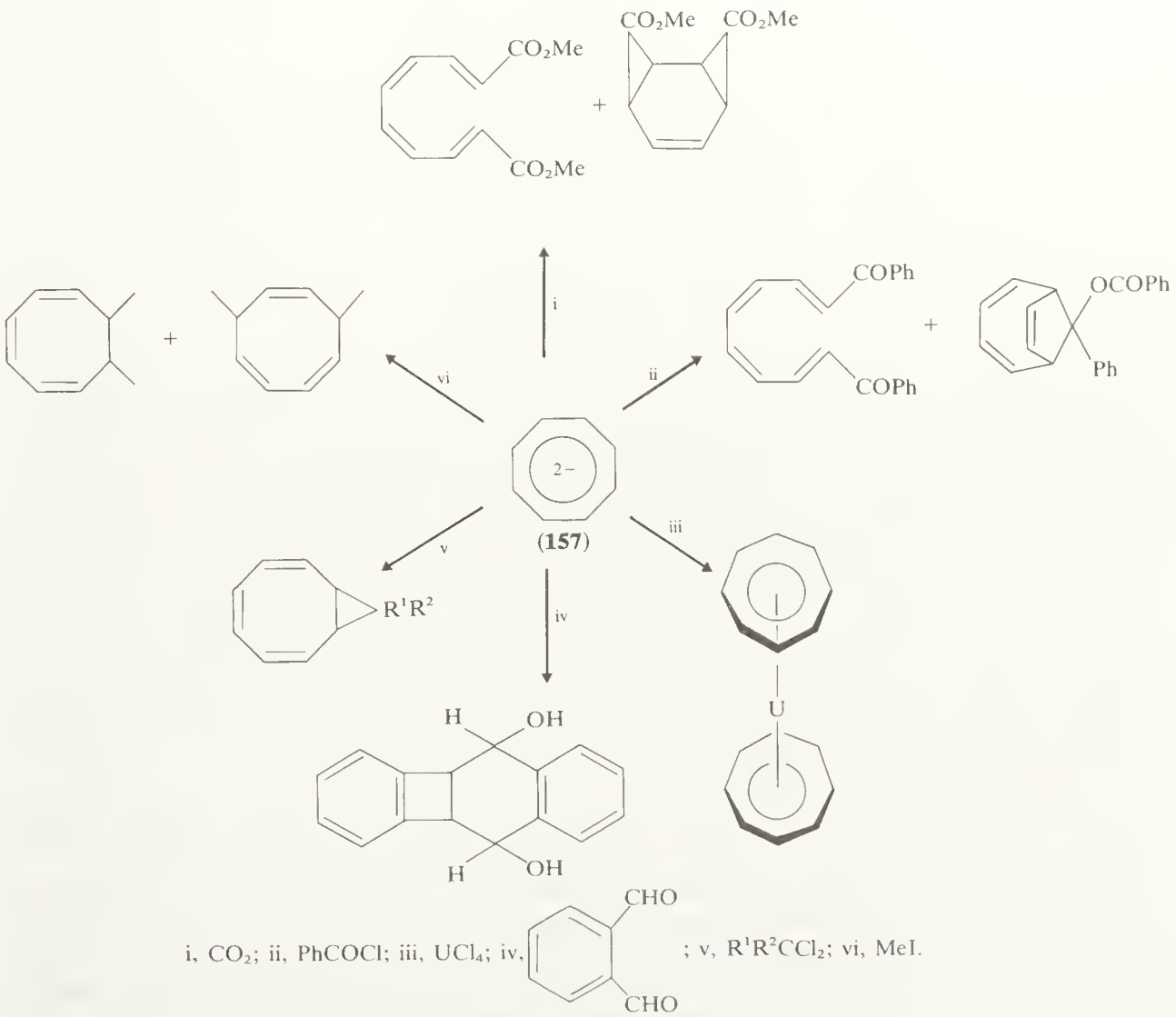
The reduction of cyclo-octatetraene (**2**) to form the radical anion (**156**) and then the dianion (**157**) was first demonstrated by Katz (equation 12).[85] Subsequent work has confirmed that the radical anion and the dianion are planar, delocalized systems. The e.s.r. spectrum of (**156**) showed the nine lines in the appropriate binomial ratio for eight

equivalent protons, and the hyperfine splitting constants were consistent with a structure of $\mathbf{D}_{8h}$ symmetry. The ^{1}H n.m.r. spectrum of (**157**) showed a singlet (δ 5.7) at an almost identical position to that of cyclo-octatetraene, indicating that the diatropicity is balanced by the shielding of the two extra electrons. The first electron added to (**2**) must enter a non-bonding orbital, removing the triplet degeneracy. The second electron also enters the triply occupied NBMO and completes the closed shell. In both cases the σ-framework becomes planar, suggesting that the non-planarity of cyclo-octatetraene (**2**) is due to the electronic configuration rather than to angle strain.



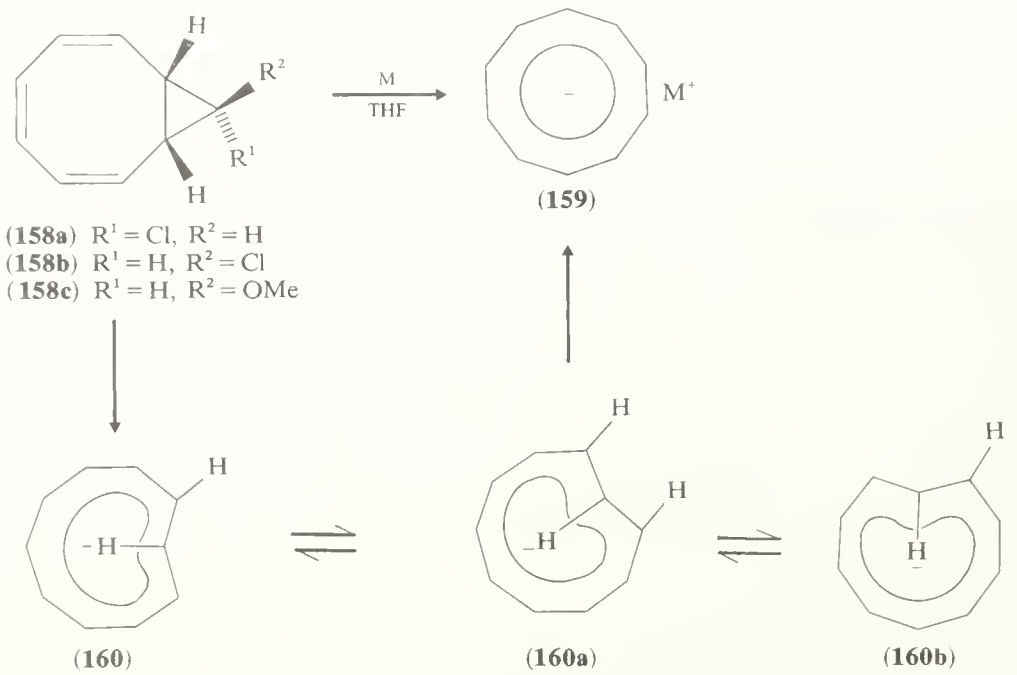
(**2**) (**156**) (**157**) (12)

The dianion (**157**) is readily available by a number of methods, the most preparatively useful being treatment of cyclo-octatetraene (**2**) with alkali metals in THF or liquid ammonia. An extensive chemistry has been developed, some of which is outlined in Scheme 28.



SCHEME 28

The cyclononatetraenyl anion has been prepared in the all-*cis* (**159**)[86] and mono-*trans* (**160**)[87] forms (see Scheme 29). Reaction of 9-chloro- (**158a,b**) or 9-methoxy-bicyclo-[6,1,0]nonatriene (**158c**) with an alkali metal in THF gave the anion (**159**). When *anti*-9-methoxybicyclo[6,1,0]nonatriene (**158c**) is reacted with potassium in THF at −80 °C, then the mono-*trans* ion (**160**) is formed, presumably by conrotatory opening of the cyclopropyl anion. In the presence of potassium the anion (**160**) is converted into (**159**) at room temperature. However, in the pure state the anion (**160**) is thermally stable and the rate of topomerization (**160**⇆**160a**⇆**160b**, *etc.*) is much faster than the rate of isomerization. The ^{1}H n.m.r. spectrum of (**160**) at −40 °C shows the outer protons at low field (δ 7.3–6.4) and the inner proton at high field (δ −3.52).



SCHEME 29

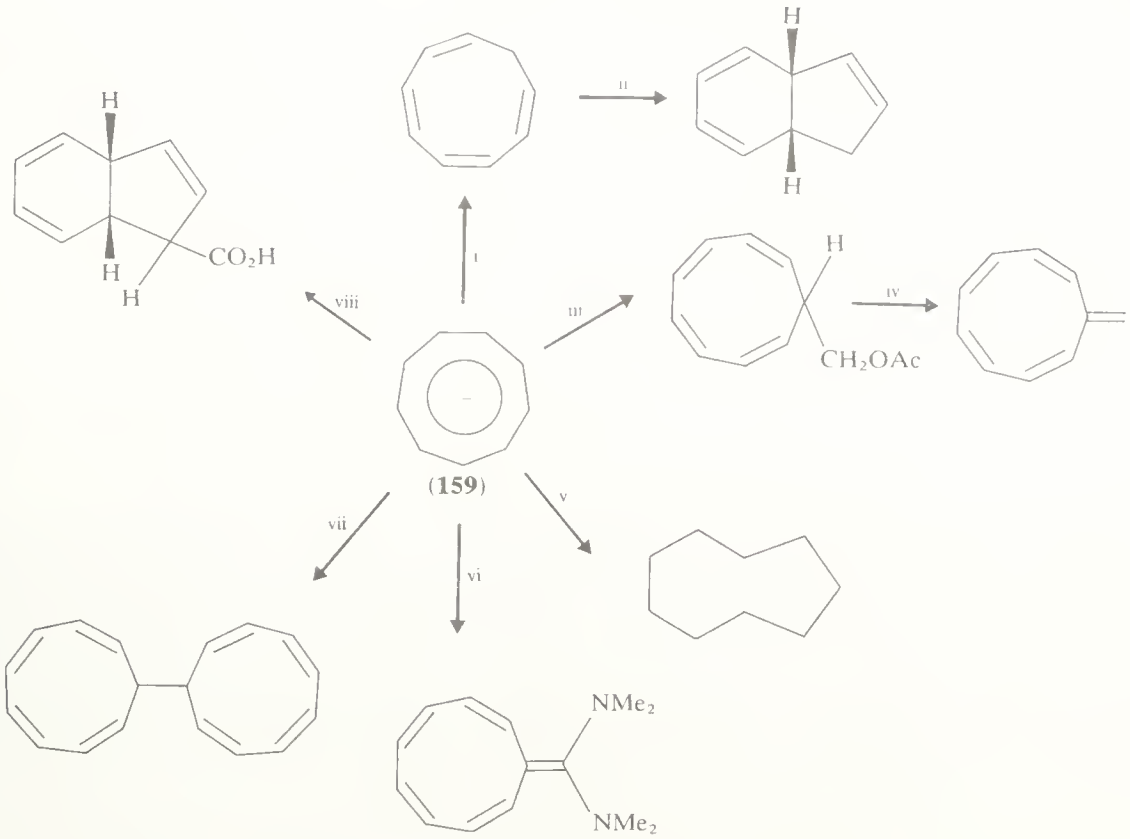
The all-*cis* ion (**159**) shows a singlet at δ 7.0 in the ^{1}H n.m.r. spectrum, although the chemical shift depends on the nature of the counter-ion and solvent. The electronic spectrum of (**159**) shows an intense band at 251 nm and a double, weaker maximum at 320 nm, in accord with the calculated spectrum for a molecule of $\mathbf{D}_{9h}$ symmetry. The anion (**159**) undergoes a variety of nucleophilic reactions (Scheme 30).

The diatropic 1,6-methanocyclononatetraenyl anion (**161**) has also been prepared, the methylene bridge protons being at high field in the ^{1}H n.m.r. spectrum.

Macrocyclic annulenyl ions have been extensively investigated over the last few years and a variety of systems have been prepared. Although the undecapentenium cation remains unknown, the bridged ion (**162**) has been prepared as the fluoroborate and shown to be diatropic.[88a] An X-ray crystallographic analysis favours a delocalized 10π-electron system rather than a benzohomotropylium structure. The distance between C-1 and C-6 is long (229·9 pm).[88b]

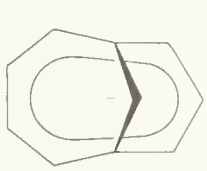
The 12π-electron anion (**164**) has been prepared by treatment of the hydrocarbon (**162**) with potassium deuterioamide in deuterioammonia.[89] The anion is strongly paratropic, the internal methylene protons appearing at very low field (δ 10.31, 14.19).

[12]Annulene (**32**), which is extremely unstable, can be reduced polarographically or with alkali metals to the 14π-electron [12]annulenyl dianion (**165**) which is a stable, diatropic system.[90] The dianion shows three signals in the ^{1}H n.m.r. spectrum at δ 6.98, 6.23 and −4.6, and is temperature independent. This indicates that there is no exchange between hydrogens in inner and outer sites, in contrast to [12]annulene (**32**) where this exchange is rapid.

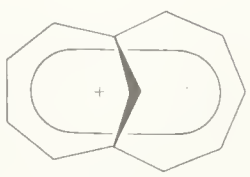


i, H_2O; ii, Δ; iii, $BrCH_2OCOMe$; iv, $KOBu^t$; v, H_2, Pt; vi, $ClC(NMe_2)_2^+$; vii, I_2; viii, CO_2.

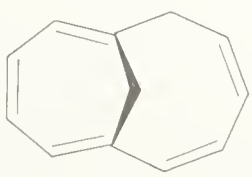
SCHEME 30



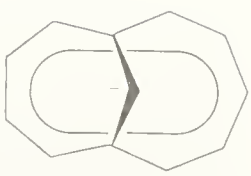
(161)



(162)

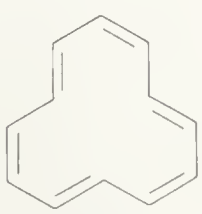


(163)



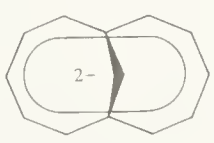
(164)

Both bridged, *e.g.* (**166**),[91a] and dehydro (**167**) [12]annulenyl dianions[91b] have been prepared from the corresponding annulenes, and the paratropic behaviour of the parent systems is completely reversed in these strongly diatropic dianions, the bridge protons of (**166**) appearing at δ −6.44 and the inner proton of (**167**) at δ −6.88 in the respective ^{1}H n.m.r. spectra.



(32)

(165)

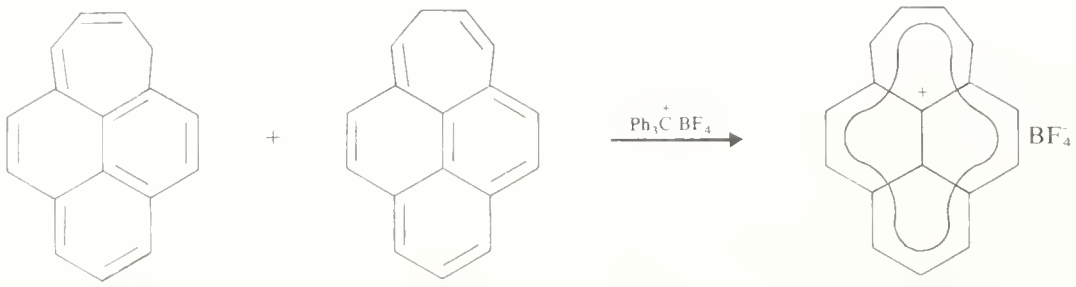


(166)

(167)

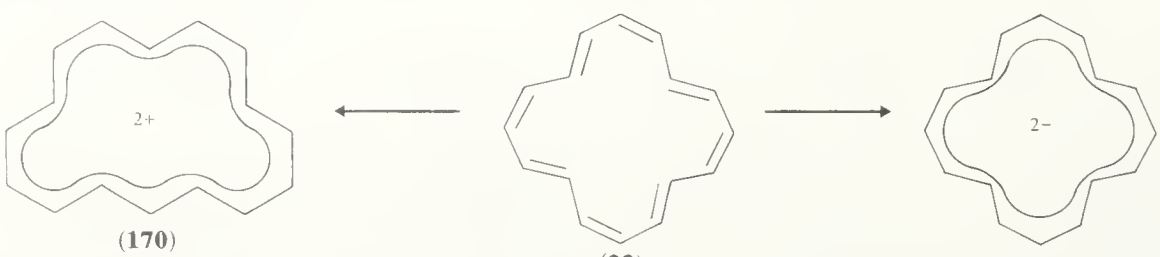
Reaction of *trans*-15,16-dimethyl-15,16-dihydropyrene (**14**) with potassium gave first the radical anion and then the paratropic 16π-electron dianion. In the ^{1}H n.m.r. spectrum of the dianion the methyl protons inside the ring appear at very low field (δ 21.0), in dramatic contrast to the chemical shift (δ −4.25)[92a] of these protons in (**14**). 1,6,8,13-Propandiylidene[14]annulene (**44**) can be converted similarly into the corresponding paratropic dianion.[92b]

The bridged [15]annulenyl cation (**169**) has been prepared by hydride abstraction from a mixture of (**168a,b**) as the crystalline, red-brown fluoroborate (equation 13).[93] The ion has a pK_{R^+} value in excess of 8.4 and is probably the most stable carbenium ion known. A number of other bridged [15]annulenyl cations have also been prepared.



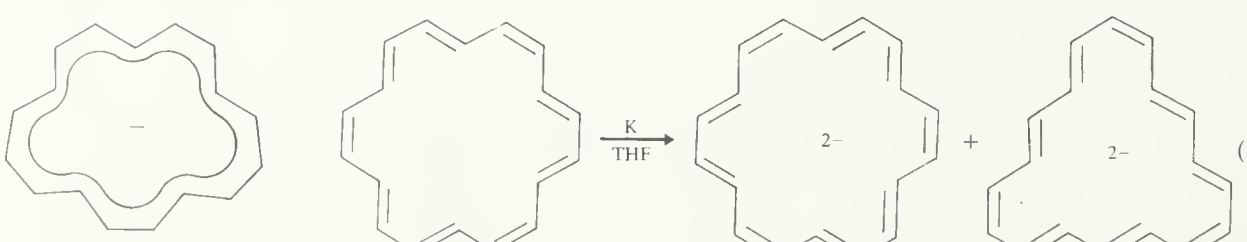
(**168a**) (**168b**) (**169**) (13)

The [16]annulenyl dication (**170**) was prepared by treating [16]annulene (**23**), in SO_2–CD_2Cl_2 at −80 °C, with fluorosulphonic acid (equation 14).[94] The violet solution of the dication is diatropic and the ^{1}H n.m.r. spectrum suggests it has the configuration shown in (**170**). [16]Annulene (**23**) can also be reduced with alkali metals to give the [16]-annulenyl dianion (**171**) (equation 14).[95] The dianion (**171**) is a diatropic, 18π-electron system with the inner protons appearing at δ −8.17 in the ^{1}H n.m.r. spectrum. Thus both the dication and dianion are completely opposite in magnetic properties to the paratropic [16]annulene. The dianion (**171**) has a different configuration to the dication (**170**) and the spectrum is temperature invariant, indicating that exchange of protons between inner and outer sites does not occur. Again the consequences of electronic structure are well illustrated: the two $4n+2$ ions exist in single, though different, configurational forms, whereas the $4n$ [16]annulene (**23**) is a mixture of configurational isomers.



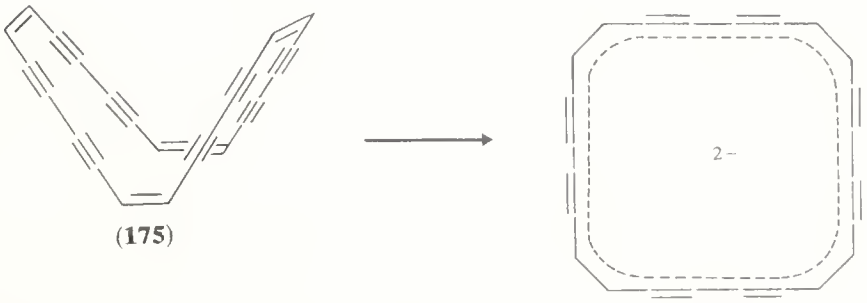
(**170**) (**23**) (**171**) (14)

The [17]annulenyl anion (**172**) has been prepared. The inner protons resonate at δ −7.97, and the outer at δ 9.52 and 8.21, in the ^{1}H n.m.r. spectrum.[96] The anion is clearly a strongly diatropic, 18π-electron system.



(**172**) (**12**) (**173**) (**174**) (15)

Reaction of [18]annulene (**12**) with potassium at −80 °C gave the [18]annulenyl dianion, a 20π-electron, paratropic system (equation 15). The inner protons resonate at *ca.* δ 29, and the outer at *ca.* δ −1.13 in the ^{1}H n.m.r. spectrum, which is also consistent with the dianion existing as a mixture of configurational isomers, (**173**) and (**174**). The only larger ion to be prepared is the dianion (**176**), derived from octadehydro[24]-annulene (**175**) (equation 16), and it appears to be a 26π-electron system.



(175) (176) (16)

For the large annulenes, the $4n$ systems often exist as a mixture of configurational isomers whereas the corresponding $4n+2$ systems exist in one configuration. This is clearly seen on going both from a neutral $4n$ to a charged $4n+2$ system (equation 16) or from a neutral $4n+2$ system to a charged $4n$ system (equation 15). In the $4n+2$ ions the barrier to interconversion of the protons between inside and outside orientations is higher than in the neutral $4n+2$ systems. This probably reflects the difficulty of localizing charge in the non-planar transition state. In contrast, it might be expected that the energy of the planar $4n$ ions, the transition states between non-planar forms, should be lowered by charge delocalization.

Plots of charge densities against ^{1}H chemical shifts and ^{13}C chemical shifts are shown in Figures 4 and 5, respectively. The plot of proton shift against charge is linear for each

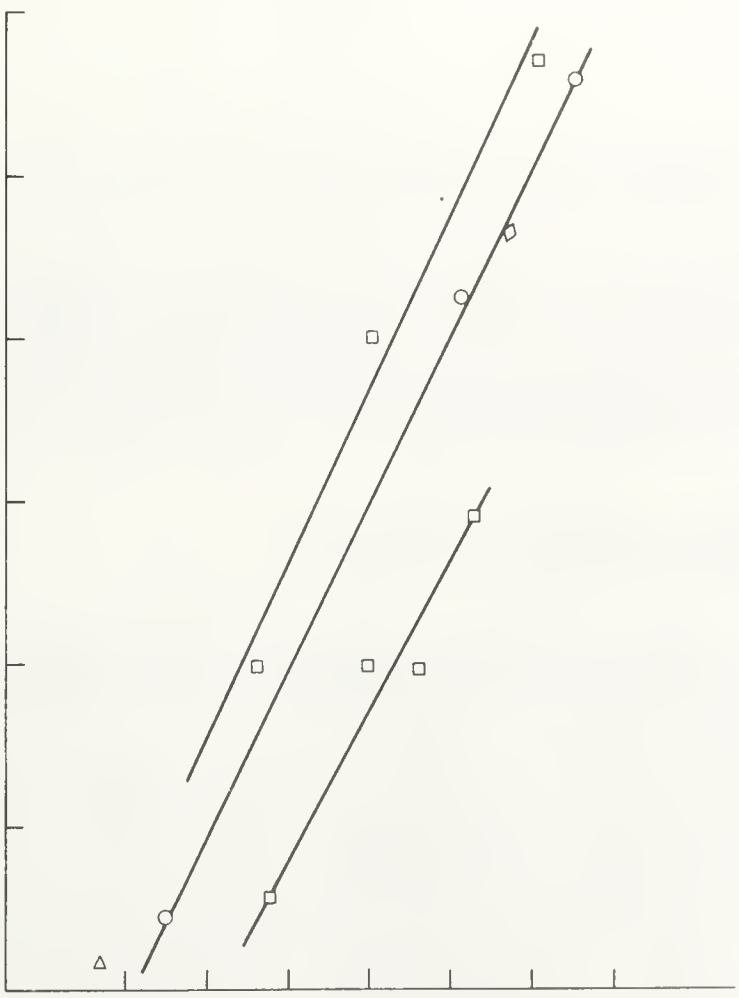


Figure 4 Plot of proton chemical shifts in p.p.m. (δ) relative to benzene against charge density ($\Delta\rho$) per carbon atom for the monocyclic $4n+2$ ions

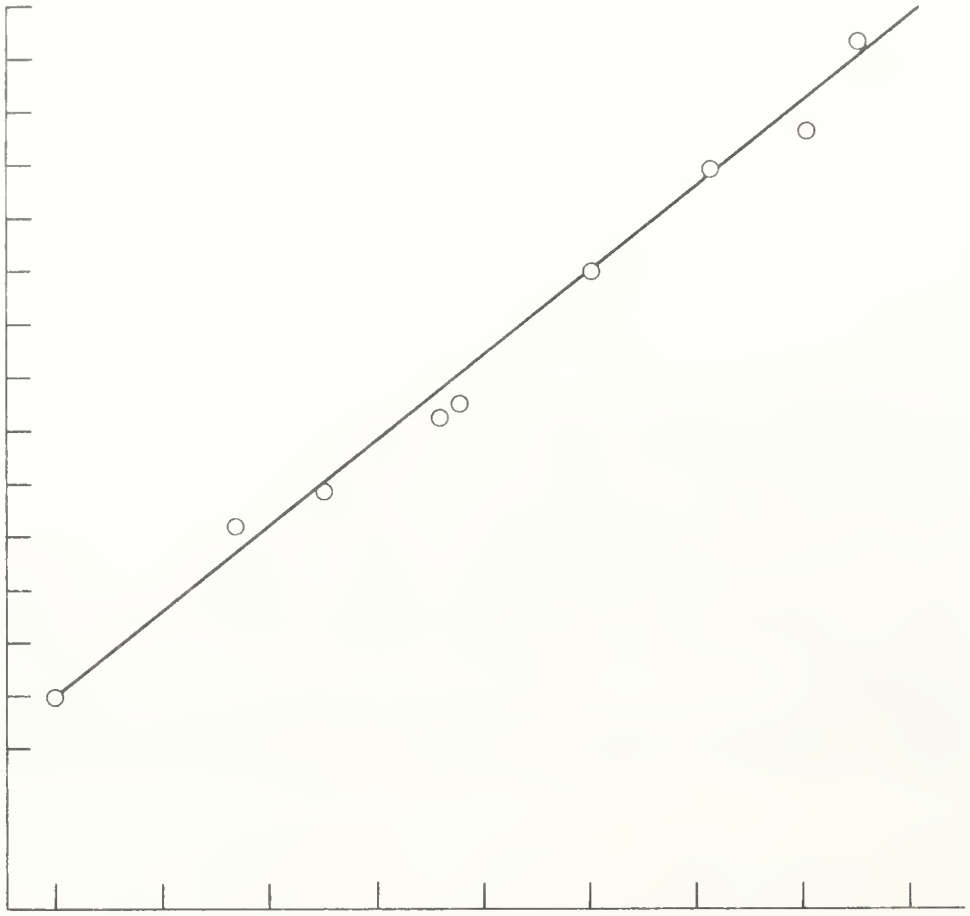


Figure 5 Plot of ^{13}C chemical shift in p.p.m. (δ) relative to benzene against charge density ($\Delta\rho$) per carbon atom for the monocyclic $4n+2$ ions

value of n investigated. The differences in the plots can be attributed to an increase in the ring current with increasing value of n. The slopes of the line of value $n = 1, 2, 4$ are approximately parallel, as would be expected for an effect dependent upon charge density. By contrast, ^{13}C chemical shifts are not greatly influenced by ring current. The shifts reflect only the charge density at each carbon and therefore all of the cyclic ions fall on the same linear plot (Figure 5).[73b]

2.6.8 AROMATIC AND ANTI-AROMATIC POLYCYCLIC IONS

A number of problems are present in conjugated polycyclic ions which are not found in monocyclic ions. Thus whereas the monocyclic ions have electrons delocalized over the whole system, the polycyclic ions may behave as if composed of discrete cycles rather than as a single system. Simply counting the total number of π-electrons and applying the Hückel rule is not, therefore, expected to lead to meaningful predictions regarding the properties of polycyclic ions. The ions can be classified into three types on the basis of the π-electron character of the component parts: (i) ions formed by the fusion of two $4n+2$ π-electron units, (ii) ions formed by the fusion of two $4n$ π-electron units, and (iii) ions formed by the fusion of a $4n$ and a $4n+2$ unit (Table 6). The ions resulting from (i) and (ii) will have a total of $4n+2$ π-electrons, whereas those from (iii) will have $4n$ π-electrons. Examples are given in Figure 6. The total number of π-electrons in a polycyclic system is given by the expression $4m+2x-2y$, where m is the sum of all the values of n for the component rings, x is the number of $4n+2$ rings, and y is the number of ring fusions. This formula can be applied to the ions shown in Figure 6.

TABLE 6

Classification of Polycyclic Ions

Type	*Unit A*	*Unit B*	*Total of π-electrons*
(i)	$4n+2$	$4n+2$	$4n+2$
(ii)	$4n$	$4n$	$4n+2$
(iii)	$4n+2$	$4n$	$4n$

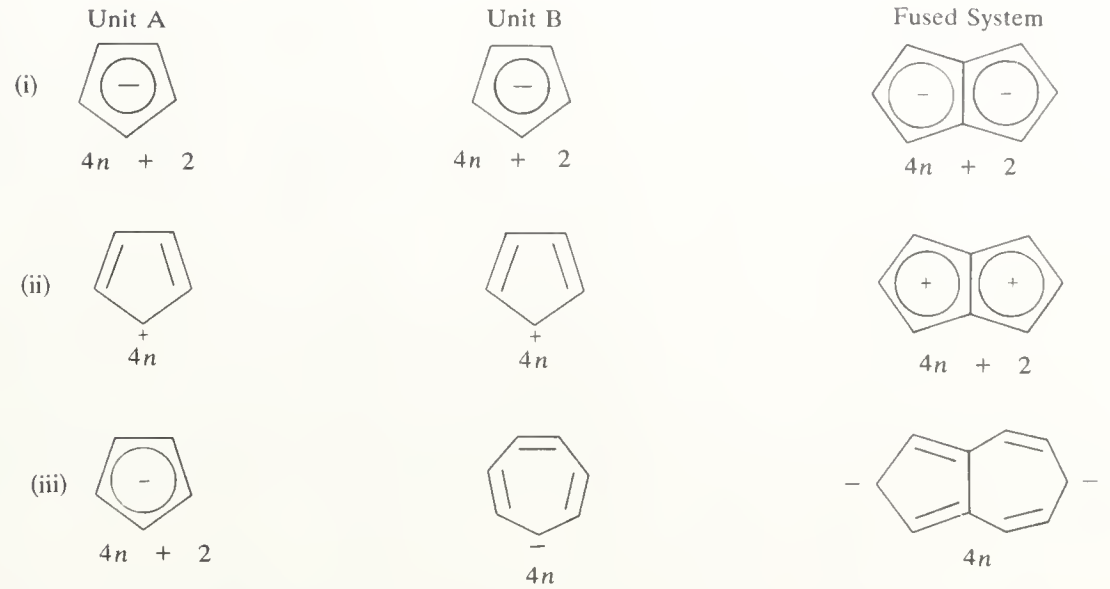
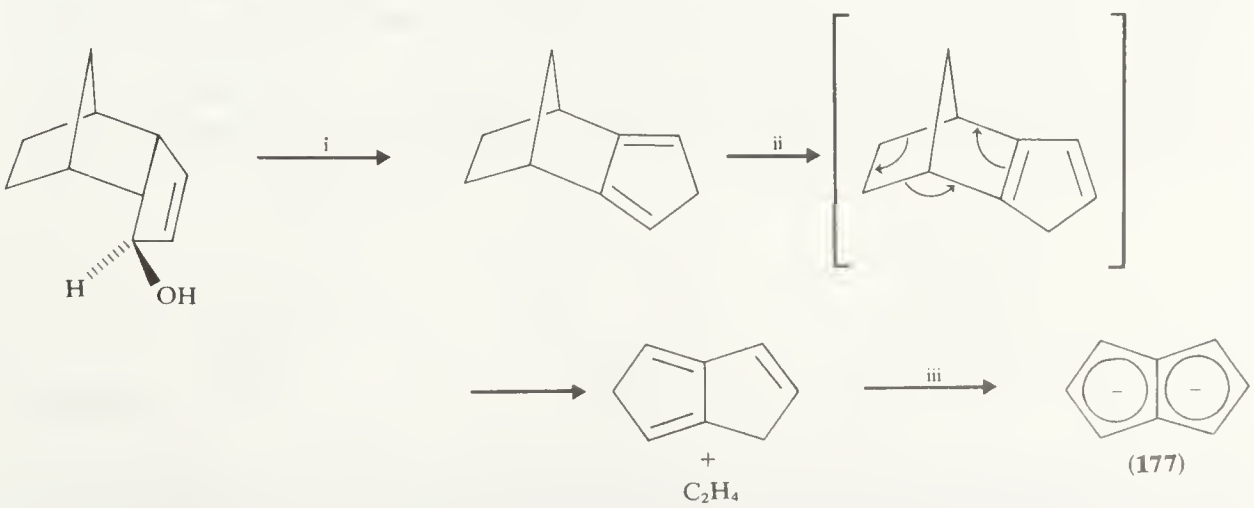


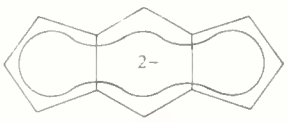
Figure 6

A number of polycyclic ions have now been prepared. The pentalene dianion (**177**) is a type (i) system with 10 π-electrons. It was prepared by Katz and Rosenberger[97] by the route shown in Scheme 31. The ^{1}H n.m.r. spectrum shows an AB_2 system consisting of a two-proton triplet at δ 5.73 and a four-proton doublet at δ 4.98. The chemical shifts are close to that of the cyclopentadienyl anion (**126**). The pentalene dianion (**177**) is related to pentalene in exactly the same way as the cyclo-octatetraenyl dianion (**157**) is related to cyclo-octatetraene (**2**). The sym- (**178**)[98] and asym- (**179**)[99] indacenyl dianions are also type (i) systems with 14 π-electrons. Both have been prepared as air-sensitive salts and appear, from the ^{1}H n.m.r. spectra, to be planar, diatropic systems.

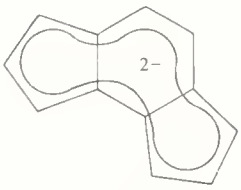


i, Al_2O_3, 320 °C; ii, 575 °C, N_2; iii, Bu^{n}Li, THF.

SCHEME 31

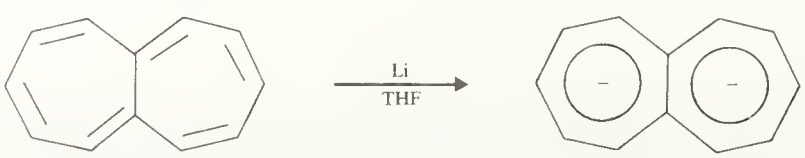


(178)



(179)

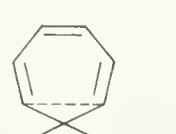
The heptalene dianion (**181**) is a type (ii) system consisting of two $4n$ cycloheptatrienyl anions and having a total of 14 π-electrons. It has recently been prepared[100] *via* the intervening anion-radical (equation 17) by treatment of heptalene (**180**) with lithium in THF. The ^{1}H n.m.r. spectrum shows a four-proton doublet at δ 7.65, a two-proton triplet at δ 6.25, and a four-proton triplet at δ 5.74, and the broad-band decoupled ^{13}C n.m.r. spectrum shows four types of carbon atoms. The dianion (**181**) is clearly a delocalized, diatropic 14π-electron system, and the properties are in marked contrast to those of the component cycloheptatrienyl anions (**153**) (Section 2.6.7). This is the only example of a type (ii) system having the properties of a $4n+2$ π-electron system rather than the properties of the two $4n$ components. This must largely be due to the delocalized form allowing a better spread of the excess of electron density. The heptalene dianion (**181**) has an analogous relationship to heptalene (**180**) as does the [12]annulenyl dianion (**165**) to [12]annulene (**32**). Attempts to prepare the heptalene dication, a type (i) system, have been unsuccessful, and no attempts to prepare the pentalene dication, a type (ii) system, have been reported. Other dianions and dications related to 'zero' bridged annulenes appear as inviting synthetic targets.



(180) (181) (17)

2.6.9 HOMOAROMATIC SYSTEMS[73b,101]

The first suggestion that cyclic delocalization might occur in an interrupted system was made by Thiele to explain the low acidity of cycloheptatriene. Later, von Doering suggested that the properties of the Buchner acids (**182**) were consistent with there being a 1,6-interaction. Recently, Wehner and Günther have shown by ^{13}C n.m.r. spectroscopy that there is a contribution from the norcaradiene structure.[102] The term homoaromatic was introduced by Winstein, who proposed this interaction in 1,4,7-cyclononatriene (**183**). If there is such an interaction then (**183**) could be represented by the trishomobenzene structure (**183a**). However, the interaction between the double bonds in (**183**) is small.

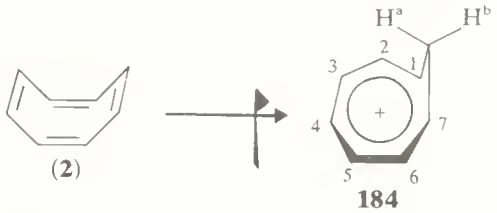


(182)

(183)

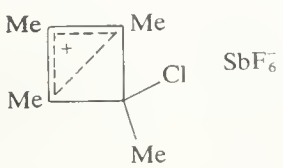
(183a)

The most convincing cases of homoaromatic participation have occurred for ions. The first to be recognized was the monohomotropylium cation (**184**), prepared by von Rosenberg, Mahler, and Pettit in 1962 from cyclo-octatetraene (**2**) by treatment with concentrated sulphuric acid (equation 18).[103] In the ^{1}H n.m.r. spectrum the protons on

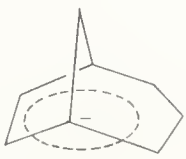


(2) **184** (18)

C-2 and C-6 appear at low field (δ 8.5) and the protons on C-1 and C-7 next to the bridge at slightly higher field (δ 6.6). The two bridge protons have very different chemical shifts, the inner H^a proton being at high (δ −0.6) and the outer H^b proton at low (δ 5.2) field. The chemical shift difference for H^a and H^b is that expected for protons in inner and outer positions in a diatropic molecule. A variety of other homotropylium ions have subsequently been prepared and all are diatropic systems. Other well-characterized homoaromatic ions are the tetramethylhomocyclopropenium ion (**185**),[104] the bishomocyclopentadienyl anion (**186**),[105] and the monohomocyclo-octatetraenyl dianion (**187**).[106]



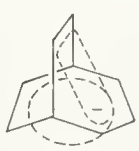
(185)



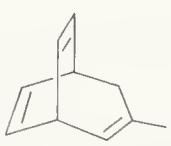
(186)

(187)

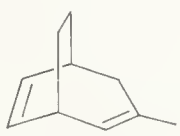
The concept of homoaromaticity has been extended by Goldstein[107] to bicycloaromaticity in which aromatic conjugation is examined in non-planar molecules. Bicycloaromaticity is predicted to occur only in odd systems with a total of $4n$ π-electrons and some evidence for an increase in the stability of the anion (**188**) has been obtained. The hydrocarbon (**189**) exchanges deuterium under base catalysis 750 times faster than does the hydrocarbon (**190**).[108] This can be considered to be due to the greater stability of the bicyclo-conjugated ion.



(188)

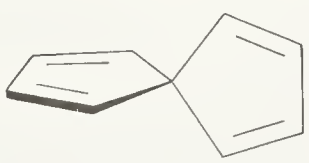


(189)

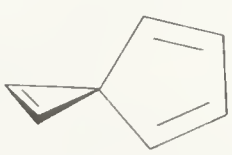


(190)

The concept of spiroconjugation has also been invoked in non-planar systems.[109] This type of interaction could be expected in molecules of type (**191**) or (**192**) but, so far, little evidence for such stabilization has been forthcoming.



(191)



(192)

References

1. F. Sondheimer and R. Wolovsky, *J. Amer. Chem. Soc.*, 1962, **84,** 260.
2. For a general review, see P. J. Garratt, 'Aromaticity,' McGraw-Hill, New York, 1971, chapters 3, 4, 5.
3. See M. P. Cava and M. J. Mitchell, 'Cyclobutadiene and Related Compounds,' Academic, New York, 1967.
4. R. Willstätter and E. Waser, *Ber.*, 1911, **44,** 3423; R. Willstätter and M. Heidelberger, *ibid.*, 1913, **46,** 517.

5. For reviews of the properties and chemistry of cyclo-octatetraene, see G. Schröder, 'Cyclooctatetraene,' Verlag Chemie, Weinheim, 1965; H. Röttele, in 'Methoden der Organischen Chemie (Houben-Weyl),' ed. E. Müller, Verlag Chemie, Stuttgart, 1972, vol. 5/1d, p. 417; L. A. Paquette, *Tetrahedron*, 1975, **31,** 2855; G. I. Fray and R. G. Saxton, 'The Chemistry of Cyclo-octatetraene and its Derivatives,' Cambridge U.P., 1978.
6. W. Reppe, O. Schlichting, and H. Meister, *Annalen*, 1948, **560,** 93.
7. C. W. Bird, 'Transition Metal Intermediates in Organic Synthesis,' Logos, London, 1967.
8. R. Huisgen and F. Mietzsch, *Angew. Chem. Internat. Edn.*, 1964, **3,** 83; R. Huisgen, W. E. Konz, and G. E. Gream, *J. Amer. Chem. Soc.*, 1970, **92,** 4105.
9. E. Vogel, H. Kiefer, and W. R. Roth, *Angew. Chem. Internat. Edn.*, 1964, **3,** 442.
10. K. Mislow, *J. Chem. Phys.*, 1952, **20,** 1489.
11. E. Vogel and H. D. Roth, *Angew. Chem. Internat. Edn.*, 1964, **3,** 228; E. Vogel, in 'Aromaticity', Special Publications, The Chemical Society, London, 1967, No. 21, p. 113.
12. V. Boekelheide and J. B. Phillips, *J. Amer. Chem. Soc.*, 1963, **85,** 1545.
13. See P. J. Garratt and K. Grohmann, in 'Methoden der Organischen Chemie (Houben-Weyl),' ed. E. Müller, Verlag Chemie, Stuttgart, 1972, vol. 5/1d, p. 527.
14. K. Stöckel and F. Sondheimer, *Org. Synth.*, 1974, **54,** 1.
15. F. Sondheimer, *Pure Appl. Chem.*, 1963, **7,** 363; *Proc. Roy. Soc.*, 1967, **A297,** 173; 'Proceedings of the Robert A. Welch Foundation Conferences on Chemical Research', XII, 'Organic Synthesis', ed. W. O. Milligan, Houston, Texas, 1969, p. 125; *Accounts Chem. Res.*, 1972, **5,** 81.
16. G. Schröder, *Pure Appl. Chem.*, 1975, **44,** 925.
17. T. L. Burkoth and E. E. van Tamelen, in 'Nonbenzenoid Aromatics', ed. J. P. Snyder, Academic, New York, 1969, vol. 1, p. 63; E. E. van Tamelen, T. L. Burkoth, and R. H. Greeley, *J. Amer. Chem. Soc.*, 1971, **93,** 6120.
18. S. Masamune, K. Hojo, Kiyomi Hojo, G. Bigam, and D. L. Rabenstein, *J. Amer. Chem Soc.*, 1971, **93,** 4966.
19. (a) J. F. M. Oth, J. M. Gilles, and G. Schröder, *Tetrahedron Letters*, 1970, 67; (b) G. Schröder and J. F. M. Oth, *ibid.*, 1966, 4083; G. Schröder, W. Martin, and J. F. M. Oth, *Angew. Chem. Internat. Edn.*, 1967, **6,** 870.
20. E. Vogel, in 'Proceedings of the Robert A. Welch Foundation Conferences on Chemical Research', XII, 'Organic Synthesis,' ed. W. O. Milligan, Houston, Texas, 1969, p. 215; *Pure Appl. Chem.*, 1971, **28,** 355.
21. E. Vogel, W. Klug, and A. Breuer, *Org. Synth.*, 1974, **54,** 11.
22. E. Vogel, H. Königshofen, K. Müllen, and J. F. M. Oth, *Angew. Chem. Internat. Edn.*, 1974, **13,** 281; E. Vogel, M. Mann, Y. Sakata, K. Müllen, and J. F. M. Oth, *ibid.*, 1974, **13,** 283.
23. K. P. C. Vollhardt, *Synthesis*, 1975, 765.
24. H. Staab, F. Graf, and B. Junge, *Tetrahedron Letters*, 1966, 743.
25. R. H. Mitchell and V. Boekelheide, *J. Amer. Chem. Soc.*, 1970, **92,** 3510.
26. G. M. Badger, J. A. Elix, and G. E. Lewis, *Austral. J. Chem.*, 1966, **19,** 1221.
27. For a compilation of annulene spectra, see R. C. Haddon, V. R. Haddon, and L. M. Jackman, *Current Topics Chem. Res.*, 1971, **16,** 105.
28. J. Bregman, F. L. Hirshfield, D. Rabinovich, and G. M. J. Schmidt, *Acta Cryst.*, 1965, **19,** 227; F. L. Hirshfield and D. Rabinovich, *ibid.*, 1965, **19,** 235.
29. J. F. M. Oth, J. C. Buenzli, and Y. de J. de Zélicourt, *Helv. Chim. Acta*, 1974, **57,** 2276.
30. K. Stöckel, P. J. Garratt, F. Sondheimer, Y. de J. de Zélicourt, and J. F. M. Oth, *J. Amer. Chem. Soc.*, 1972, **94,** 8644.
31. R. B. DuVernet, T. Otsubo, J. A. Lawson, and V. Boekelheide, *J. Amer. Chem. Soc.*, 1975, **97,** 1629.
32. H. J. Dauben, J. D. Wilson, and J. L. Laity, in 'Nonbenzenoid Aromatics', ed. J. P. Snyder, Academic, New York, 1971, vol. 2, p. 167.
33. M. Dobler and J. D. Dunitz, *Helv. Chim. Acta*, 1965, **48,** 1429.
34. E. Vogel, W. Maier, and J. Eimer, *Tetrahedron Letters*, 1966, 655; J. J. Bloomfield and J. R. Smiley Irelan, *ibid.*, 1966, 2971.
35. S. Masamune, D. W. Brooks, K. Morio, and R. L. Sobczak, *J. Amer. Chem. Soc.*, 1976, **98,** 8277.
36. C. C. Chiang and I. C. Paul, *J. Amer. Chem. Soc.*, 1972, **94,** 4741.
37. E. Vogel, J. Sombroek, and W. Wagemann, *Angew. Chem. Internat. Edn.*, 1975, **14,** 564.
38. A. Alscher, W. Bremser, D. Cremer, H. Günther, H. Schmickler, W. Sturm, and E. Vogel, *Chem. Ber.*, 1975, **108,** 640.
39. V. Boekelheide, in 'Topics in Nonbenzenoid Aromatic Chemistry', ed. T. Nozoe *et al.*, Hirokawa, Tokyo, 1973, vol. 1, p. 47; *Pure Appl. Chem.*, 1975, **44,** 751.
40. R. M. McQuilkin, B. W. Metcalf, and F. Sondheimer, *Chem. Comm.*, 1971, 338.
41. S. M. Johnson, I. C. Paul, and G. S. D. King, *J. Chem. Soc.* (*B*), 1970, 643.
42. G. Schröder, W. Martin, and J. F. M. Oth, *Angew. Chem. Internat. Edn.*, 1967, **6,** 870.
43. L. Watts, J. D. Fitzpatrick, and R. Pettit, *J. Amer. Chem. Soc.*, 1965, **87,** 3253; 1966, **88,** 623.
44. C. Y. Lin and A. Krantz, *J.C.S. Chem. Comm.*, 1972, 1111.
45. O. L. Chapman, C. L. McIntosh, and J. Pacansky, *J. Amer. Chem. Soc.*, 1973, **95,** 1337.
46. G. Maier, H.-G. Hartan, and T. Sayrac, *Angew. Chem. Internat. Edn.*, 1976, **15,** 226; G. Maier and H. P. Reisenauer, *Tetrahedron Letters*, 1976, 3591.
47. G. Maier, *Angew. Chem. Internat. Edn.*, 1974, **13,** 425.

48. See R. Gompper and G. Seybold, *Angew. Chem. Internat. Edn.*, 1968, **7,** 824; 'Topics in Nonbenzenoid Aromatic Chemistry', ed. T. Nozoe *et. al.*, Hirokawa, Tokyo, 1977, vol. 2, p. 29; M. Neuenschwander and A. Niederhauser, *Helv. Chim. Acta*, 1970, **53,** 519.
49. H. Kimling and A. Krebs, *Angew. Chem. Internat. Edn.*, 1972, **11,** 932.
50. H. Irngartinger and H. Rodewald, *Angew. Chem. Internat. Edn.*, 1974, **13,** 740.
51. G. Lauer, C. Müller, K. W. Schulte, A. Schweig, and A. Krebs, *Angew. Chem. Internat. Edn.*, 1974, **13,** 544.
52. L. T. J. Delbaere, M. N. G. James, N. Nakamura, and S. Masamune, *J. Amer. Chem. Soc.*, 1975, **97,** 1973.
53. S. Masamune, N. Nakamura, M. Suda, and H. Ona, *J. Amer. Chem. Soc.*, 1973, **95,** 8481; G. Maier and A. Alzérreca, *Angew. Chem. Internat. Edn.*, 1973, **12,** 1015.
54. M. J. S. Dewar and H. W. Kollmar, *J. Amer. Chem. Soc.*, 1975, **97,** 2933.
55. W. T. Borden, *J. Amer. Chem. Soc.*, 1975, **97,** 5968.
56. G. Maier and W. Sauer, *Angew. Chem. Internat. Edn.*, 1977, **16,** 51.
57. L. A. Paquette, J. M. Photis, and G. D. Ewing, *J. Amer. Chem. Soc.*, 1975, **97,** 3538; L. A. Paquette and J. M. Photis, *ibid.*, 1976, **98,** 4936.
58. L. A. Paquette, J. M. Gardlik, and J. M. Photis, *J. Amer. Chem. Soc.*, 1976, **98,** 7096.
59. N. A. Bailey and R. Mason, *Proc. Roy. Soc.*, 1966, **A290,** 94.
60. M. Nakagawa, 'Topics in Nonbenzenoid Aromatic Chemistry', ed. T. Nozoe *et al.*, Hirokawa, Tokyo, 1973, vol. 1, p. 191; *Pure Appl. Chem.*, 1975, **44,** 885.
61. K. Grohmann and F. Sondheimer, *J. Amer. Chem. Soc.*, 1967, **89,** 7119.
62. H. A. Staab, F. Graf, and B. Junge, *Tetrahedron Letters*, 1966, 743; H. A. Staab and F. Graf, *Chem. Ber.*, 1970, **103,** 1107.
63. U. E. Meissner, A. Gensler, and H. A. Staab, *Angew. Chem. Internat. Edn.*, 1976, **115,** 365.
64. R. H. Mitchell and R. J. Carruthers, *Tetrahedron Letters*, 1975, 4331.
65. H. Günther, H. Schmickler, H. Königshofen, K. Recker, and E. Vogel, *Angew. Chem. Internat. Edn.*, 1973, **12,** 243.
66. U. E. Meissner, A. Gensler, and H. A. Staab, *Tetrahedron Letters*, 1977, 3.
67a. H. N. C. Wong and F. Sondheimer, *Angew. Chem. Internat. Edn.*, 1976, **15,** 117.
67b. H. N. C. Wong, P. J. Garratt, and F. Sondheimer, *J. Amer. Chem. Soc.*, 1974, **96,** 5604.
68. H. A. Staab and R. Bader, *Chem. Ber.*, 1970, **103,** 1157.
69. See H. Günther, A. Shyoukh, D. Cremer, and K. H. Frisch, *Tetrahedron Letters*, 1974, 781.
70. T. M. Cresp and F. Sondheimer, *J. Amer. Chem. Soc.*, 1975, **97,** 4412; *ibid.*, 1977, **99,** 194.
71. T. Kashitani, S. Akiyama, M. Iyoda, and M. Nakagawa, *J. Amer. Chem. Soc.*, 1975, **97,** 4424; S. Akiyama, M. Iyoda, and M. Nakagawa, *ibid.*, 1976, **98,** 6410.
72. For review see (a) T. Nozoe, *Prog. Org. Chem.*, 1961, **5,** 132; (b) P. J. Garratt and M. V. Sargent, in 'Nonbenzenoid Aromatics', ed. J. P. Snyder, Academic, New York, 1971, vol. 2, p. 207.
73. R. Breslow, J. T. Groves, and G. Ryan, *J. Amer. Chem. Soc.*, 1967, **89,** 5048; R. Breslow and J. T. Groves, *ibid.*, 1970, **92,** 984.
74. D. G. Farnum, G. Mehta, and R. G. Siberman, *J. Amer. Chem. Soc.*, 1967, **89,** 5048.
75. R. Breslow, *J. Amer. Chem. Soc.*, 1957, **79,** 5318.
76. G. A. Olah and J. S. Staral, *J. Amer. Chem. Soc.*, 1976, **98,** 6290.
77. R. Breslow and W. Chu, *J. Amer. Chem. Soc.*, 1970, **92,** 2165.
78. M. Saunders, R. Berger, A. Jaffe, J. M. McBride, J. O'Neill, R. Breslow, J. M. Hoffman, C. Perchonock, E. Wasserman, R. S. Hutton, and V. J. Kuck, *J. Amer. Chem. Soc.*, 1973, **95,** 3017.
79. J. S. McKennis, L. Brener, J. R. Schweiger, and R. Pettit, *J.C.S. Chem. Comm.*, 1972, 365.
80. See P. L. Pauson, 'Organometallic Chemistry', Arnold, London, 1967; D. E. Bublitz and K. L. Rinehart, *Org. Reactions*, 1969, **17,** 1; M. Rosenblum, 'Chemistry of the Iron Group Metallocenes', Wiley, New York, 1965, vol. 1.
81. G. A. Olah, J. S. Staral, and L. A. Paquette, *J. Amer. Chem. Soc.*, 1976, **98,** 1267.
82. H. J. Dauben and M. R. Rifi, *J. Amer. Chem. Soc.*, 1963, **85,** 3041.
83. R. Breslow and H. W. Chang, *J. Amer. Chem. Soc.*, 1965, **87,** 2200.
84. S. W. Staley and A. W. Orvedal, *J. Amer. Chem. Soc.*, 1973, **95,** 3382.
85. T. J. Katz, *J. Amer. Chem. Soc.*, 1960, **82,** 3784, 3785.
86. T. J. Katz and P. J. Garratt, *J. Amer. Chem. Soc.*, 1963, **85,** 2852; 1964, **86,** 5194; E. A. LaLancette and R. E. Benson, *ibid.*, 1963, **85,** 2853; 1965, **87,** 1941.
87. G. Boche, H. Böhme, and D. Martens, *Angew. Chem. Internat. Edn.*, 1969, **8,** 594; G. Boche, D. Martens, and W. Danzer, *ibid.*, 1969, **8,** 984; G. Boche, A. Bieberbach, and H. Weber, *ibid.*, 1975, **14,** 562.
88. (a) W. Grimme, H. Hoffmann, and E. Vogel, *Angew, Chem. Internat. Edn.*, 1965, **4,** 354; (b) R. Destro T. Pilati, and M. Simonetta, *J. Amer. Chem. Soc.*, 1976, **98,** 1999.
89. S. W. Staley and A. W. Orvedal, *J. Amer. Chem. Soc.*, 1973, **95,** 3384.
90. J. F. M. Oth and G. Schröder, *J. Chem. Soc. (B)*, 1971, 904.
91a. J. F. M. Oth, K. Müllen, H. Königshofen, M. Mann, Y. Sakata, and E. Vogel, *Angew. Chem. Internat. Edn.*, 1974, **13,** 284.
91b. P. J. Garratt, N. E. Rowland, and F. Sondheimer, *Tetrahedron*, 1971, **27,** 3157.
92a. R. H. Mitchell, C. E. Klopfenstein, and V. Boekelheide, *J. Amer. Chem. Soc.*, 1969, **91,** 4931.
92b. F. Gerson, K. Müllen, and E. Vogel, *J. Amer. Chem. Soc.*, 1972, **94,** 2924.
93. I. Murata, K. Yamamoto, and Y. Kayane, *Angew. Chem. Internat. Edn.*, 1974, **13,** 808.

94. J. F. M. Oth, D. M. Smith, U. Prange, and G. Schröder, *Angew. Chem. Internat. Edn.*, 1973, **12,** 327.
95. J. F. M. Oth, G. Anthoine, and J.-M. Gilles, *Tetrahedron Letters*, 1968, 6265.
96. G. Schröder, G. Plinke, D. M. Smith, and J. F. M. Oth, *Angew. Chem. Internat. Edn.*, 1973, **12,** 325.
97. T. J. Katz, M. Rosenberger, and R. K. O'Hara, *J. Amer. Chem. Soc.*, 1964, **86,** 249.
98. K. Hafner, *Angew. Chem. Internat. Edn.*, 1964, **3,** 165.
99. T. J. Katz and J. Schulman, *J. Amer. Chem. Soc.*, 1964, **86,** 3169.
100. J. F. M. Oth, K. Mullen, H. Konigshofen, J. Wassen, and E. Vogel, *Helv. Chem. Acta,* 1974, **57,** 2387.
101. See S. Winstein, in 'Aromaticity', Special Publications, The Chemical Society, London, 1967, No. 21, p. 5; *Quart. Rev.*, 1969, **23,** 141; P. M. Warner, in 'Topics in Nonbenzenoid Aromatic Chemistry', ed. T. Nozoe *et al.*, Hirokawa, Tokyo, 1977, vol. 2, p. 283.
102. R. Wehner and H. Günther, *J. Amer. Chem. Soc.*, 1975, **97,** 923.
103. J. L. von Rosenberg, J. E. Mahler, and R. Pettit, *J. Amer. Chem. Soc.*, 1962, **84,** 2842.
104. T. J. Katz and E. H. Gold, *J. Amer. Chem. Soc.*, 1964, **86,** 1600.
105. J. M. Brown and J. L. Occolowitz, *Chem. Comm.*, 1965, 376; J. M. Brown, *Chem. Comm.*, 1967, 638; S. Winstein, M. Ogliaruso, M. Sakai, and J. M. Nicholson, *J. Amer. Chem. Soc.*, 1967, **89,** 3656.
106. M. Ogliaruso, R. Rieke, and S. Winstein, *J. Amer. Chem. Soc.*, 1966, **88,** 4731.
107. M. J. Goldstein, *J. Amer. Chem. Soc.*, 1967, **89,** 6357; M. J. Goldstein and R. Hoffmann, *ibid.*, 1971, **93,** 6193.
108. See G. B. Trimitsis and A. Tuncay, *J. Amer. Chem. Soc.*, 1976, **98,** 1977, and references therein.
109. H. E. Simmons and T. Fukunaga, *J. Amer. Chem. Soc.*, 1967, **89,** 5208; R. Hoffmann, A. Imamura and G. D. Zeiss, *ibid.*, 1967, **89,** 5215.

2.7

Carbocations and Carbanions

D. BETHELL
University of Liverpool

2.7.1 CARBOCATIONS 411
2.7.1.1 Definitions and nomenclature 411
2.7.1.2 A brief historical survey of the development of carbocation chemistry 412
2.7.1.3 The generation of carbocations 413
2.7.1.4 A survey of known types of carbocation 417
2.7.1.5 The study of carbocations: methods and results 419
2.7.1.6 Reactions of carbocations 431
2.7.2 CARBANIONS 436
2.7.2.1 Definitions and nomenclature 436
2.7.2.2 The generation of carbanions 437
2.7.2.3 Survey of types of carbanion 441
2.7.2.4 Physical properties of carbanions 441
2.7.2.5 Reactions of carbanions 446

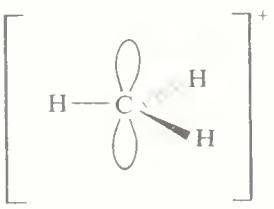
2.7.1 CARBOCATIONS[1]

2.7.1.1 Definitions and nomenclature

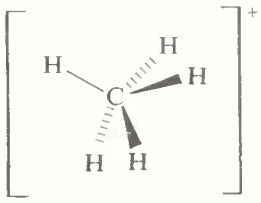
The term *carbocation* is used to denote any positively charged organic species containing an even number of electrons in which the charge is predominantly associated with one or more of the constituent carbon atoms. Two sub-species, carbenium ions and carbonium ions, may be distinguished.

Carbenium ions are derivatives of the trivalent carbocation CH_3^+ (**1**) notionally derived by protonation of carbenes, *e.g.* $CH_2{:} + H^+ \rightarrow CH_3^+$. Although delocalization of the positive charge occurs in appropriate structures, an essential feature of this type of carbocation is that in the most important contributing valence-bond formulations there should be a tricovalent carbon atom bearing the positive charge and associated with only six valence electrons (the carbenium centre). In the absence of overwhelming steric constraints, the three bonds attached to the carbenium carbon atom are coplanar (sp^2 hybridization of carbon) and it is convenient to associate the positive charge with a vacant carbon $2p$ atomic orbital perpendicular to that plane.

By contrast, *carbonium ions* are derivatives of the pentacovalent carbocation CH_5^+ (**2**), an ion having $\mathbf{C}_s$ symmetry and notionally obtained by protonation of methane. Such species, unlike carbenium ions, are electron deficient in the sense that they possess insufficient valence electrons to permit their formulation in terms of electron-pair bonds



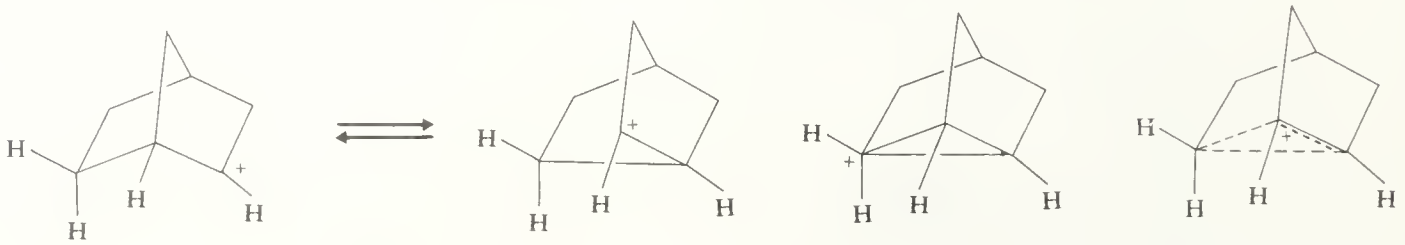
(1)



(2)

alone; a two-electron three-centre bond is necessary, as in boron hydrides, and the analogy between carbocations and boron compounds has often been stressed. Since the term carbonium ion has for many years been incorrectly employed for carbenium ions, the expression penta-coordinate carbonium ion will be used here to emphasize the distinction.

In this section, carbocation, carbenium ion, and penta-coordinate carbonium ion will be used as generic terms only. Individual carbenium ions will be named wherever possible as alkyl cations and penta-coordinate carbonium ions as cationated (usually protonated) alkanes. Some carbocations, however, defy unequivocal categorization. For example, carbocation (**3**), the 2-norbornyl cation, can be formulated either as a pair of rapidly equilibrating carbenium ions (**3a**) or as a single penta-coordinate carbonium ion (**3b**). Much controversy has surrounded the interpretation of the chemistry of (**3**)[2] and related 'bridged' or 'non-classical' carbenium ions, for which more non-committal formulations such as (**3c**) are often used.



(3a) (3b) (3c)

2.7.1.2 A brief historical survey of the development of carbocation chemistry[3]

The generation of coloured solutions when compounds such as triphenylmethanol dissolve in sulphuric acid, and the salt-like behaviour of, for example, triphenylmethyl chloride in solution in sulphur dioxide, led chemists, most notably Baeyer, Gomberg, Walden, and Hantzsch, to lay the foundations of carbenium ion chemistry in the early years of this century. Baeyer used the word 'carbonium' in connection with the species so generated, but the analogy with other 'onium ions which he had in mind was criticized by Gomberg who preferred the expression 'carbyl salts', The term carbenium ion was put forward some 20 years later by Dilthey as being more logical, but in much of the literature up to 1970 the original carbonium ion nomenclature was retained. Then, with the growing interest in electron-deficient species like CH_5^+ arising from experimental work in the gas phase and in superacidic media, and from quantum mechanical calculations, the more rational scheme in Section 2.7.1.1 was advocated again, most forcefully by Olah.

In the 1920s, carbenium ions began to be suggested as intermediates having a fleeting existence during the course of certain organic reactions. Thus Meerwein interpreted the rearrangement of camphene hydrochloride into isobornyl chloride (equation 1) in terms of

(1)

the rearrangement of an intermediate carbenium ion. Subsequently, the crucial role played by intermediates having a reactive centre associated with an 'open sextet of electrons' was explored in a wide variety of situations, particularly by Whitmore. Around this time the idea that carbenium ions might be formed in some cases during nucleophilic substitution at a saturated carbon atom was developed most notably by Ingold and Hughes. Such reactions, designated S_N1, were formulated as in equation (2). An important feature of the work was the establishment of kinetic and stereochemical criteria of reaction mechanism. Using the same basic techniques in the post-war years. Winstein, in particular, elaborated the picture of carbenium ions in solution; the concept of bridged ('non-classical') carbocations was developed to explain the rate-enhancing participation of neigbouring groups in carbocation-forming heterolyses, and the important part played by ion association in directing the behaviour of carbenium ions was detailed.

$$R_3CX \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R_3C^+ + X^- \xrightarrow[k_2]{Y^-} R_3CY \qquad (2)$$

The years since 1965 have seen the perfection of the technique of generating carbocations at low temperatures in superacidic media, thus permitting the direct structural examination (most effectively using n.m.r. spectroscopy) of ions previously known only as transient intermediates. Also, during this period, the development of mass spectrometric and related gas-phase techniques has produced new structural ideas and also quantitative information facilitating direct comparison of experimental data on carbocations with predictions made using the rapidly proliferating quantum theoretical methods which began with Hückel.

Carbocation chemistry has been of profound importance in the development of organic chemical theory and mechanistic understanding. It continues to have an important role in synthesis, in industrial chemistry, *e.g.* of petroleum, and in biochemical processes as diverse as the biosynthesis of terpenes and the mechanism of action of lysozyme.

2.7.1.3 The generation of carbocations

Carbenium ions may be produced by the following general types of process: (i) heterolytic cleavage of a σ-bond, (ii) addition of an electrophile to an unsaturated functional group, (iii) transfer of a negatively charged entity (an electron or hydride ion) from a neutral species to a suitable electrophilic acceptor, and (iv) rearrangement of another carbenium ion. Equations (3)–(5) give formal expression to the first three of these.

$$R_3CX \longrightarrow R_3C^+ + X^- \qquad (3)$$

$$E^+ + \diagup C{=}C \diagdown \longrightarrow E{-}C{-}C^+ \qquad (4)$$

$$R_3CH + A \longrightarrow R_3C^+ + AH^- \qquad (5a)$$

$$R_3C^\bullet + A \longrightarrow R_3C^+ + A^{\bullet -} \qquad (5b)$$

The simple *cleavage* process (equation 3) is not generally expected in the gas phase. The enthalpy change for such ionization of alkyl bromides (*e.g.* CH_3Br, ~895; $CH_2{=}CHCH_2Br$, 635; $C_6H_5CH_2Br$, 614 kJ mol^{-1}) is very much larger than the bond dissociation energies [$D(CH_3{-}Br)$, ~280; $D(CH_2{=}CHCH_2{-}Br)$, 190; $D(C_6H_5CH_2{-}Br)$, 211 kJ mol^{-1}] so that homolytic cleavage is preferred. However, if the reactant R_3CX is first converted to the radical cation $R_3CX^{\bullet +}$, for example by impact with energetic electrons, the excess of energy facilitates the fragmentation to R_3C^+ and $X^\bullet$, although this

TABLE 1

Solvent Effects on Rate Constants for Heterolytic Cleavage

Solvent	ε_r (25 °C)	Y (25 °C)[a]	log k_{ion} (75 °C)[b]
Water	78.5	3.493	−1.180
Formic acid	57.9	2.054	−0.929
Dimethyl sulphoxide	48.9	—	−3.738
Acetonitrile	37.5	—	−4.221
Dimethylformamide	36.7	—	−4.298
Methanol	32.6	−1.090	−2.796
Ethanol	24.3	−2.033	−3.204
Acetone	20.5	—	−5.067
t-Butyl alcohol	12.2	−3.26	—
Tetrahydrofuran	7.4	—	−6.073
Acetic acid	6.2	−1.639	−2.772
Diethyl ether	4.2	—	−7.3

[a] $Y = \log k/k_0$ for solvolysis of t-butyl chloride; k_0 refers to the standard solvent, 80% aqueous ethanol.
[b] This refers to the production of titratable acid from p-$MeOC_6H_4CMe_2CH_2OTs$ and is believed to be free of interference from 'internal return' of ion pairs (see p. 429).

process will generally be accompanied by competing and consecutive fragmentation processes.

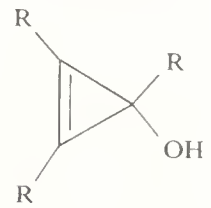
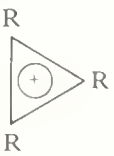
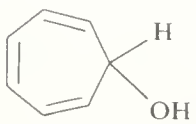
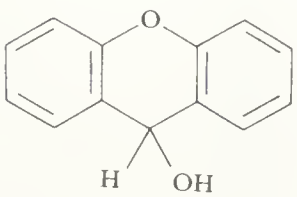
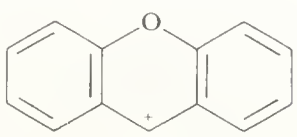
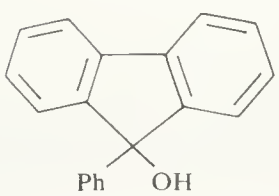
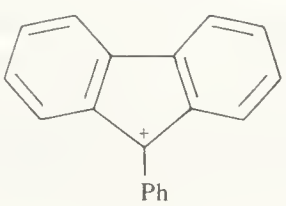
In solution the stabilizing interaction of the product ions with solvent molecules makes heterolytic cleavage the preferred process in most cases. The stronger the solvation the more favourable is the ionization process. The dielectric constant (ε_r) might be thought the best measure of the solvent's ability to mitigate the effect of charges and this certainly gives general guidance, but the results in Table 1, obtained from rates of unimolecular substitution and elimination reactions, indicate that the parallelism with solvent effects on gross rates of carbenium ion formation as measured by Y and log k_{ion} is not perfect. Despite its large contribution to the stabilization of carbenium ions, solvation is remarkably insensitive to carbenium ion structure,[4] presumably as a consequence of charge delocalization in the ions studied.[5] Formation of a given carbenium ion is favoured by those groups X which form the most stable anion under the reaction conditions. The best leaving groups are thus the anions of strong acids, and a rough order of decreasing ability is $ClO_4^- > CF_3SO_3^- > ArSO_3^- > Br^- > Cl^- > p\text{-}NO_2C_6H_4CO_2^-$. Anions derived from much weaker acids, such as OH^-, are very poor leaving groups; their departure has to be assisted by catalysts such as Brønsted acids, which make the leaving group a neutral molecule rather than an anion (for quantitative equilibrium data, see Table 2), Lewis acids, which make the leaving group a more stable anion, or Lewis acid sites on solid surfaces, *e.g.* of silica–alumina. Likewise, the heterolysis of organic halides can be electrophilically catalysed by Lewis acids such as $AlCl_3$ and BF_3, and this is the favoured means of producing stable carbenium salts.[6] Silver ion, which removes the leaving halide as AgX, also promotes carbenium ion formation from organic halides.

Other cleavages can be assisted by more extensive modification of the leaving group. Thus NH_2 groups can be induced to depart by diazotization with nitrous acid, giving the diazonium ion ($R_3C\overset{+}{N}{\equiv}N$), cleavage of which is a highly exothermic process of low activation energy. The resultant carbenium ions show especially high reactivity and are sometimes described as 'hot'.[7] Acyl cations, R_3CCO^+, are isoelectronic with diazonium ions and readily lose carbon monoxide. Another interesting method which permits the generation of carbenium ions under very basic conditions is the deoxidation of alcohols, as shown in equation (6).

$$R_3COH + CHBr_3 + OH^- \longrightarrow R_3CO^- + :CBr_2$$
$$\longrightarrow R_3C\ddot{O}CBr \longrightarrow R_3C^+ + CO + Br^- \qquad (6)$$

TABLE 2

Equilibrium Constants for the Formation of Carbenium Ions by Cleavage of Alcohols in Aqueous Acid[a]

Alcohol	*Carbenium ion*		pK_{R^+}[b]
		$R = Pr^n$ $R = Ph$	7.2 3.2
			4.7.
			−0.17
Ph_3COH	Ph_3C^+		−6.44
Ph_2COH	Ph_2CH^+		−13.3
			−10.8

[a] From the more extensive complications of D. Bethell and V. Gold, 'Carbonium Ions. An Introduction', Academic, New York, 1967, pp. 76,79. [b] K_{R^+} is the equilibrium constant for the reaction $R^+ + H_2O \rightleftarrows ROH + H^+$.

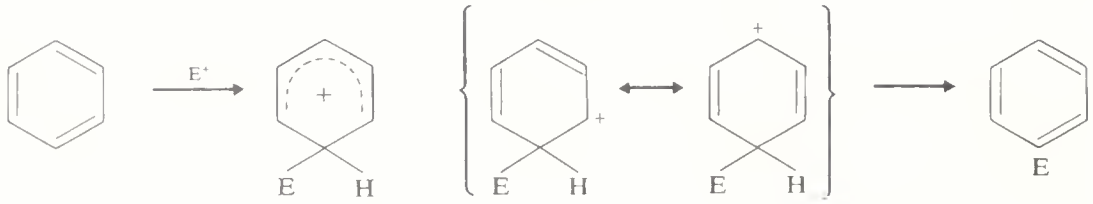
A rather special cleavage is that which follows nuclear β-decay of an atom attached to a potential carbenium centre. Thus β-decay of tritium in gaseous tritiomethane leads to the highly unstable methylhelium cation which cleaves to yield (**1**), as shown in equation (7)[8a],

$$CH_3{}^3H \xrightarrow{\beta} CH_3{}^3He \longrightarrow CH_3^+ + {}^3He \qquad (7)$$

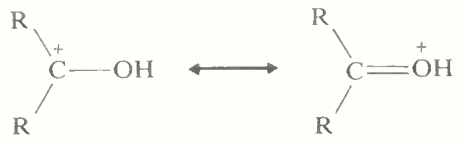
and 2-hydroxyphenyl cations have been generated by β-decay of the corresponding aryl iodide.[8b]

The addition route (equation 4) to carbenium ions is an important step in electrophilic addition to olefins and acetylenes, in cationic vinyl polymerization, and in electrophilic aromatic substitution (equation 8). Furthermore, attachment of an electrophile to unsaturated functions containing heteroatoms (*e.g.* carbonyl, imine) gives rise to cations which may be formulated either as carbenium (**4a**) or heteronium (**4b**) ions and show behaviour consistent with both.

The simplest electrophile is the proton. Table 3 gives some values of H_0, a measure of the relative ability of an acidic solvent to transfer a proton to an organic base of the



(8)



(4a) **(4b)**

TABLE 3

H_0 Values for Selected Acidic Media[a]

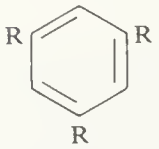
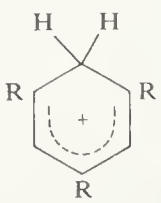
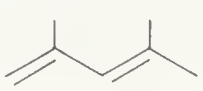
Acid	$-H_0$
CF_3CO_2H	3.03[b]
HF	*ca.* 11.0
H_2SO_4 (100%)	11.93
(98% w/w)	10.44
HSO_3Cl	13.80
$H_2S_2O_7$	14.44
HSO_3F	15.07
$HSO_3F + SbF_5$ (4 mol %)	18.35

[a] Taken from R. J. Gillespie and T. E. Peel, *Adv. Phys. Org. Chem.*, 1971, **9,** 1. [b] H. H. Hyman and R. A. Garber, *J. Amer. Chem. Soc.*, 1959, **81,** 1847.

nitroaniline type.[9a] Protonation of olefins and aromatics is imperfectly correlated[9b] by H_0 — the more appropriate function, H'_R, is only available in aqueous acidic systems — but the values serve to indicate that, for example, HSO_3F/SbF_5 ('magic acid') is about 10^6 times more effective than sulphuric acid in protonating weak organic bases: Table 4 indicates the acidities necessary to protonate some unsaturated hydrocarbons.

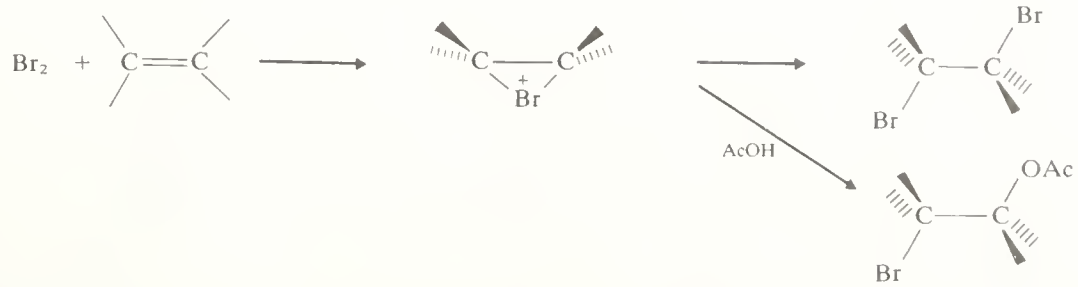
TABLE 4

Carbenium-ion Formation by Protonation of Unsaturated Compounds in Aqueous Acid[a]

Base	*Carbenium ion*		pK_a	*Acid conc. for half ionization*
Azulene	See equation (12)		−1.7	2.3M $HClO_4$
		R = OMe	−5.1	7M $HClO_4$
		R = Me	—	94.5% H_2SO_4
$Ph_2C=CH_2$	$Ph_2\overset{+}{C}CH_3$		—	71% H_2SO_4
			—	73% H_2SO_4

[a] Taken from a more extensive compilation in D. Bethell and V. Gold, 'Carbonium Ions. An Introduction', Academic, New York, 1967, p. 82.

Other important electrophiles are other carbenium ions, including acyl cations, the nitronium ion, and the halogens, and these have been extensively investigated in electrophilic aromatic substitution. In the addition of halogen (*e.g.* bromine) to olefins, there is strong chemical and physical evidence[10] (*e.g.* high *trans* stereoselectivity, n.m.r. spectroscopy) that the cationic intermediate is best formulated as a cyclic bromonium ion as shown in equation (9) rather than as a β-bromocarbenium ion. Competition for the intermediate from nucleophiles other than bromide ion does not distinguish between the two formulations.



(9)

Transfer processes for the generation of carbenium ions cover two important categories of reaction. The first of these is intermolecular hydride transfer (equation 5a),[11] in which a hydride ion is transferred to a suitable acceptor electrophile, usually another, less thermodynamically stable, carbenium ion. A typical example is shown in equation (10). Analogous intramolecular processes (carbenium ion rearrangements) are dealt with in Section 2.7.1.6. In the course of the reaction the transferred hydrogen does not usually undergo exchange with labile protons in the solvent. Exchange and acid catalysis of the transfer step have been reported[12] in the reaction between pentamethylbenzyl cation and isobutane, however, and this reaction may provide a link between carbenium ion chemistry and penta-coordinate carbonium ion chemistry in solution.

(10)

In an analogous fashion, carbenium ions can be formed by electron removal from an organic radical (equation 5b). As with hydride transfer the electron is transferred directly to the acceptor, which might be a chemical reagent such as a copper(II) cation[13] or an electrode surface.[14] In the gas phase an important process is electron removal by collision of the radical with an energetic electron or photon, but this is not a transfer process.

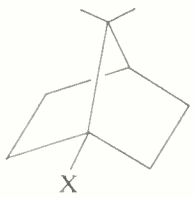
Of necessity, penta-coordinate carbonium ions are formed by addition processes in which a cation is attached to an already saturated molecular centre. The least equivocal evidence for this type of process comes from gas-phase studies (high-pressure mass spectrometry and ion cyclotron resonance spectroscopy) in which protons or larger cationic (carbenium) species interact with saturated molecules as shown in equation (11).[15] In solution, the occurrence of hydrogen isotope exchange in methane dissolved in FSO_3H/SbF_5 can be interpreted in terms of the intermediate formation of protonated alkanes, but alternative interpretations are possible.[16] Protonated alkanes may be involved in isomerization and fragmentation[16] and in anodic oxidation[14] of saturated hydrocarbons in superacidic media.

$$C_2H_5^+ + H_2 \longrightarrow C_2H_7^+ \qquad (11)$$

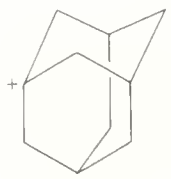
2.7.1.4 A survey of known types of carbocation

Although usually classed as reactive intermediates, carbocations span a very wide range of stability, some occurring as indefinitely stable salts while others have lifetimes measured in nanoseconds.

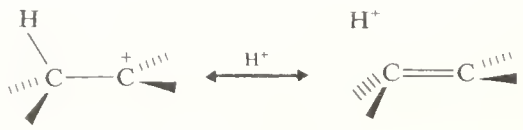
Primary alkyl cations are known in the gas phase and as transient intermediates in solution. The more stable secondary and tertiary alkyl cations can be produced in solution in superacidic media in which they can be studied conveniently by spectroscopic means at low temperatures.[17] Tertiary ions are, however, difficult to generate at the bridgehead of rigid bicycloalkane systems such as (**5**) because of the difficulty in achieving coplanarity of the bonds to the trivalent carbon, but the 1-adamantyl cation (**6**) is well known. Charge delocalization in alkyl cations is usually discussed in terms of inductive charge spreading and C—H hyperconjugation (**7**), the importance of the latter being determined by the carbenium ion conformation (see, however, Section 2.7.1.5).



(**5**)

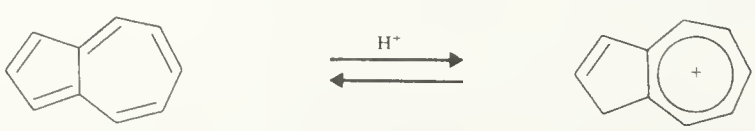


(**6**)



(**7**)

Delocalization of the positive charge of the carbenium ion through attachment of a π-system offers stabilization provided that the appropriate geometry can be achieved. Thus allylic and especially cyclopentenyl cations are much more stable than their saturated counterparts. Likewise the cyclohexadienyl cations produced by protonation of arenes show considerable stability and their study lends strong support to the usual $S_E'2$ formalism of electrophilic aromatic substitution.[18] Aryl substituents attached in the carbenium centre are a particularly potent stabilizing influence. Triarylmethane dyes like Crystal Violet and Malachite Green are highly stabilized carbenium salts, and, as indicated in Section 2.7.1.2, triarylmethyl cations were the first carbenium ions to be recognized as such. π-Delocalization achieves its greatest importance in fully-conjugated monocyclic cations. Thus ions having $(4n+2)$ π-electrons such as cyclopropenyl ($n=0$) and cycloheptatrienyl cations are said to be aromatic. Stable salts of the latter ('tropylium salts') are well known, and hydrocarbons which on protonation give rise to such ions, *e.g.* azulene, are particularly basic (equation 12). Cyclic conjugation is sufficiently strong that

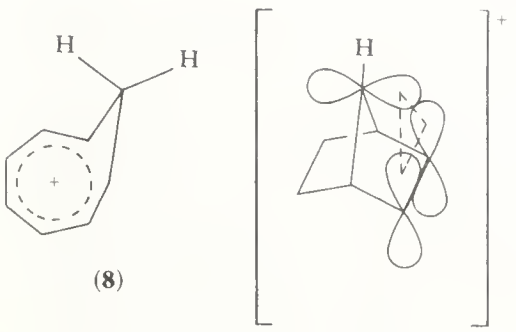


(12)

it is still an important stabilizing influence even when the conjugated system is interrupted; thus protonation of cyclo-octatetraene gives the homocycloheptatrienyl cation (**8**). In contrast, cyclic cations with $4n$ π-electrons are less stable and are often referred to as anti-aromatic. $p\pi$-Delocalization of a different sort stabilizes the ion (**9**). Interaction of metal *d*-orbitals with the cationic carbon may be responsible for the remarkable stability of α-ferrocenylalkyl cations.[19]

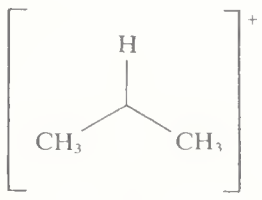
Most of the work on penta-coordinate carbonium ions comes from gas-phase work in which their identity is based on the ratio of mass to charge. This in itself contains little structural information. Nevertheless, there is clear evidence of two isomeric ions of composition $C_2H_7^+$ with different stability characteristics, the more stable being assigned the C–C protonated structure (**10**) and the less stable the C–H protonated structure (**11**) on theoretical grounds.[15c] Similar three-centre bonding is thought to be involved in protonated cyclopropanes suggested as intermediates in certain rearrangements.[16b,c]

Bridged carbocations form an interesting and controversial[20] group which usually show stability greater than anticipated on the basis of a carbenium-ion formulation. Thus (**3**) appears to be formed by cleavage more readily than related secondary ions. Even more unusual structures have been suggested for other carbocations;[21] examples are (**12**)–(**14**).

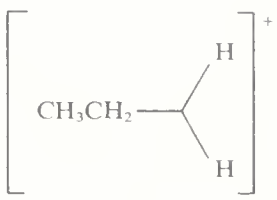


(8)

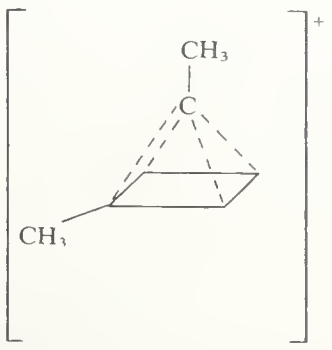
(9)



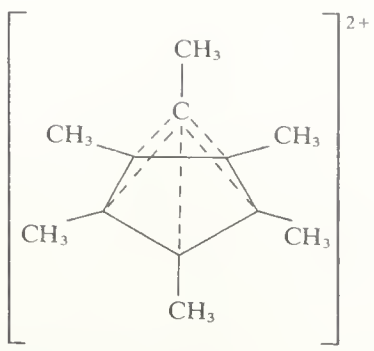
(10)



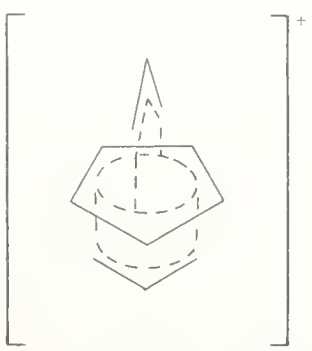
(11)



(12)



(13)



(14)

2.7.1.5 The study of carbocations: methods and results

As indicated in Section 2.7.1.3, carbocations can be generated in the gas phase, in liquid solution, and solid salts are also known. Methods of study necessarily depend upon the physical state of the ion, its lifetime and upon the type of information required, whether it be simple detection as a transient intermediate or quantitative information on structure and stability. Counter anions are also normally present with the carbocation and often modify its behaviour.

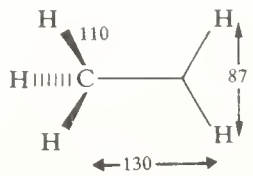
(i) Theoretical methods

Of the plethora of quantum mechanical methods which have been applied to carbocations, only the Hückel molecular orbital (HMO) procedure for conjugated systems, *ab initio*, and perturbational methods will be mentioned. These methods necessarily deal with carbocations in the gas phase.

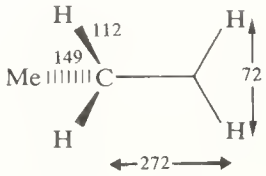
Being the first simple procedure, the HMO method[23] has probably had the greatest influence by providing a theoretical basis for qualitative and semiquantitative thinking about conjugated carbenium ions. The π-electron system is dealt with separately from the σ-bonded framework of the organic molecule, and the energies of the π-orbitals, constructed by the LCAO method, evaluated in terms of constant Coulomb and resonance integrals (α and β, respectively). Its total disregard of electron correlation and the non-self-consistent field in carbenium ions make the results quantitatively unsatisfactory, but, with appropriate parameterization, remarkably good predictions can be made of, for example, electronic absorption maxima.[22] A valuable prediction of HMO theory is that conjugated odd alternant hydrocarbons (carbenium ions, carbanions, and free radicals) possess a non-bonding molecular orbital (vacant for carbenium ions) which is a linear combination of carbon $2p$ atomic orbitals on starred atoms only. It follows from this that the ionic charge is, at this level of approximation, restricted to the starred atoms, and its distribution can be predicted by a very simple procedure. Perhaps the greatest success of the HMO method has been the prediction, well in advance of experiment, of the special

stability of the monocyclic aromatic carbenium ions possessing $(4n+2)$ π-electrons, the cyclopropenyl and cycloheptatrienyl cations and the cyclobutadienyl dication,[24] and of the triplet ground state of the cyclopentadienyl cation.[25]

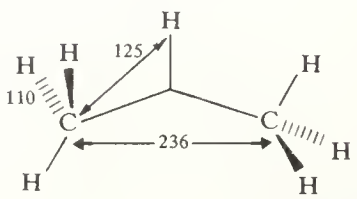
A number of more complex procedures including self-consistent field (SCF) methods have been developed, but all need parameterization to yield quantitative results.[26] The most recent work, however, uses *ab initio* SCF procedures which do not require the input of experimental information.[27] By minimizing the energy of a carbocation with respect to geometrical parameters, detailed structures can be predicted and these appear to be in close agreement with experiment. At present, bond lengths for penta-coordinate carbonium ions are only available theoretically; some values (in pm), obtained using the STO-3G basis set, are given in (**15**)–(**17**).



(**15**)



(**16**)



(**17**)

Useful qualitative insights into carbocation structure can be obtained with perturbational (PMO) procedures, using, for example, HMO orbitals as a basis. The energy change (perturbation) resulting from the interaction of the orbitals of smaller molecular fragments can be determined, and this decreases in magnitude as the energy separation of the interacting orbitals increases. The procedure is illustrated schematically in Figure 1 for the

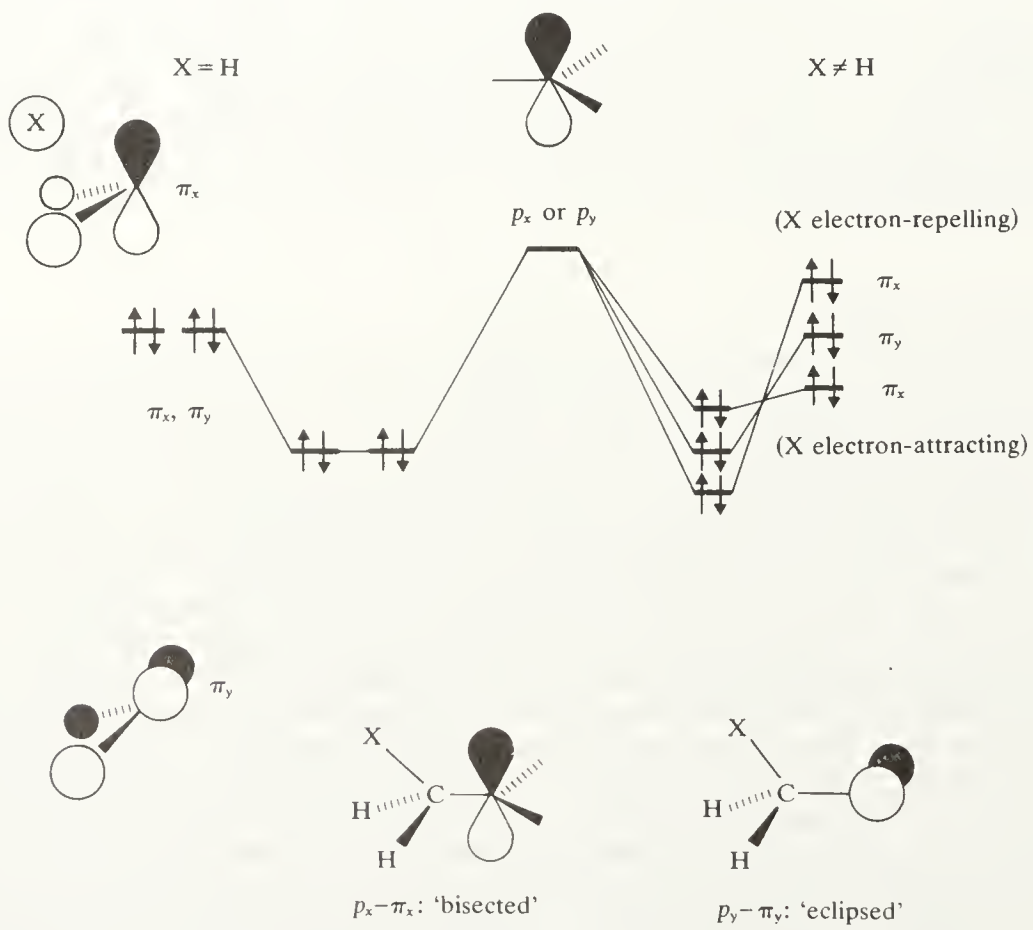


Figure 1 The interaction of a carbenium ion with an attached group CH_2X

π-interaction of a group CH_2X with an adjacent carbenium centre. When X = H, it can be seen that both the 'bisected' and 'eclipsed' conformations are of equal energy, *i.e.* there is no conformational preference. However if X is an electron-attracting group the bisected conformation is less favoured than the eclipsed, whereas the converse is true if X is electron-repelling.

(*ii*) *Gas phase methods*

Mass spectrometric methods yield mass-to-charge ratios which reveal the composition of the ions generated by, for example, electron impact or photoionization, together with the energies (appearance potentials) required to produce the ions. Structural information cannot be obtained directly but must be inferred from the subsequent fragmentation of the ions in the mass spectrometer[28] or by double-resonance experiments in the case of ion cyclotron resonance spectroscopy.[29]

Ignoring excess energy of the fragments, the appearance potential, A, of a carbenium ion R^+ formed in the process $RX - e^- \rightarrow R^+ + X^\bullet$ is given by $A = I(R\cdot) + D(RX)$ where $I(R\cdot)$ is the ionization potential of the radical R· and $D(RX)$ is the bond dissociation energy. Values of $I(R\cdot)$ may also be directly determined. Knowing $I(R\cdot)$ and the heat of formation of R·, heats of formation of R^+ may be derived. Values for selected carbenium ions are in Table 5.

TABLE 5

Ionization Potentials of Radicals, R·, and Heats of Formation of the Corresponding Carbenium Ions, R^+[a]

R	$I(R\cdot)$	$\Delta H_f(R^+)$ (kJ mol^{-1})
CH_3	949	1078
CH_3CH_2	846	941
$(CH_3)_2CH$	762	811
$(CH_3)_3C$	718	727
$CH_2{=}CH$	911	—
$CH_2{=}CHCH_2$	787	957
Cycloheptatrienyl	636	907–936
Cyclopentadienyl	838	944
$C_6H_5CH_2$	748	899
$(C_6H_5)_2CH$	706	949
$(C_6H_5)_3C$	700	1003

[a] Taken from J. L. Franklin, in 'Carbonium Ions', ed. G. A. Olah and P. von R. Schleyer, Wiley, New York, 1968, vol. I, p. 77.

By working at higher gas pressures than normally used in analytical mass spectrometry, a variety of ion–molecule reactions can be studied. Carbenium ions and penta-coordinate carbonium ions can be generated by protonation of olefins or saturated hydrocarbons respectively, and the energetics of the processes studied. These gas-phase basicities are usually expressed as $-\Delta H$ for the protonation, referred to as proton affinities. Some values are in Table 6.

(*iii*) *Solid salts*

The most direct and detailed structural information is provided by X-ray crystallography, but this technique has been applied to relatively few carbocations. A selection of

TABLE 6
Proton Affinites of some Hydrocarbons[a]

Hydrocarbon	*PA* (kJ mol^{-1})	*Hydrocarbon*	*PA* (kJ mol^{-1})
CH_4	527	$CH_3CH_2CH{=}CH_2$	765
$CH{\equiv}CH$	635	$CH_3CH{=}CHCH_3$ *trans*	752
$CH_2{=}CH_2$	669	*cis*	757
$CH_3CH{=}CH_2$	748	$(CH_3)_2C{=}CH_2$	815

[a] Taken from J. L. Beauchamp, *Ann. Rev. Phys. Chem.*, 1971, **22**, 527.

results is in Table 7. In general, carbenium ions are found to be planar at the carbenium centre and acyl cations linear. The 'aromatic' cation (c) has a planar ring as expected. Steric interactions between the stabilizing aryl substituents in (a)–(d) usually lead to some degree of rotation, as indicated by the angles inscribed in the rings in Table 7. The rotation about the central bond in the dication (d) effectively restricts unit positive charge to each half of the structure. In every case the conjugation and delocalization of the positive charge leads to a reduction in length of the bond by which the attached groups are linked to the carbenium centre.

Vibrational (infrared and Raman) spectroscopy[30] can be applied both to solid salts and to solutions and provides information on molecular symmetry as well as on force constants for the various modes of vibration. Thus the simplicity of the infrared spectrum of cycloheptatrienyl bromide and of trichlorocyclopropenyl tetrachloroaluminate and triphenylmethyl salts indicates very symmetrical structures ($\mathbf{D}_{7h}$ and $\mathbf{D}_{3h}$, respectively). The force constants derived for the two 'aromatic' ions form a consistent series with that for benzene, correlating with the crystallographic C—C bond lengths. Carbenium ions usually display absorption in the 1250–1550 cm^{-1} region (Table 8) which is strong because of the large dipole moment change during excitation. Infrared and laser Raman spectra for a series of tertiary alkyl cations permit detailed assignments of absorption bands. In particular the spectrum of the t-butyl cation is analogous to that of the isoelectronic trimethylboron and consistent with a planar arrangement of bonds to the carbenium centre, the overall $\mathbf{C}_{3v}$ symmetry implying that the methyl groups adopt a conformation which maximizes hyperconjugative stabilization (see above, however). Infrared studies both on solids salts and in solution permit characterization of acyl cations by their absorption at 2200–2300 cm^{-1}.

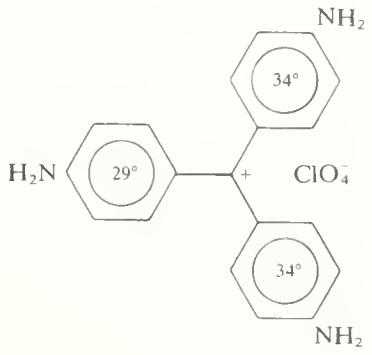
X-ray photoelectron spectroscopy (ESCA) can be applied to solid carbocation salts.[31] By measuring the kinetic energy of the photoejected electrons (E_k) when the salt is irradiated at liquid nitrogen temperature with X-rays (typically of 1485.6 eV), the carbon 1*s* binding energy (E_b) is evaluated from the expression $E_b = E_{h\nu} - E_k - \phi_s$, where ϕ_s is the spectrometer work function (4.6 eV). E_b is expected to increase with increasing positive charge on carbon, thus providing information on charge distribution. Only gross differences can be resolved since line widths are 1–2 eV. Some results for carbenium salts and non-ionic precursors are in Table 9. Only the t-butyl cation has carbon atoms with resolvable binding energies; the separation, 3.4 eV, is about 1 eV lower than predicted by *ab initio* calculation; the other salts give results consistent with a highly delocalized positive charge.

(*iv*) *Spectroscopy of solutions*

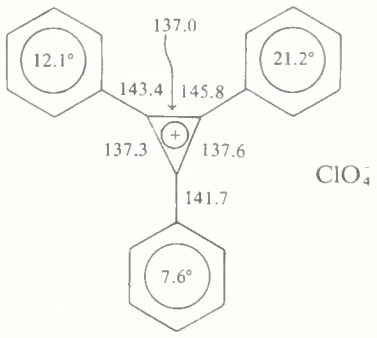
The visible colour of the triphenylmethyl cation was the first property of carbenium ions to be recognized and electronic spectroscopy continues to be valuable, especially for the quantitative study of equilibria in which carbenium ions are formed.[22] The data in Tables 2 and 4 were obtained in this way. Because of its sensitivity, care has to be taken in assigning the spectrum since some carbenium ions can react with other species present,

TABLE 7

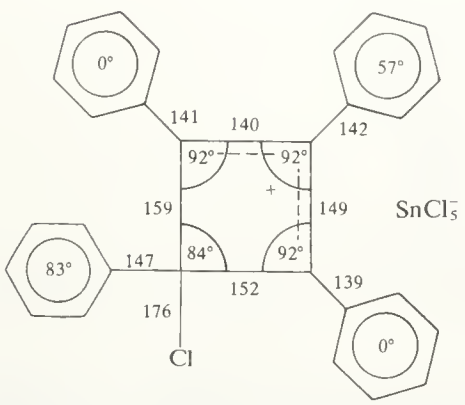
Structural Parameters for some Carbenium Salts by X-ray Crystallography



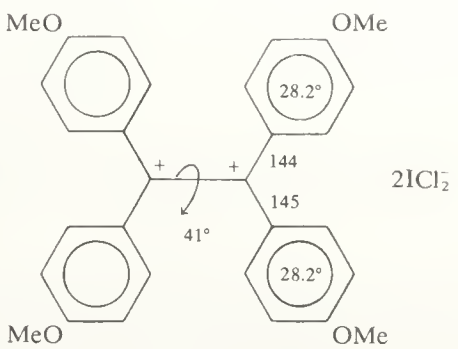
(a)[a]



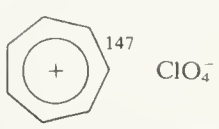
(b)[b]



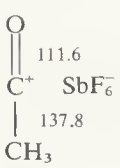
(c)[c]



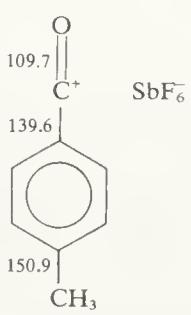
(d)[d]



(e)[e]



(f)[f]



(g)[g]

[a] K. Eriks and L. L. Kon, *Petrol. Res. Fund Rep. No.* 8, 1963, 5; in the unsubstituted triphenylmethyl cation each C–phenyl bond is 144 pm, A. H. Gomes de Mesquita, C. H. MacGillavry, and K. Eriks, *Acta Cryst.*, 1965, **18,** 437. [b] M. Sundaralingam and L. H. Jensen, *J. Amer. Chem. Soc.*, 1966, **88,** 198; for the tris(dimethylamino)cyclopropenyl cation, see A. T. Ku and M. Sundaralingam, *J. Amer. Chem. Soc.*, 1972, **94,** 1688. [c] R. F. Bryan, *J. Amer. Chem. Soc.*, 1964, **86,** 733. [d] N. C. Baenziger, R. E. Buckles, and T. D. Simpson, *J. Amer. Chem. Soc.*, 1967, **89,** 3405; for another carbodication, see J. S. McKechnie and I. C. Paul, *J. Amer. Chem. Soc.*, 1967, **89,** 5482. [e] A. I. Kitaigorodskii, Y. T. Struchkov, T. L. Khotsyanova, M. E. Vol'pin, and D. N. Kursanov, *Izv. Akad. Nauk S.S.S.R.*, 1960, 39. The cation is planar and the bond length estimated from the radius of the quasi-cylindrical cavity assuming all C—C bond lengths equal. [f] F. P. Boer, *J. Amer. Chem. Soc.*, 1966, **88,** 1572; see also J.-M. Le Carpentier, B. Chevrier and R. Weiss, *Bull. Soc. Fr. Mineral Crist.*, 1968, **91,** 544. [g] B. Chevrier, J.-M. Le Carpentier and R. Weiss, *J. Amer. Chem. Soc.*, 1972, **94,** 5718.

TABLE 8

Proposed Correlation of Carbenium-ion Structure with Infrared Absorption[a]

Cation	*Strong absorption* (cm^{-1})
Allylic (open chain or cyclohexenyl)	1530
Cycloheptatrienyl	1480
Cyclobutenyl	1465
Cyclopropenyl	1400
Alkyl (planar)	1300–1250

[a] J. C. Evans, in 'Carbonium Ions', ed. G. A. Olah and P. von R. Schleyer, Wiley, 1968, vol. I, p. 223.

TABLE 9

Carbon 1*s* Binding Energies (E_b) for Carbenium Ions[a]

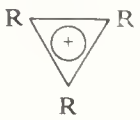
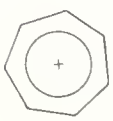
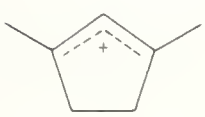
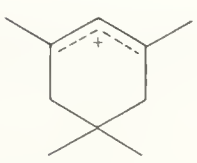
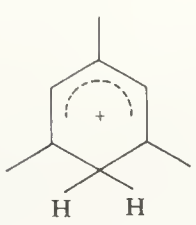
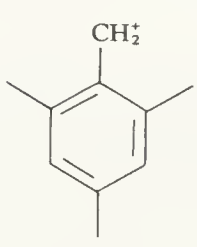
Compound	E_b (eV)[b]
Me_3CCl	284.1
$Me_3C^+ SbF_5Cl^-$	285.2, 288.6[c]
Ph_3CCl	284.7
$Ph_3C^+ SbF_6^-$	284.7
$C_7H_7^+ SbF_6^-$	284.7
Graphite (reference)	284.0

[a] G. A. Olah, G. D. Mateescu, L. A. Wilson and M. H. Gross, *J. Amer. Chem. Soc.*, 1970, **92**, 7231. [b] Accuracy ±0.1 eV; reproducibility ±0.03 eV. [c] Relative intensity 3 : 1.

e.g. their precursors, to give product ions showing more intense absorption. The assignments of the representative data in Table 10 are all unambiguous. The spectrum of the cycloheptatrienyl cation is noteworthy in that, in low dielectric constant solvents such as CH_2Cl_2, the halide salts display intramolecular charge-transfer absorption, the wavelength of which varies according to the ion-solvating characteristics of the solvent and can be used as a measure of solvent polarity.[32] For the most part, however, ion association does not appear to give rise to qualitative changes in carbenium ion spectra.

The single most powerful solution spectroscopic method for investigating the structures of carbocations is nuclear magnetic resonance (n.m.r.) spectroscopy (of ^1H, ^{13}C, and, to a lesser extent, ^{19}F nuclei).[33] Carbenium ion solutions are usually prepared in superacidic media at low temperature so as to minimize reactions of the ion, especially rearrangement. Nevertheless, after recording spectra, solutions should be quenched (*e.g.* in methanol) to establish that the products so formed are consistent with the carbenium structure proposed. In certain cases, *e.g.* the 1,2-shift in (**3**), rearrangements cannot be frozen out even at very low temperature, whereas in others it is possible to examine the rearrangement process kinetically by n.m.r. spectroscopy. Table 11 contains a selection of ^1H and ^{13}C chemical shifts for carbenium ions. The downfield shifts are a rough guide to the decreased electron density at the nucleus, but special factors operate in the vicinity of the carbenium centre and simple relationships between δ and calculated charge density are rarely found.[34] Nuclear–nuclear coupling constants, especially $^1J_{CH}$, also give an indication of the electron distribution in carbenium ions. Using the expression % *s*-character = 0.2 $^1J_{CH}$, the expected value of $^1J_{CH}$ for the carbenium centre of a secondary carbenium ion is 167 Hz (*cf.* 2-propyl cation 168, diphenylmethyl cation 164 Hz). The cyclohexadienyl cation (protonated benzene) shows a single ^{13}C signal (146 p.p.m.) with $^1J_{CH}$ 26 Hz as a result of rapid equilibration of the protons between the six equivalent carbon atoms of the ring; averaging of the coupling for two C(sp^3)–H and five C(sp^2)–H interactions among the six sites gives $^1J_{CH} = (2\times125 + 5\times167)/(7\times6) = 26$ Hz. The failure

TABLE 10
Electronic Absorption Spectral Data for Carbenium Ions[a]

Cation	*Anion*	*Solvent*	λ_{max} (nm)	log ε
Me_3C^+	—	FSO_3H/SbF_5	210	—
 R = Pr^n	—		185	—
R = Ph	—		307	4.62
	BF_4^-	H_2O	288	3.27
			274	3.65
			217	4.60
	I^-	CH_2Cl_2	278	
			422	
			575	
			275	4.06
			315	3.96
	—	HF/BF_3	256	3.94
			355	4.04
	—	FSO_3H/SbF_5	318	4.04
			370	3.64
			480	3.08
Ph_2CH^+	—	FSO_3H/SbF_5	292	3.46
			440	4.58
Ph_3C^+	—	FSO_3H/SbF_5	403	4.59
			429	4.59

[a] Taken from the extensive compilation by G A. Olah, C. U. Pittman, and M. C. R. Symons, in 'Carbonium Ions', ed. G. A. Olah and P. von R. Schleyer, Wiley, New York, 1968, vol. 1, p. 153.

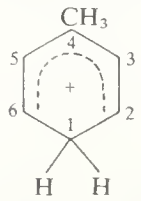
of averaging processes such as this when applied to chemical shift data has been used as evidence for bridged structures, *e.g.* (**3b**), in carbocations rather than pairs of equilibrating carbenium structures (**3a**).[2]

(*v*) *Electrical properties*

The conductance of carbocation salts in solution is not a widely exploited property. Results tend to be complicated by incomplete dissociation.[35] A reversible electrochemical

TABLE 11

Chemical Shifts in ^{1}H and $^{13}CN.M.R.$ Spectra of Carbenium Ions[a]

Cation		*Chemical shifts* (p.p.m.)[b] δ_H	δ_C	*Solvent*
$(CH_3)_2CH^+$	C_α	13.5	319.6	SO_2ClF/SbF_5
	C_β	5.06	61.8	
$(CH_3)_3C^+$	C_α	—	330.0	
	C_β	4.35	48.3	
$(CH_3)_2\overset{+}{C}CH_2CH_3$	C_α	—	333.8	
	C_β	4.50	44.5	
	$C_{\beta'}$	4.93		
	C_γ	2.27		
$(CH_3)_2\overset{+}{C}Ph$	C_α	—	254.3	
	C_β	3.60	34.9	
	C_1	—	140.0	
	$C_{2,6}$	8.30	142.4	
	$C_{3,5}$	7.95	133.3	
	C_4	8.24	155.9	
Ph_3C^+	C_α	—	210.9	FSO_3H
	C_1	—	139.9	
	$C_{2,6}$	7.69	143.3	
	$C_{3,5}$	7.87	130.3	
	C_4	8.24	143.1	
Cyclopropenyl		10.80	177	
Cycloheptatrienyl		9.18	155	
	C_1	5.05	49.5	HF/SbF_5
	$C_{2,6}$	9.38	181.2	
	$C_{3,5}$	8.40	139.4	
	C_4	—	201.9	
	4-CH_3	3.30	—	

[a] Compiled from data in L. M. Jackman and S. Sternhell, 'Applications of NMR Spectroscopy in Organic Chemistry', Pergamon, Oxford, 1969; J. B. Stothers, 'Carbon-13 NMR Spectroscopy', Academic Press, New York, 1972; D. G. Farnum, *Adv. Phys. Org. Chem.*, 1975, **11**, 123. [b] In p.p.m. downfield from TMS.

cell has been devised[36] for studying equilibria of the type $R_3C^+ + e^- \rightleftarrows R_3C\cdot$ and hence estimating free energy differences between carbenium ions; its use seems to have been restricted to triarylmethyl cations. Table 12 gives half-wave potentials for the reduction of carbenium ions to the corresponding radicals by cyclic voltammetry.

(*vi*) *The study of transient carbenium ions in solution*

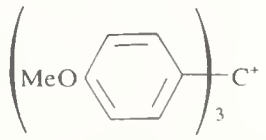
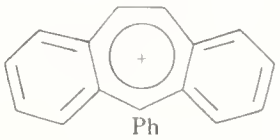
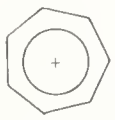
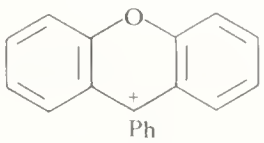
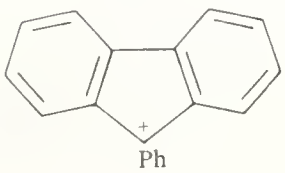
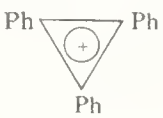
Important evidence indicating the intermediate formation of reactive carbenium ions in a particular chemical transformation is often provided by the *reaction products*, specifically their structure, stereochemistry, and the proportions in which they are formed. The most diagnostic reaction products are those in which a rearrangement of the carbon skeleton has taken place, a simple example being that in equation (13).

$$Me_3CCHIMe \xrightarrow{Ag^+,\ EtOH} Me_2C(OEt)CHMe_2 + Me_2C{=}{=}CMe_2 \qquad (13)$$

In some instances, similar product mixtures are observed from a number of different reactants (RX), all of which are capable of generating the same carbenium ion (R^+); such observations constitute strong evidence for the reactive intermediate. More often, however, association of an intermediate carbenium ion with the leaving group modifies the competitive situation between the possible reaction pathways available to the carbocation, *e.g.* as between substitution and elimination. This is particularly true in solvents of low polarity; thus solvolysis of t-butyl bromide and t-butyldimethylsulphonium perchlorate in

TABLE 12

Half-wave Reduction Potentials of some Carbenium Ions[a]

Ion	$E_{1/2}$ (V)[b]	*Ion*	$E_{1/2}$ (V)[b]
	1.09		−0.71
	1.05		−0.81
Ph_3C^+	0.58		
	−0.01		−1.83

[a] M. Feldman and W. C. Flythe, *J. Amer. Chem. Soc.*, 1969, **91**, 4577; 1971, **93**, 1547. [b] In 10.2M H_2SO_4 at 25 °C relative to $Hg|Hg_2SO_4$ (17M H_2SO_4).

water (75 °C) gives very similar ratios of substitution to elimination (*ca.* 14) whereas in acetic acid solution (75 °C) the ratios are 0.44 and 7.5, respectively.[35]

Because of the planarity expected at the carbenium centre, heterolysis of a bond to a chiral carbon atom giving a carbenium ion in the course of a substitution reaction might be expected to lead to total loss of optical activity. The usual observation, however, is of some racemization but with predominant inversion of configuration, increasing as the stability of the carbenium ion decreases (Table 13). Inversion is the expected stereochemical course of the alternative heterolytic pathway, the concerted bimolecular (S_N2) displacement; its occurrence in substitutions involving carbenium ions is interpreted in terms of attack by the nucleophile on an ion pair. It may be noted that some workers[30] interpret *all* substitution reactions of this type in terms of intermediate formation of ion pairs, the extent of inversion increasing as the components of the pair are more tightly associated during the subsequent attack by nucleophiles. The idea of a concerted displacement pathway (S_N2 mechanism) has, however, been stoutly defended,[37] and current views on the course of substitution at a saturated carbon atom are based on Winstein's formulation of the ionization process (equation 14).[38] Evidence for the existence of at least two types

TABLE 13

Stereochemical Course of some Unassisted S_N1 Reactions in Acetic Acid[a]

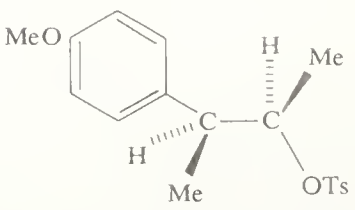
Reactant	*Temperature* (°C)	*Racemization* (%)	*Net inversion* (%)
1-[1-^{2}H]Butyl brosylate	99	—	96±8
2-Octyl tosylate	75	7	93
[α-^{2}H]Benzyl tosylate	25	20	80
1-Phenylallyl chloride	50	85	15
1-Phenylallyl tosylate	room	88	12

[a] Taken from the compilation in S. R. Hartshorn, 'Alipatic Nucleophilic Substitution', Cambridge University Press, 1973, p. 69.

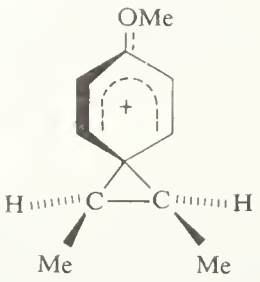
of ion pair between the covalent reactant and the free ions comes from observations that, for (**18**), the rate constant for ionization giving (**19**) determined from the rate of loss of optical activity (k_α) exceeds that obtained from the rate of production of titratable acid (k_t) even when there is no recombination of kinetically free ions generated by the heterolytic cleavage. Low concentrations of lithium perchlorate increase k_t more rapidly than k_α but do not make $k_\alpha/k_t = 1$ even at very high concentration. This so-called special salt effect indicates that perchlorate ion is able to intercept some but not all of the ion pairs, those that are intercepted being regarded as the more loosely associated solvent-separated pairs.

The stereochemical course of substitution in systems when ion association is important is illustrated in Scheme 1. Also included in the scheme is a general formulation of reactions in systems where the carbenium centre interacts with a neighbouring group (G) having nucleophilic properties; the usual stereochemical outcome is of substitution by the

$$\underset{}{RX} \rightleftharpoons \underset{\text{Contact ion pair}}{R^+X^-} \rightleftharpoons \underset{\text{Solvent-separated ion pair}}{R^+ \,||\, X^-} \rightleftharpoons \underset{\text{Free ions (solvated)}}{R^+ + X^-} \qquad (14)$$



(**18**)



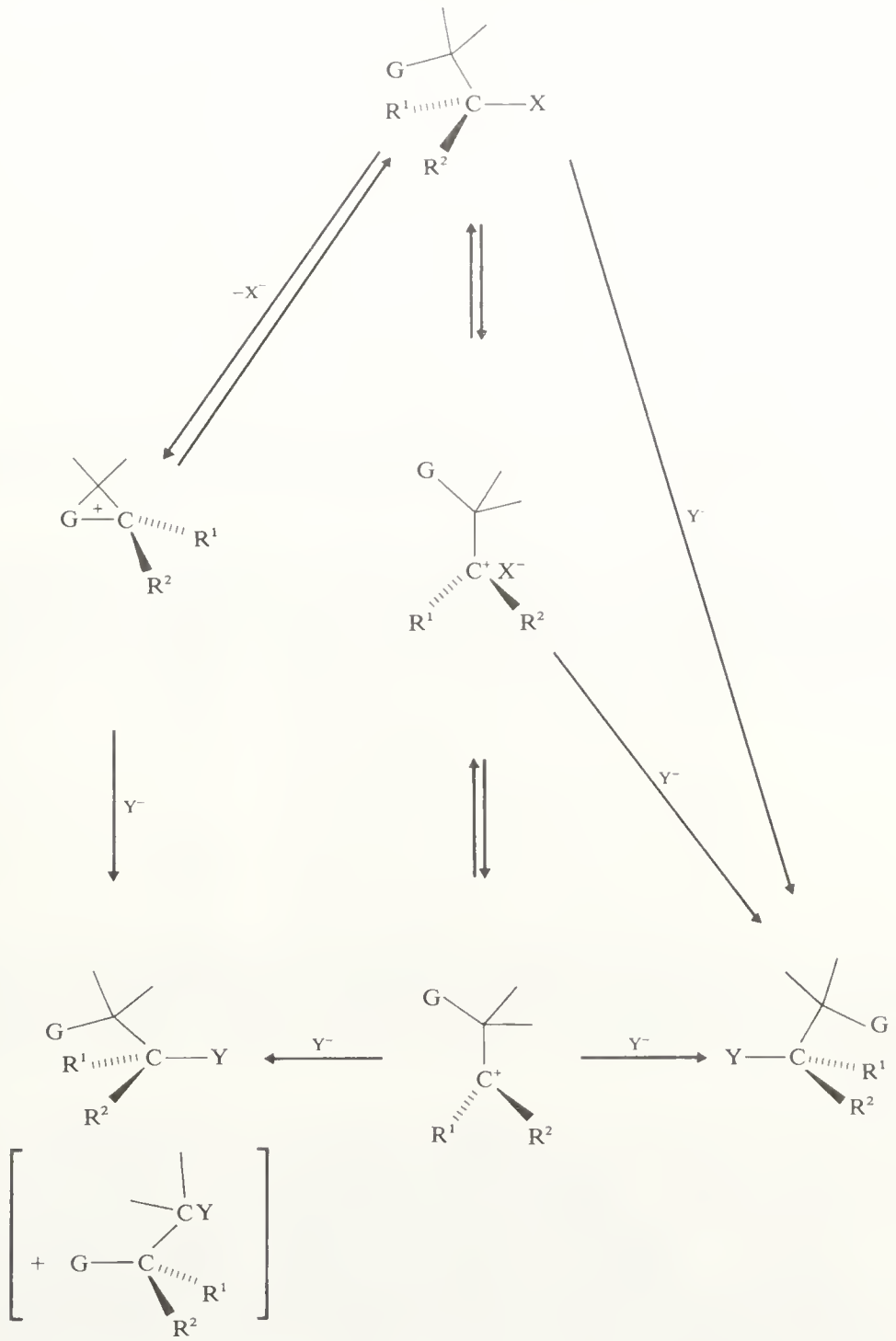
(**19**)

external nucleophile (Y^-) with retention of configuration, and this is observed, for example for (**18**) and its *erythro* isomer. Rearranged product may also be formed, as shown in Scheme 1.

The kinetic study of nucleophilic substitution can be used for the detection of intermediate carbenium ions and also to provide information about their stability relative to their precursors. For substitution by the S_N1 mechanism (equation 2), assuming that the intermediate ions are kinetically free, $-d[RX]/dt = k_1[RX]/(1 + k_{-1}[X^-]/k_2[Y^-])$. Particularly if the nucleophile Y is a solvent molecule, $k_1[X^-]/k_2[Y^-] \ll 1$ and the observed velocity constant $k_{obs} = -[RX]^{-1}d[RX]/dt = k_1$, the rate constant for ionization. Under these conditions the reaction rate is independent of the concentration of nucleophiles in the system, although these affect product proportions. The kinetic form does not, however, distinguish S_N1 and S_N2 mechanisms in solvolytic reactions. Addition of the common ion X^- to reaction mixtures should, in general, retard S_N1 reactions. Such behaviour is only found for reactants giving fairly stable intermediate carbenium ions, *e.g.* for Ar_3CCl and Ar_2CHCl, but not for $(CH_3)_3CCl$.

Apart from the problem of solvolyses, the kinetic form of substitution reactions is not diagnostic of carbenium ion formation if the intermediate ions do not become kinetically free. Both S_N1 and S_N2 mechanisms give the same kinetic form and less direct evidence for the ionization step has to be used, *e.g.* solvent effects on the reaction rate and their correlation using the equation $\log(k/k_0) = mY$, where Y is defined in Table 1 and m is *ca.* 1 for unassisted unimolecular substitutions; stereochemical changes in suitable systems, or isotopic scrambling in reactants such as $R^{18}OSO_2Ar$ and $R^{18}OCOAr$, can also be used.

In cases where $k_{obs} = k_1$, the rate constant for ionization is often used as a guide to the stability, and hence structure, of the intermediate carbenium ion. This procedure implies



SCHEME 1

that (i) the transition state for ionization has a structure close to that of the intermediate ion — this is likely to be true only for highly endothermic processes (Hammond's postulate) — (ii) the stability of the ion is to be reckoned against that of the reactant. The large body of results especially from solvolyses needs very careful assessment because relative rate data may be confused by nucleophilic assistance by the solvent to the departure of the leaving group (which is dependent upon the structure of the reactant as well as the nature of the solvent) and 'internal return' of ion pairs to reactant, that from contact ion pairs sometimes being extremely difficult to detect.[39] A selection of kinetic data for solvolyses of alkyl derivatives is given in Table 14. Trifluoroacetic acid is the least nucleophilic of the solvents and the relative rates reflect most accurately the stabilities of

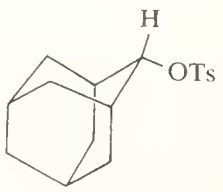
TABLE 14

Relative Rates[a] of Solvolysis of Alkyl Derivatives

Alkyl group	CF_3CO_2H	HCO_2H	EtOH
2-Adamantyl	(1.0)[b]	(1.0)[b]	(1.0)[b]
exo-2-Norbornyl	520	1940	10 400
endo-2-Norbornyl	0.46	1.14	34
Cyclohexyl	0.30	1.5	108
Cyclopentyl	3.0	27	6250
2-Propyl	0.024	0.9(1.0)[c]	(1.0)[d]
Methyl		0.02	3.5
Ethyl		0.04	1.4
t-Butyl		4×10^6	1140

[a] By titrimetry or conductimetry. Taken from compliations by A. Streitwieser, 'Solvolytic Displacement Reactions', McGraw Hill, New York, 1962, and T. W. Bentley and P. v. R. Schleyer, *Adv. Phys. Org. Chem.*, 1977, **14**, 1. [b] Tosylates at 25 °C. [c] Bromides at 100 °C. [d] Bromides at 55 °C.

the intermediate carbenium ions. Formic acid is somewhat more nucleophilic and rates for reactants which would yield very unstable carbenium ions are magnified by the incursion of nucleophilic solvent assistance. This becomes very much more apparent with ethanol as solvent. 2-Adamantyl tosylate (**20**) is a particularly useful standard in these studies since



(**20**)

its cage structure makes the S_N2 mechanism of solvolysis very difficult and it is thought to solvolyse solely by the ionization mechanism. The solvolysis of alkyl chlorides bearing groups capable of π-delocalization of the carbenium charge is greatly accelerated as expected (Table 15).

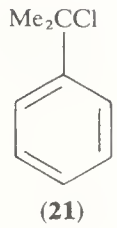
TABLE 15

Relative Rates of Solvolysis at 50 °C of Allylic and Aralkyl Chlorides (RCl) in 80% Aqueous Ethanol[a]

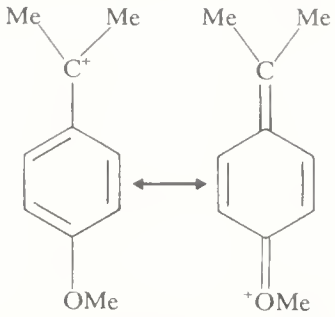
R	Me_2CH	$CH_2{=}CHCH_2$	$PhCH_2$	PhCHMe	Ph_2CH
Relative rate	0.7	52	(100)	7400	*ca.* 10^7

[a] Taken from A. Streitwieser, 'Solvolytic Displacement Reactions', McGraw Hill, New York, 1962.

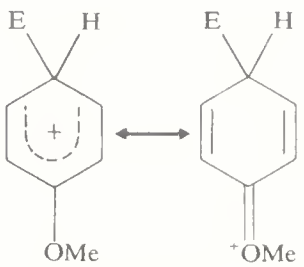
The effect of substituents on the rate of solvolysis of t-cumyl chloride (**21**) in 90% aqueous acetone has been used to define a series of substituent constants, labelled σ^+, using the linear free energy relation (LFER) $(k_X/k_H) = -4.54\sigma_X^+$, where k_X refers to *m*- or *p*-X-substituted (**21**).[40] Values of σ^+ (Table 16) are used as standard measures of the ability of substituents to stabilize carbenium ions, not only those of the benzylic type but also the cyclohexadienyl cations generated during electrophilic aromatic substitution, as indicated in (**22**) and (**23**). Also in Table 16 are values of σ, the Hammett substituent constant based on the ionization of *m*- and *p*-substituted benzoic acids; these do not reflect the ability of the substituents to conjugate directly with the carbenium centre. For aliphatic systems the correlation of solvolysis rates usually makes use of the Taft–Ingold structural constants σ^*; excellent (linear free energy) correlations for t-alkyl chlorides



(21)



(22)



(23)

TABLE 16

Substituent Constants σ_X^+ and σ_X[a]

X	*meta*		*para*	
	σ_X^+	σ_X	σ_X^+	δ_X
MeO	0.047	0.115	−0.778	−0.268
Me	−0.066	−0.069	−0.311	−0.170
Et	−0.064	−0.07	−0.295	−0.150
Pr^i	−0.060	—	−0.280	−0.151
Bu^t	−0.059	−0.10	−0.256	−0.197
Ph	0.109	0.06	−0.179	−0.01
H	(0.0)	(0.0)	(0.0)	(0.0)
F	0.352	0.337	−0.073	0.062
Cl	0.399	0.373	0.114	0.227
Br	0.405	0.391	0.150	0.232
CO_2Et	0.366	0.37	0.482	0.45
CF_3	0.520	0.42	0.612	0.54
CN	0.562	0.56	0.659	0.660
NO_2	0.674	0.71	0.790	0.778

[a]Taken from L. M. Stock and H. C. Brown, *Adv. Phys. Org. Chem.*, 1963, **1**, 35.

have been reported.[41] Deviations from such correlations are taken to indicate the operation of special factors in accelerating or retarding the reaction, such as neighbouring group participation, steric acceleration, or steric hindrance to ionization. Examples are given in Table 17, which contains some instances where the special factors were detected by comparison of the reaction rate with that of a single model compound or with that calculated using equations proposed by Foote and Schleyer.[42]

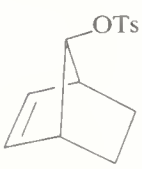
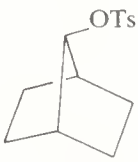
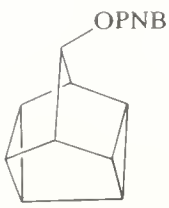
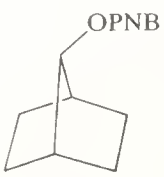
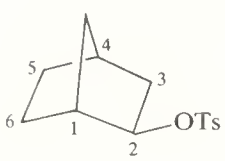
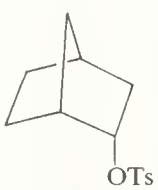
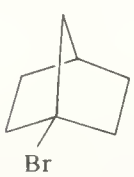
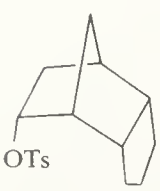
When neighbouring group participation is detected, it is customary to formulate the intermediate carbocation with the participating group sharing in the delocalization of the positive charge. If the participating group is a saturated alkyl group the carbocation then has to be formulated as a penta-coordinate carbonium ion.

2.7.1.6 Reactions of carbocations

In general, the reactions of carbocations are the reverse of the types of reaction by which carbocations are formed. Penta-coordinate carbonium ions generally give up a proton to yield a neutral hydrocarbon or, in carbocyclic systems, are converted into carbenium ions by C—C cleavage. Carbenium-ion reactions for the most part can be classified according to the type of electron pair (n, σ, or π) with which the cationic centre interacts, and both intra- and inter-molecular examples can usually be found. In intra-molecular cases the interaction may occur in the transition state leading to formation of

TABLE 17

Kinetic Detection of Special Factors in Carbenium Ion Formation

Reactant	*Standard*	*Solvent*	k/k_0	*Interpretation*
ICH_2CMe_2Cl	LFER	80% EtOH	740[a]	NGP by I (n-electrons)
		AcOH	$10^{11,3}$[b]	NGP by C=C (π-electrons)
(**18**)	LFER	AcOH	100[c]	NGP by *p*-anisyl (π-electrons)
		65% Acetone	10^{10}–10^{12}[d]	NGP by *trans*-cyclopropyl (σ-electrons)
		CF_3CO_2H	1130[e]	NGP by C-1—C-6 (σ-electrons)
Bu^t_3COPNB	Bu^tOPNB	60% Dioxan	13 500[f]	Relief of steric compression in reactant
	Bu^tBr		10^{-13}[g]	Steric hindrance to planarity at carbenium centre
		AcOH	0.104[h]	Steric hindrance to departure of TsO^-

[a] A. Streitwieser, *J. Amer. Chem. Soc.*, 1956, **78,** 4935. [b] S. Winstein, M. Shatavsky, C. Norton, and R. B. Woodward, *J. Amer. Chem. Soc.*, 1955, **77,** 4183. [c] C. J. Lancelot, D. J. Cram, and P. v. R. Schleyer, in Ref. 1(b), vol. III, p. 1347. [d] R. M. Coates and J. L. Kirkpatrick, *J. Amer. Chem. Soc.*, 1970, **92,** 4883. [e] From Table 14. [f] P. D. Bartlett and T. T. Tidwell, *J. Amer. Chem. Soc.*, 1968, **90,** 4421. [g] R. C. Fort, in Ref. 1(b), vol. IV, p. 1783. [h] H. C. Brown, I. Rothberg, P. v. R. Schleyer, M. M. Donaldson and J. J. Harper, *Proc. Nat. Acad. Sci. U.S.A.*, 1966, **56,** 1653; the rate constant, *k*, predicted using the Foote–Schleyer equation is 10^4 times larger than the experimental value.

the intermediate ion, giving rise to enhanced rates (neighbouring group participation) and characteristic stereochemistry.

Reactions with non-bonding (n) electron pairs on a nucleophile is one of the commonest carbenium-ion reactions, occurring widely in S_N1 processes. The nucleophiles may be anions (*e.g.* RO^-, Cl^-, N_3^-) or neutral molecules (*e.g.* ROH, CO); in the latter cases, stable electrically neutral molecules can only result after a further reaction such as proton transfer. The reactions are generally very rapid and can be conveniently measured only in the case of very stable carbenium ions such as those of the triarylmethyl type. However,

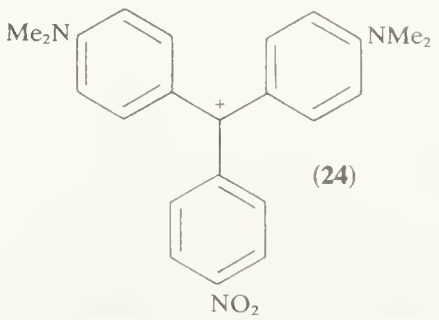
TABLE 18

Relative Reactivities of Nucleophiles towards Carbenium Ions and Methyl Bromide in Aqueous Media

Nucleophile	N_+[a]	$\log k_{rel}$[b]	n[c]
H_2O	(0.0)	(0.0)	(0.0)
$CH_3CO_2^-$	>2.95	3.04	2.72
Cl^-	—	3.49	3.04
Pyridine	5.00	—	3.6
N_3^-	7.6	4.95	4.00
OH^-	4.75	3.99	4.20
$PhNH_2$	4.10	3.57	4.49
SCN^-	—	4.11	4.77
CN^-	3.67	—	5.1
SO_3^{2-}	—	—	5.1
$S_2O_3^{2-}$	7.90	3.49	6.36

[a] C. D. Ritchie, *J. Amer. Chem Soc.*, 1975, **97**, 1170. [b] C. G. Swain, C. B. Scott, and K. H. Lohmann, *J. Amer. Chem. Soc.*, 1953, **75**, 136. [c] J. E. Laffler and E. Grunwald, 'Rates and Equilibria of Organic Reactions', Wiley, New York, 1963, p. 247.

benzyl, diphenylmethyl, and triphenylmethyl cations all react with halide ions at diffusion-controlled rates when generated by pulse radiolysis methods in dichloroethane.[43] The reactivities of nucleophiles are more often obtained from competitive experiments. Logarithmic relative reactivities [*i.e.* $\log(k/k_0)$ where k_0 refers to reaction with the standard nucleophile, H_2O] are in Table 18; N_+ refers to directly observed rates of reaction with *p*-nitro-Malachite Green (**24**), $\log k_{rel}$ to competitive reaction of triphenyl-



(**24**)

methyl cation and n to nucleophilic reactivities in concerted displacement reactions on methyl bromide. Comparison of the figures shows significant differences in the sequence of reactivities between reactions involving carbenium ions and the concerted process (*e.g.* N_3^-, OH^- and $S_2O_3^{2-}$). An interesting and important aspect of the N_+ values is that they correlate directly the reactivity of the nucleophiles with a variety of carbenium ions and other electrophiles of widely divergent reactivity according to the equation $\log(k/k_0) = N_+$ (k refers to the nucleophile and k_0 to the standard reaction with water).[44] This correlation is apparently in defiance of the usual inverse relationship between reactivity and selectivity,[45] and its precise cause is still a matter for debate.

Nucleophilic and basic properties tend to go roughly hand in hand. Thus reagents with n-electron pairs can react with carbenium ions by abstraction of a proton on a carbon atom β to the cationic centre and oriented parallel to the vacant *p*-orbital, yielding an olefin. However, for simple alkyl cations, coordination of the nucleophile at the carbenium centre usually predominates. In cases where more than one olefin can be generated, that with the most alkylated double bond is favoured in the absence of overriding steric influences. Conformational factors in the carbenium ion and eclipsing in the transition state for proton removal usually control the proportions of diastereoisomers

produced. Carbenium ions generated by loss of nitrogen from diazonium ions behave differently, however; they are generated in an exothermic process, have a short lifetime, and the course of their subsequent reactions is largely determined by the conformation of the amine from which they were generated. Olefin formation can also occur by β-cleavage of cations other than protons; typically those cations are *N*-stabilized carbenium ions as shown in equation (15).

(15)

Discussion of the reactions of carbenium ions with π-electron pairs will be restricted to reactions with olefins and benzenoid aromatics. In both cases the initial product is another carbenium ion which reacts further to yield stable products. The restoration of the aromatic sextet, usually by proton loss, dominates the reactions of the cyclohexadienyl cations generated by electrophilic attack on benzenoid compounds, whereas, for the carbenium ions produced by reaction of carbenium ions with olefins, several pathways compete, among which attack on further olefin molecules leading to polymer is one. Because of the importance of transfer processes compared with chain propagation, the cationic polymerization of simple α-olefins leads to products of low molecular weight. For high polymers the usual substrates are vinyl ethers and styrenes. Typical values for the relative reactivity of vinyl monomers obtained from co-polymerization studies in nitrobenzene are[46] butadiene, 0.02; isoprene 0.12; vinyl acetate, 0.4; styrene (1.0); isobutene, 4; vinyl ethers, very fast. Stereoregularity is sometimes observed in cationic polymerization.

Attack by any electrophile on an aromatic nucleus gives rise to a carbenium ion. Rate constants for attack are thus rate constants for formation of delocalized carbenium ions. The subsequent proton transfer is rate-limiting only in special circumstances, such as when it is very sterically hindered. Reactivities of positions in monosubstituted benzenes are usually recorded relative to attack on a single position in benzene (partial rate factors, o_f, m_f, and p_f). For a given reagent, $\log m_f$ and $\log p_f$ are proportional to σ^+ for the *m*- or *p*-substituent, the proportionality constant, ρ, negative for electrophilic attack, being a measure of the selectivity of the electrophile.[40] Some values of ρ are in Table 19; notable values in the present context are the very low selectivity in Friedel–Crafts ethylation, implying a very potent reagent plausibly formulated as an ethyl cation, and the much greater selectivity of the electrophile in Friedel–Crafts acetylation.

Intermolecular carbenium-ion reactions with σ-electron pairs are well-known when the electrons bind a hydrogen atom to a potentially more stable carbenium centre, the overall reaction being hydride transfer, *e.g.* equation (10). The analogous direct intermolecular transfer of an alkyl residue with its electron pair to a carbenium centre has not been

TABLE 19

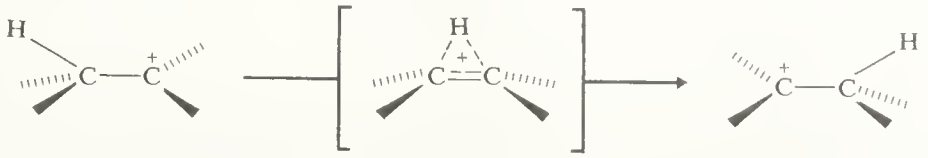
Selectivity in Electrophilic Aromatic Substitutions[a]

Reaction	*Reactant/catalyst*	ρ
Bromination	Br_2	−12.1
Chlorination	Cl_2	−10.0
Acetylation	$CH_3COCl/AlCl_3$	−9.1
Nitration	HNO_3/H_2SO_4	−6.0
Mercuration	$Hg(OAc)_2$	−4.0
Ethylation	$CH_3CH_2Cl/AlCl_3$	−2.4

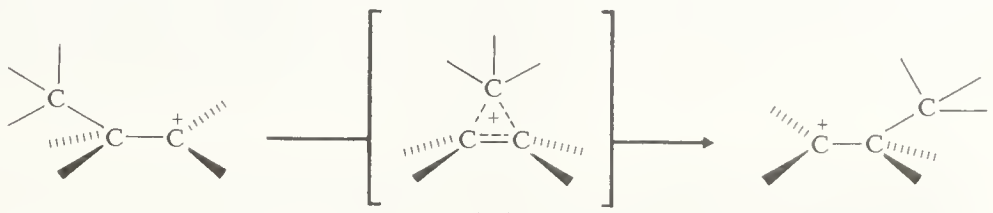
[a] L. M. Stock and H. C. Brown, *Adv. Phys. Org. Chem.*, 1963, **1**, 35.

unequivocally identified.[16] However, the gas-phase generation of penta-coordinate carbonium ions by coordination of carbenium ions to C—H and C—C bonds is well documented.[15]

More important and characteristic are the intramolecular reactions of carbenium ions with σ-bond electrons. The usual outcome is an intramolecular 1,2-hydride or alkide shift, generating a more thermodynamically stable rearranged carbenium ion as shown in equations (16) and (17). 1,3-Rearrangement and transfer over longer distances are much less common. It is worth noting that the transition state for the 1,2-alkide as formulated in (**25**) is equivalent to a penta-coordinate carbonium ion. Much debate has centred around whether, in reactions where skeletal rearrangements occur and there is kinetic or stereochemical evidence of neighbouring group participation by σ-bonded groups, the penta-coordinate carbocation is better regarded as the sole (ambident) *intermediate*, giving rise to both rearranged and unrearranged products. In either case (**25**) is stable with respect to small displacements along all molecular coordinates except that defining the rearrangement of the related carbenium ions; the two views differ only in whether (**25**) corresponds to an energy maximum or minimum along that rearrangement coordinate.



(16)



(17)

(**25**)

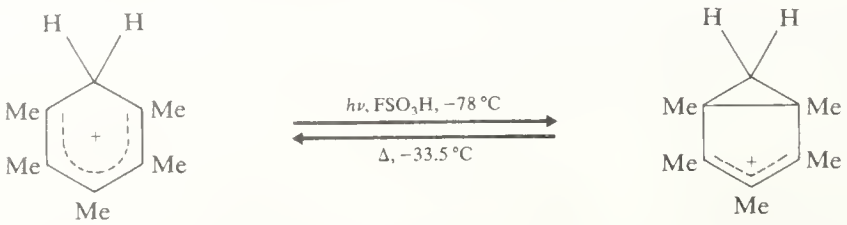
1,2–Shifts in carbenium ions can be formulated as pericyclic (specifically, sigmatropic) reactions.[47] The orbitals involved in the suprafacial shifts indicated in equations (16) and (17) are topologically analogous to the π-orbitals of the cyclopropenyl cation, a carbenium ion which is aromatic according to the usual Hückel considerations. 1,2-Hydride shifts are therefore thermally allowed concerted processes, as are alkide shifts with retention of configuration in the migrating group, a stereochemical result which has been established experimentally.[48]

Intramolecular 1,2-shifts are usually rapid at room temperature, but many can be followed kinetically at low temperatures, usually by n.m.r. spectroscopy. A number of instances are known where carbocation rearrangement is still very rapid on the n.m.r. timescale even at temperatures of −150 °C, corresponding to an activation energy for rearrangement of less than 20 kJ mol^{-1}; the distinction between a rapidly equilibrating pair of carbenium ions and a single carbocation of intermediate structure is then difficult to make.

The ease with which different groups migrate in carbenium-ion rearrangements is determined by a number of factors. The correct conformation, in which the bond by which the migrating group is attached to the migration origin lies in the same plane as that of the vacant *p*-orbital at the carbenium centre, must be achieved. This will depend on the nature of the other groups attached at the origin and terminus of migration, and these will also determine the thermodynamics of the rearrangement and, by their effect on the eclipsing strain in the transition state, *e.g.* (**25**), the rate. In addition, the intrinsic migratory aptitude of the shifting group will also influence the reaction, and the sequence aryl > H > alkyl is usually taken to apply.

Complex rearrangements, particularly in polycyclic carbenium ions, can generally be formulated in terms of sequential 1,2-shifts. An important example is the conversion of squalene epoxide into lanosterol. Graph theoretical procedures coupled with quantum theoretical or molecular mechanics calculations of the energies of the possible intermediate cations can sometimes enable a choice to be made between alternative sequences of 1,2-shifts.[49]

Photochemical reactions of carbenium ions[50] fall into two categories: (i) valence isomerizations and (ii) electron transfer processes. The former group is exemplified by the conversion of pentamethylcyclohexadienyl cation into the corresponding bicyclo[3,1,0]-hexenyl cation (equation 18). This is a photochemically allowed concerted disrotatory electrocyclic closure of the pentadienyl moiety of the reactant ion. The reverse reaction, however, occurs under remarkably mild conditions for the thermally disallowed disrotatory opening, and a stepwise mechanism has been proposed.



(18)

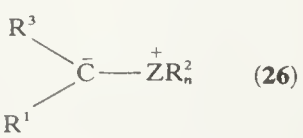
Triphenylcyclopropenyl cation in 10% H_2SO_4 on irradiation yields hexaphenylbenzene. It is believed that electron transfer occurs on absorption of light, giving the cyclopropenyl radical which is known to dimerize. The dimer then rearranges photochemically into the final product. Electron abstraction by photo-generated triplet triphenylmethyl cation is thought to be the key step in the carbenium-ion sensitized photo-oxidation of triarylmethanes.[51]

2.7.2 CARBANIONS[52]

2.7.2.1 Definitions and nomenclature

Carbanion is the generic term for negatively charged organic species having an even number of electrons in which the charge is largely associated with one or more of the constituent carbon atoms. Individual carbanions are named as alkyl anions. Carbanions are all derivatives of the methyl anion, CH_3^-, formally generated by proton removal from methane; they may therefore be regarded as the conjugate bases of carbon acids. Valence bond representations of the structure of carbanions all contain a trivalent carbon atom bearing a non-bonded electron pair (the carbanion centre). A counter ion (often a metal cation) is normally present; where the counter ion needs to be specified the salt is sometimes referred to as a metal alkanide. This cation may be strongly associated with the carbanion centre and modify its behaviour. Thus carbanion chemistry and the chemistry of monomeric organometallic compounds, especially of the alkali metals, are very closely related and phenomenological distinctions between them are not always possible.[53] Ylides in which the carbanion centre is adjacent to a positive 'onium centre as in (**26**) form a special category of carbanion having distinctive behaviour.

In the absence of attached conjugating substitutents the carbanion centre adopts a tetrahedral geometry with the non-bonded electron pair occupying an essentially sp^3-hybrid carbon orbital (*cf.* amines which are isoelectronic with carbanions). Inversion of



(**26**)

$ZR^2_n = NR^2_3, PR^2_3, SR^3_2$, *etc.*

carbanions is generally expected to be a fairly rapid process. Delocalization of the negative charge by π-conjugating substituents tends to change the hybridization of the carbanionic carbon atom to sp^2 and hence lead to planarity at the carbanion centre.

2.7.2.2 The generation of carbanions

Depending upon their strength the deprotonation of carbon acids[54] may be brought about by amines (pK_a 3–10), alkali hydroxides in water or alkoxides in alcohols (pK_a 15–20), or by more powerful bases such as sodamide in liquid ammonia (pK_a 33), sodium dimsyl ($Na^+ {}^-CH_2SOCH_3$) in dimethyl sulphoxide (DMSO pK_a 35), other carbanions, sodium hydride, or lithium alkyls. Nucleophilic reaction is sometimes a problem with these reagents, but this can often be reduced by having bulky groups around the basic atom, as in lithium di-isopropylamide, sodium triphenylmethanide, and potassium t-butoxide.

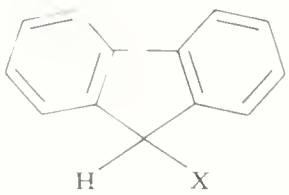
Table 20 gives a selection of pK_a values for carbon acids in water and spectrophotometrically determined pK values in DMSO referred to a standard state of infinite dilution in that solvent.[55] It should be noted that $pK_a < pK$ usually when the negative charge of the conjugate base can be associated with atoms more electronegative than carbon which can act as hydrogen-bond acceptors; carbanions without heteroatoms are generally more readily formed in DMSO than in water. For comparison, Table 20 also contains values of gas phase acidities (ΔG_{ion}) of some carbon acids; these refer to the gas-phase equilibrium (equation 19) and were obtained by high-pressure mass spectrometry. Attention has been drawn to the remarkable correlation between pK values and heats of deprotonation in DMSO and the gas phase.[56]

TABLE 20

Equilibrium and Kinetic Acidities of Carbon Acids

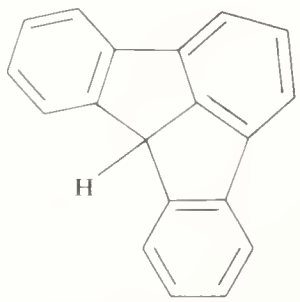
Compound	pK_a	*H_2O*[a] $k_1(s^{-1})$	k_{-1} ($l\,mol^{-1}\,s^{-1}$)	*DMSO*[b] pK	*Gas*[c] ΔG_{ion} ($kJ\,mol^{-1}$)
$CH_2(NO_2)_2$	3.57	0.83	3.1×10^3	—	—
$CH_2(COMe)_2$	9.0	1.7×10^{-2}	1.7×10^7	13.3[d]	117
CH_3NO_2	10.2	4.3×10^{-8}	6.8×10^2	17.2	—
$CH_2(CN)_2$	11.2	1.5×10^{-2}	2.3×10^9	11.1	71.9
HFlCN (**27a**)	11.2[e]	—	—	8.3	—
$HFlCO_2Me$ (**27b**)	12.9	—	—	10.35	—
$CH_2(CO_2Et)_2$	13.3	2.5×10^{-5}	5×10^8	—	136
Fluoradene (**28**)	13.9[f]	—	—	10.5[g]	—
Cyclopentadiene	~15	—	—	18.1[d]	163
HFlPh (**27c**)	—	—	—	17.9	—
HFlMe (**27d**)	—	—	—	22.3	—
HFlH (**27e**)	—	—	—	22.6	146
$PhCOCH_3$	—	—	—	24.7	191
$Ph_2CHCH{=}CHPh$	—	—	—	25.6	—
CH_3COCH_3	20	4.7×10^{-10}	5×10^{10}	26.5	211
$PhC{\equiv}CH$	—	—	—	28.8	—
$PhSO_2CH_3$	—	—	—	29.0	—
Ph_3CH	—	—	—	30.6	—
CH_3CN	~25	7×10^{-14}	—	31.3	47.9
Ph_2CH_2	—	—	—	32.3[d]	47.0

[a] From the compilation of R. G. Pearson and R. L. Dillon, *J. Amer. Chem. Soc.*, 1953, **75,** 2439. [b] W. S. Matthews, J. E. Bares, J. E. Bartmess, F. G. Bordwell, F. J. Cornforth, G. E. Drucker, Z. Margolin, R. J. McCallum, G. J. McCollum, and N. R. Vanier, *J. Amer. Chem. Soc.*, 1975, **97,** 7006. [c] T. B. McMahon and P. Kebarle, *J. Amer. Chem. Soc.*, 1976, **98,** 3399. [d] F. G. Bordwell, J. E. Bartmess, G. E. Drucker, Z. Margolin, and W. S. Matthews, *J. Amer. Chem. Soc.*, 1975, **97,** 3226. [e] 50% aqueous methanol. [f] H. Fischer and D. Rewicki, *Prog. Org. Chem.*, 1968, **7,** 116. [g] C. D. Ritchie and R. E. Uschold, *J. Amer. Chem. Soc.*, 1968, **90,** 2821.



a, X = CN; **b**, X = CO_2Me;
c, X = Ph; **d**, X = Me;
e, X = H

(27)



(28)

(19)

The rate of deprotonation of a carbon acid (k_1 in Table 20; k_{-1} refers to the reverse process) under specified conditions can be used as a measure of its kinetic acidity and, assuming a close structural similarity between the transition state of deprotonation and the product carbanion, the stability of the carbanion. Reactions, the rates of which are deprotonation rates, are base-catalysed halogenations and hydrogen isotope exchange. Such rates are quantitatively valid measures of kinetic acidity provided that internal return of ion pairs containing the carbanion to reactant carbon acid is not important, and provided that other special factors such as transition state steric effects do not affect the rate. The kinetic acidity is sometimes the only way by which the stability of a carbanion can be gauged, for example with very weak carbon acids such as benzene and alkanes. Kinetic and equilibrium acidities generally show a linear free energy correlation and this may be used to predict equilibrium acidities from rates of deprotonation; some pK_a values determined in this way are cycloheptatriene 36, benzene 37, cyclopropane 39, methane 40, and cyclohexane 45. Carbanions stabilized by attached nitro groups are generally formed more slowly by deprotonation than would be predicted from their pK_a values and this is usually attributed to a large reorganization of electron distribution between the deprotonation transition state and the product anion.[56b]

Nucleophilic addition to a carbon–carbon multiple bond produces carbanions (equation 19). The multiple bond is too electron-rich in simple alkenes for this reaction to be other than rare. However, electron-withdrawing substituents on the double bond, such as NO_2, CN, COR and CO_2R, provide the necessary stabilizing effect on the product ion. Carbanions of this sort, generated in this way, are intermediates in synthetically important reactions (*e.g.* the Michael reaction), in the addition–elimination mechanism of nucleophilic vinylic and aromatic substitution,[57] and in industrially important processes such as anionic vinyl polymerization. The overall reaction is determined by the subsequent behaviour of the intermediate carbanion in each case. In anionic polymerization, the conditions are such that the carbanion can only react by addition to a further molecule of vinyl monomer and, when this is all consumed, reaction ceases but the carbanion remains since there are no termination processes. Such polymeric carbanions are often referred to as living polymers because further addition of monomer causes polymerization to recommence.

Table 21 gives some reactivity data which indicate some of the structural effects which control the rate of carbanion formation in the simple nucleophilic addition of sulphite ion. Table 22 gives results from anionic copolymerization for variation in the monomer reacting with living polystyrene (k_{12}) and for styrene reacting with different terminal units in the living polymer (k_{21}). Both sets of data illustrate the importance of substituents capable of electron delocalization in increasing the reactivity of olefins. Methyl substitution in the vicinity of the reaction site generally retards reaction both by virtue of electron

TABLE 21

Reactivity of Olefins towards Sulphite Ions in Aqueous Acetate buffers (pH 6) at 25 °C[a]

Olefin	$10^2 k$ (l mol^{-1} s^{-1})
Methyl acrylate	29
Acrylonitrile	18
Methyl methacrylate	0.13
Methacrylonitrile	0.035

[a] M. Morton and H. Landfield, *J. Amer. Chem. Soc.*, 1952, **74,** 3523.

TABLE 22

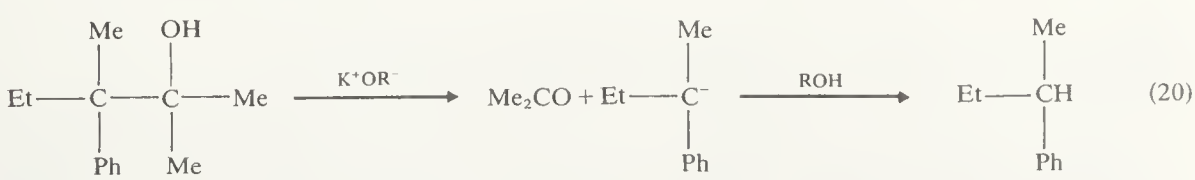
Monomer and End-group Reactivity in Anionic Polymerisation in Tetrahydrofuran at 25 °C
$[\sim\!\!\sim S^- Na^+] \approx 3 \times 10^{-3}$ mol l^{-1}

Monomer	k_{12} (l mol^{-1} s^{-1})	k_{21} (l mol^{-1} s^{-1})	*Ref.*
2,3-Dimethylbutadiene	0.4	—	a
Vinylmesitylene	0.9	77	b
Isoprene	17.0	—	a
β-Methylstyrene	18	—	b
α-Methylstyrene	27	780	b
Butadiene	32.7	—	a
p-Methoxystyrene	50	1100	b
p-Methylstyrene	180	1150	b
Styrene	950	950	b
p-Vinylbiphenyl	1660	—	b
1,1-Diphenylethylene	2500	0.7	b
1-Vinylnaphthalene	8000	30	b
p-Chlorostyrene	23 000	—	b
4-Vinylpyridine	>30 000	—	b

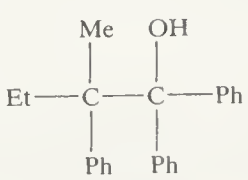
[a] M. Shima, J. Smid, and M. Szwarc, *J. Polymer Sci.* (*B*), 1964, **2,** 735.
[b] M. Shima, D. N. Bhattacharyya, J. Smid, and M. Szwarc, *J. Amer. Chem. Soc.*, 1963, **85,** 1306.

donation and by steric effects. Suitably located nitro, cyano, or polyhalogeno substitution is similarly a prerequisite for carbanion formation in nucleophilic aromatic and vinyl substitution.

Carbanions can also be generated by the reverse of the addition of carbanions to unsaturated systems, typically carbonyl groups. An example of such a retro-reaction is in equation (20). Caution is necessary in interpreting such cleavages since homolytic mechanisms can compete as in the cleavage of (**29**).



(20)



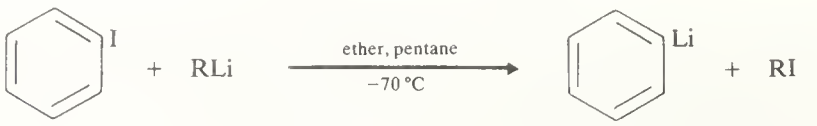
(**29**)

Finally, brief mention is made of carbanion-forming reactions involving metals and metal alkyls.

(i) Metallation of hydrocarbons, *e.g.* equation (21); TMEDA = *N,N,N′N′*-tetramethylethylenediamine.

(21)

(ii) Metal–halogen interchange, *e.g.* equation (22). Equilibrium constants have been measured in some instances and these can be used as a measure of the stability of carbanions (Table 23). It is worth noting that such reactions show chemically induced dynamic nuclear polarization, indicating a radical pathway for the establishment of equilibrium.[58]



(22)

TABLE 23

Equilibrium Constants for Metal–Halogen Interchange and Transmetallation and the MSAD Scale of Acidities

R	log *K* *Equation* (22) −70 °C	log *K* *Equation* (24) 33 °C	pK_a *MSAD scale*
PhC≡C	—	<−3	18.5
$PhCH_2$	—	−0.7	35
CH_2=$CHCH_2$	—	−0.4	35.5
CH_2=CH	−2.41	+0.3	36.5
Ph	(0.0)	(0.0)	37
Cyclopropyl	0.98	0.7	39
Me	—	1.8	40
Et	3.50	4.0	42
Bu^i	4.59	4.3	—
Bu^t	—	>6	44
Cyclopentyl	6.90	—	44
Ref.	a	b	c

[a] D. E. Applequist and D. H. O'Brien, *J. Amer. Chem. Soc.*, 1963, **85**, 743. [b] R. E. Dessy, W. Kitching, T. Psarras, R. Salinger, A. Chen, and T. Chivers, *J. Amer. Chem. Soc.*, 1966, **88**, 460. [c] D. J. Cram, 'Fundamentals of Carbanion Chemistry', Academic, New York, 1965, p. 19.

(iii) Reactions of metals with organic compounds (equation 23).

(iv) Transmetallation, *e.g.* equation (24), in which organometallic compounds of reactive metals exchange with derivatives of less reactive metals. Equilibrium constants for such reactions form the basis of part of the so-called MSAD scale of acidities of carbon acids (Table 21).

$$RX + 2M \longrightarrow R^-M^+ + M^+X^- \quad (23)$$

(X = Halogen, OR^1)

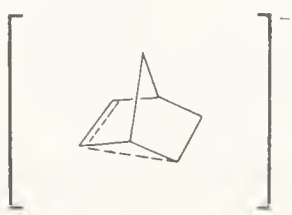
$$RMgX + PhHgX \xrightarrow{(CH_2OMe)_2} PhMgX + RHgX \quad (24)$$

2.7.2.3 Survey of types of carbanion

As indicated by the data in Tables 20–23 carbanions span an enormous range of stability with respect to the parent carbon acid. Lifetimes of carbanions also vary widely depending upon structure, solvent, counter-ion, and the availability of suitable reaction partners.

The structural factors controlling the stability of carbanions are principally the state of hybridization of the carbon at the anionic centre and the nature and number of substituents. The ease of carbanion formation increases in the sequence C—CH < C=CH < C≡CH, that is to say as the *s*-character of the CH bond increases; the acidity of cyclopropane thus falls between that of ethane and ethylene. The sequence of stability of simple alkyl anions, primary > secondary > tertiary, is the reverse of that for the corresponding carbenium ions. Conjugation with resultant delocalization of the negative charge greatly increases stability; the prediction of HMO theory is that alternant hydrocarbon anions will possess a doubly occupied non-bonding molecular orbital and in consequence the π-electron delocalization energy of the carbanion should be the same as that of the related carbenium ion. Carbanions are usually most stable when delocalization permits the sharing of the negative charge with atoms more electronegative than carbon, *e.g.* oxygen in enolate ions. Even more importantly perhaps, the sulphur atom in sulphides, sulphoxides, sulphones, and sulphonium salts stabilizes a negative charge on an adjacent carbon atom very effectively, but without forcing the carbanion centre to adopt a planar configuration as happens with electronegative atoms of the first row.[59]

A number of cyclic conjugated molecules predicted by HMO theory to be aromatic are carbanions. The simplest of these is the cyclopentadienyl anion (6π-electrons) and this also appears fused into such relatively stable species as the indenyl, fluorenyl, and fluoradenyl anions. Hückel's rule also predicts aromaticity for 10π-electron systems and these have been found in the cyclononatetraenyl anion and the cyclo-octatetraene dianion. Conversely, anionic cyclic conjugated systems with $4n$ π-electrons should be particularly disfavoured. Homoaromaticity is also known among carbanions, for example in (**30**).



(**30**)

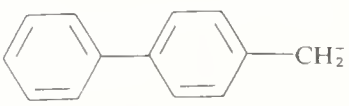
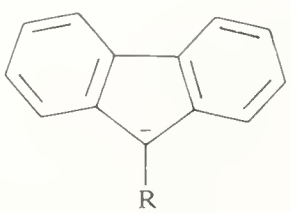
2.7.2.4 Physical properties of carbanions

Conjugated carbanions display intense electronic absorption spectra in the visible region, whereas their parent carbon acids absorb only in the ultraviolet. This is readily understandable in terms of transitions between a high-energy, doubly occupied HOMO and the LUMO. A selection of spectral data for caesium salts in cyclohexylamine solution is in Table 24.

In a number of cases, the appearance of the carbanion spectrum changes markedly on changing the solvent, the counter-ion, or the temperature. Figure 2 shows the variation with temperature of the spectrum of sodium fluorenide. No change is observed on dilution at constant temperature nor on addition of a dissociated sodium salt, and the spectral changes are therefore attributed to variation in the position of an equilibrium between two different types of ion pair, contact and solvent-separated, *cf.* equation (14). In fact the spectra of free carbanions turn out to be very similar to those of the corresponding solvent-separated ion pairs. The spectra of contact ion pairs show a cation dependence

TABLE 24

Electronic Spectral Data for Carbanion Caesium Salts in Cyclohexylamine Solution at 30 °C[a]

Carbanion		λ_{max} (nm)	ε_{max}
$PhCH_2^-$		470	—
		474	21 400
Ph_2CH^-		443	47 400
Ph_3C^-		422	13 600
		488	28 000
	R = H	367	10 450
		425	560
		452	950
		476	1200
		508	870
	R = Ph	371	19 700
		398	23 200
		455	1730
		485	2140
		516	1670

[a] G. Häfelinger and A. Streitwieser, *Chem. Ber.*, 1968, **101,** 657, 672.

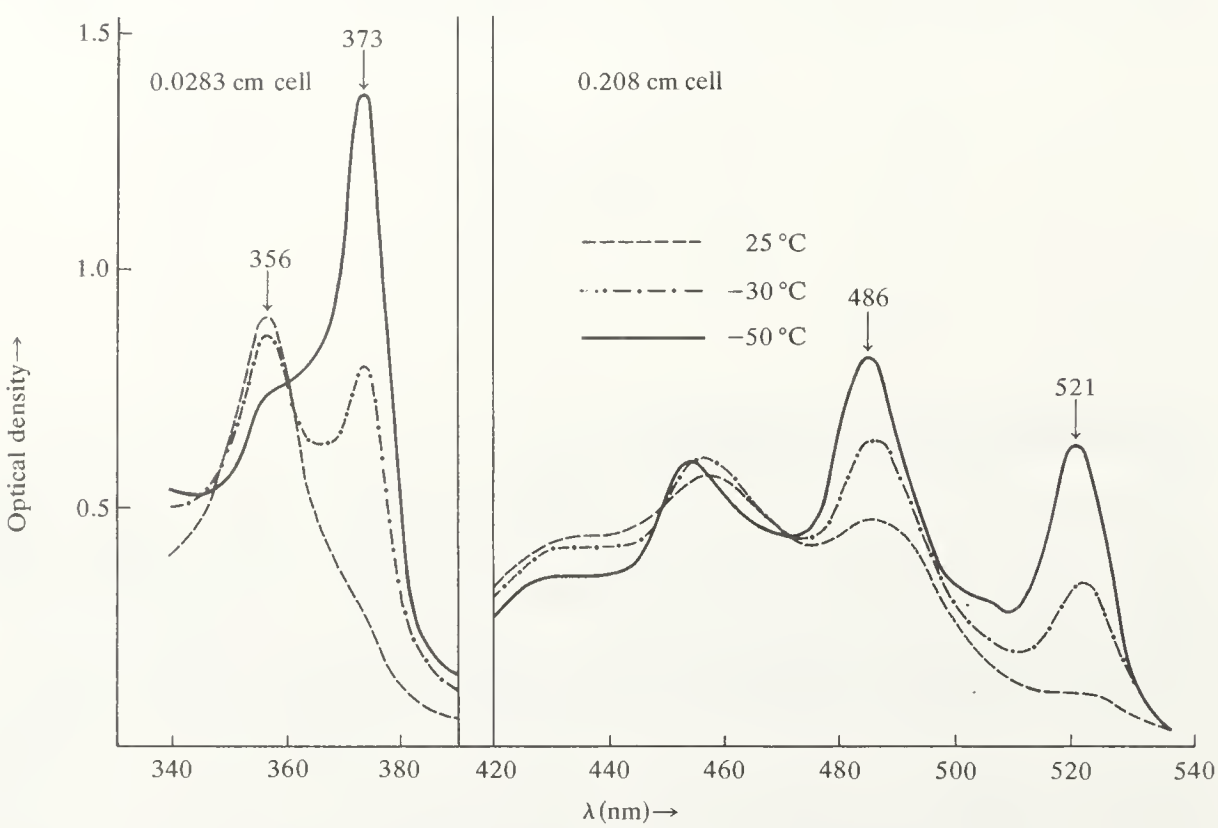


Figure 2 The temperature effect on the electronic spectrum of sodium fluorenide in solution in THF (Reproduced with permission from T. E. Hogen Esch and J. Smid, *J. Amer. Chem. Soc.*, 1966, **88,** 307)

TABLE 25

Principal Electronic Spectral Maxima (nm) of Free and Paired Fluorenyl Anions in THF Solution at 25 °C[a]

Counter-ion (M^+)	*Ion pair* *Contact*	*Solvent-separated*	*Free ion*
Li^+	349	373	374[b,c]
Na^+	356	373 (−50 °C)	b
K^+	362	b	b
Cs^+	364	b	b
NBu_4^+	368	b	b

[a] T. E. Hogen Esch and J. Smid, *J. Amer. Chem. Soc.*, 1966, **88**, 307. [b] Peak not detectable. [c] Obtained by extrapolation of the linear plot of (radius of $M^+)^{-1}$ *vs.* ν_{max} (contact ion pair) to $r_M^{-1} = 0$.

(Table 25). The position of the equilibrium between the ion pairs depends critically on the counter-ion and the solvent; chelating solvents (dimethoxyethane, glymes) favour solvent separation by solvation of the cation, and analogous effects can be achieved using crown ethers and other compounds.[60]

Chemical shifts from ^1H and ^{13}C n.m.r. spectra of a selection of carbanion salts are in Tables 26 and 27. The primary determinant of carbon shifts appears to be the hybridization of the carbanion centre, between sp^3 and sp^2 in the cases in Table 26 on the basis of $^1J_{CH}$, since there is a downfield shift relative to the parent carbon acid. However, compared with the related carbenium ions, the shift is upfield as expected on the basis of considerations of π-electron density. The aromatic carbanions in Table 27 form part of the well-known linear correlations of ^1H and ^{13}C shifts with π-electron density which lead to shifts of 10 p.p.m. (^1H) and 160 p.p.m. (^{13}C) per unit charge.[34a]

N.m.r. spectroscopy has also been used for the investigation of ion association and agglomeration of carbanion salts in solution. Thus $^1J_{CH}$ is smaller for the lithium salt of toluene than for that of diphenylmethane, suggesting hybridization of C-α closer to sp^3 in the former case and this can be taken as evidence of greater association. Cation effects on carbanion spectra are also suggestive of varying association,[61] and the upfield shifts of ^{13}C n.m.r. signals for C-α in diphenylmethyl anion salts as the temperature is raised have also been interpreted in terms of equilibration of contact and solvent-separated ion pairs, with

TABLE 26

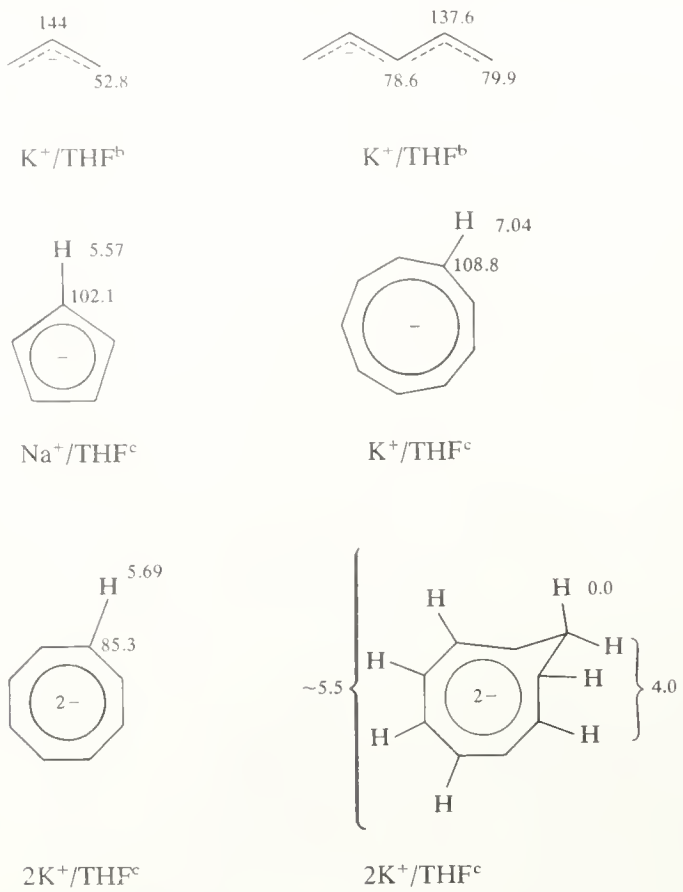
^1H and ^{13}C N.M.R. Spectra of Carbanion Salts in THF Solution

Salt	$\delta_{C\text{-}\alpha}$[a]	$^1J_{CH}$ (Hz)	δ_H[b] *o*	*m*	*p*
$Ph_3C^-\ Li^+$	91	—	7.28	6.48	5.93
Na^+	—	—	7.30	6.58	6.03
K^+	88.3	—	7.30	6.60	6.05
Cs^+	—	—	7.23	6.64	6.09
$Ph_2CH^-\ Li^+$	79	142	6.51	6.54	5.65
K^+	78.5	—	—	—	—
$PhCH_2^-\ Li^+$	30	133	6.09	6.30	5.50
K^+	52.7	—	—	—	—

[a] In p.p.m. downfield from TMS. Li salts: R. Waack, M. A. Doran, E. B. Baker, and G. A. Olah, *J. Amer. Chem. Soc.*, 1966, **88**, 1272; A. J. Jones, D. M. Grant, J. G. Russell, and G. Fraenkel, *J. Phys. Chem.*, 1967, **73**, 1624. K salts: D. H. O'Brien, A. J. Hart, and C. R. Russell, *J. Amer. Chem. Soc.*, 1975, **97**, 4410. [b] In p.p.m. downfield from TMS. Li salts: V. R. Sandel and H. H. Freedman, *J. Amer. Chem. Soc.*, 1963, **85**, 2328. Others: J. B. Grutzner, J. M. Lawlor, and L. M. Jackman, *ibid.*, 1972, **94**, 2306.

TABLE 27

^1H and ^{13}C N.M.R. Spectra of Selected Carbanions[a]



[a] In p.p.m. downfield from TMS. [b] D. H. O'Brien, A. J. Hart, and C. R. Russell, *J. Amer. Chem. Soc.*, 1975, **97**, 4410. [c] Proton spectra taken from the compilation in L. M. Jackman and S. Sternhell, 'Applications of N.M.R. Spectroscopy in Organic Chemistry', Pergamon, Oxford, 1969, p. 266. ^{13}C N.m.r. spectra from J. B. Stothers, 'Carbon-13 NMR Spectroscopy', Academic, New York, 1972, p. 91.

quantitative conclusions in line with results from electronic spectra.[62] ^7Li N.m.r. spectroscopy has also been used to investigate association in lithium salts of fluorene and related hydrocarbons.[63]

Two electrochemical properties of carbanions are of importance, namely, ion pair dissociation constants, K_d, and redox potentials. Some representative values of K_d obtained from conductance data are given in Table 28. Because of the equilibrium between contact ion pairs, solvent-separated pairs, and free ions (Scheme 2), $K_d = K_s K_i/(1+K_i)$. The values demonstrate that K_d is small but can vary widely. Crown ethers (CE) have a profound effect not only upon dissociation but also upon the equilibrium between ion pairs. Results such as these, in conjunction with kinetic data at varying carbanion and free counter-ion concentrations, have been used to evaluate reactivities of free and paired carbanions.[64]

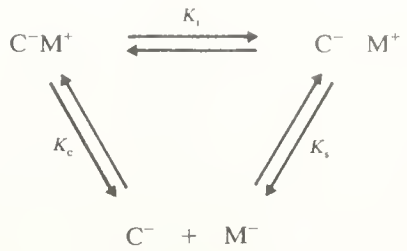
Electrochemical measurements on the reduction of free radicals, R·, to carbanions, R^-, yield approximate free energy differences between the two species. The process is irreversible in protic media since the carbanion is readily protonated. The radical is most conveniently generated by reduction of the corresponding (stable) carbenium ion, and the results in Table 29 refer to the second one-electron reduction of the cation. The results are in line with theoretical predictions, and the reduction potentials have been used to estimate pK_a values for the generation of anti-aromatic carbanions such as triphenylcyclopropenyl anion (estimated pK_a 58).

TABLE 28

Dissocation Constants and Thermodynamic Parameters of Fluorenyl Anion Salts in THF at 20 °C[a]

	$10^8 K_d$ (mol l^{-1})	$10^2 K_i$	ΔH_d (kJ mol^{-1})	ΔH_i (kJ mol^{-1})
$Fl^- Li^+$	440	290	−13.4	−29.3
$Fl^- Na^+$	75.2	6	−34.7	−31.8
$Fl^-(CE)Na^+$	375	10^9	0	—
$Fl^- Cs^+$	1.69	1	−11.3	—

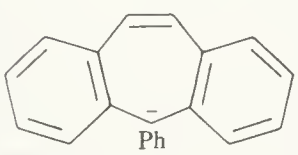
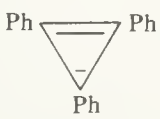
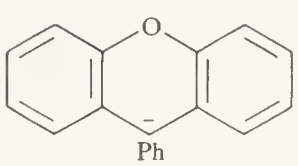
[a] Taken from T. E. Hogen Esch, *Adv. Phys. Org. Chem.*, 1977, **15**, 153.



SCHEME 2

TABLE 29

Half-wave Reduction Potentials of Radicals

Carbanion formed	$-E_{1/2}$ H_2SO_4[a]	HMPA[b]	MeCN[c]
Ph_3C^-	1.11	0.83	0.97
$PhFl^-$	—	—	—
	1.20	—	—
	—	1.56	—
	1.28	—	
$(p\text{-}MeOC_6H_4)_3C^-$	1.21	—	—
$CH_2{=}CHCH_2^-$	—	—	1.61
$PhCH_2^-$	—	—	1.86
Me_3C^-	—	—	2.56

[a] M. Feldman and W. C. Flythe, *J. Amer. Chem. Soc.*, 1969, **91**, 4577. Reference electrode, $Hg|Hg_2SO_4(17M\ H_2SO_4)$. [b] R. Breslow and K. Balasubramanian, *J. Amer. Chem. Soc.*, 1969, **91**, 5182. HMPA = Hexamethylphosphoramide. Reference electrode, $Ag|AgClO_4$(0.1M in HMPA). [c] R. Breslow and J. L. Grant, *J. Amer. Chem. Soc.*, 1977, **99**, 7745. Reference electrode, SCE.

2.7.2.5 Reactions of carbanions

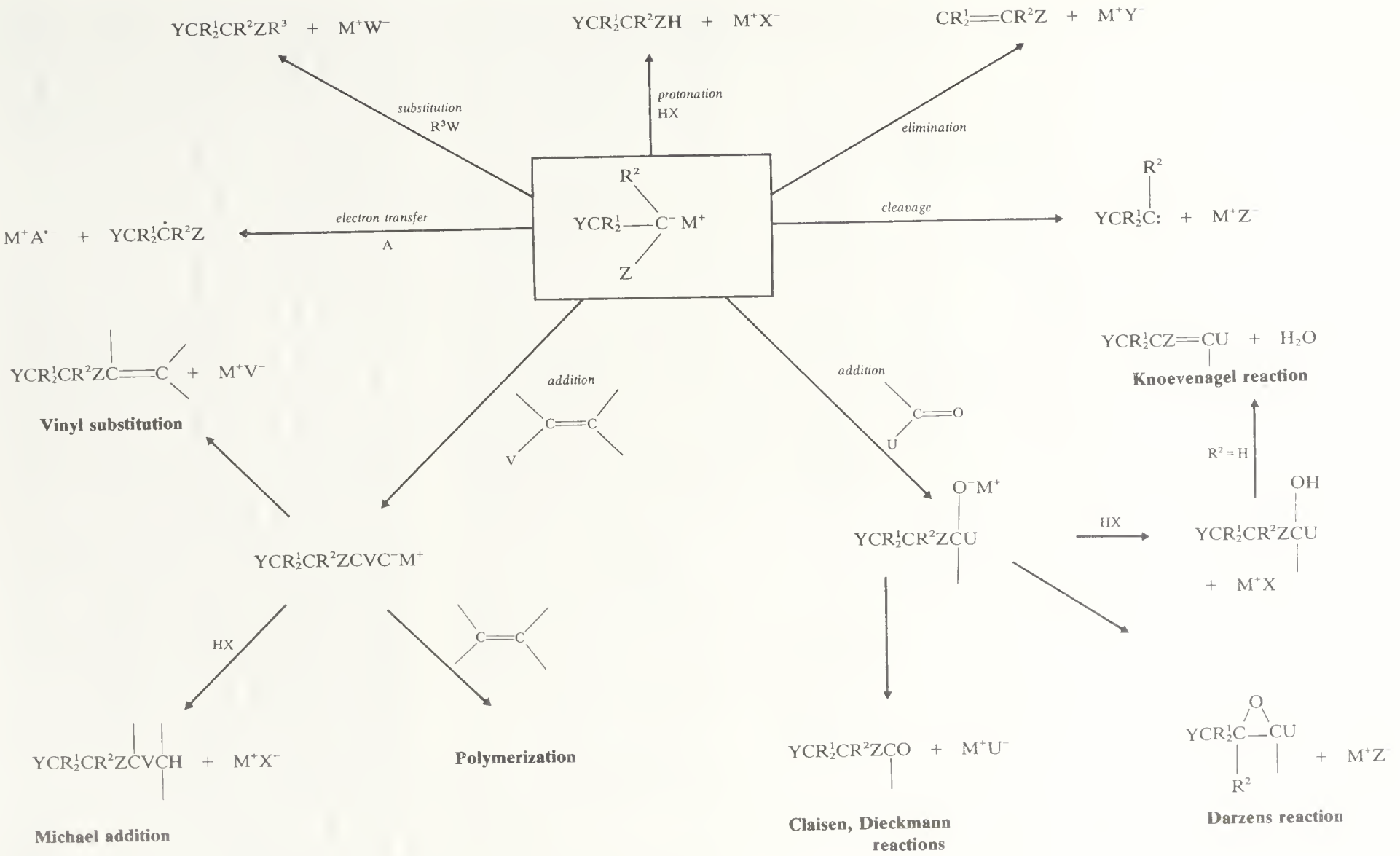
Carbanions display basic and nucleophilic properties and additionally can act as one-electron donors. The fundamental reactions, protonation, nucleophilic substitution at a saturated carbon atom, nucleophilic addition to unsaturated functions and electron transfer, are summarized in Scheme 3. Carbanion rearrangement is dealt with separately. The chemical outcome of these carbanion reactions is dependent upon the structure of the reactants and a number of synthetically important transformations, which are closely related from the point of view of carbanion chemistry, are often distinguished by the names of their discoverers. The interrelation of some of these reaction is indicated in Scheme 3.

Under given reaction conditions, the reactivity of carbanions usually depends on the extent of charge delocalization. For highly delocalized ions, reaction may take place through any of the formal sites of negative charge; thus carbonyl-stabilized carbanions (enolate ions) can react through carbon or oxygen depending on the reaction partner and the conditions. The other important determinant of carbanion reactivity is the extent of ion association. Free carbanions and ion pairs often show quite different behaviour as regards reactivity, reaction pathway, regioselectivity, and stereochemistry.[64] Moreover, since ion association in most common solvents increases as the temperatures rises, there can be unusual temperature effects on carbanion reactions. The time scale of events in the solvation of cations is of the order 10^{-8}–10^{-9} s. For sufficiently short-lived carbanions, planarity at the carbanion centre is no guarantee of racemic reaction products. For some carbanions, such as cyclopropyl or vinyl anions, the energy barrier for inversion at the anionic centre is so large that retention of configuration is observed for reactions under a wide variety of conditions.

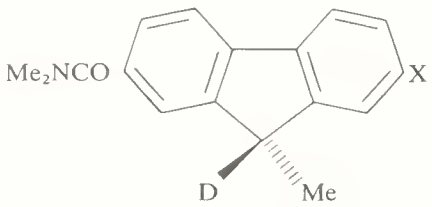
Carbanion protonation, the reverse of carbanion formation from carbon acids, is sometimes used synthetically; thus triphenylmethyl anion acts as a powerful base of low nucleophilicity and has been used to generate other carbanions.

As the results in Table 20 show, the rate of protonation of carbanions varies widely, even when the process is thermodynamically favourable. Unlike protonation of oxyanions and nitranions, diffusion controlled rates are rarely achieved. The reason seems to be that the negative charge on carbanions is usually well delocalized and much electronic and nuclear reorganization is necessary during protonation.[65] Where ion association occurs, the free ion might be expected to be protonated more rapidly, and indeed, this is so in the protonation of living polystyrene by triphenylmethane. However, protonation of sodium fluorenide by 1,2-benzofluorene in THF shows no acceleration on dilution, the expected result if the free ion is substantially more reactive than the ion pair, as is found for the same reaction in dimethoxyethane. Protonation of free benzyl anions by alcohols also proceeds more slowly than protonation of ion pairs, but here the observation can be understood more easily since coordination of the alcohol oxygen atom to the counter-ion should acidify the alcohol molecules near the carbanion. The dominant influence could well be the degree of charge localization which should be greater in the ion pair under the polarizing influence of the associated cation.

The stereochemistry of protonation of short-lived carbanions has been extensively studied by examination of hydrogen isotope exchange under basic conditions in chiral carbon acids and comparing its rate (k_e) with that of loss of optical activity (k_α). The ratio k_e/k_α then indicates the stereochemical course of the protonation of the intermediate carbanions; large values indicate protonation with retention of configuration, 1 implies complete racemization, 0.5 total inversion, and when $k_e/k_\alpha = 0$ racemization occurs without exchange (termed isoracemization). Some results for compounds (**31**) are in Table 30. Retention results when the amine base, which abstracts the deuteron to produce the cation, is capable of re-protonating the carbanion before separation of the ion pair (expt. 1) or when protonation occurs within an ion pair from solvent molecules coordinated to the counter cation (compare expts. 3 and 4). When protonation is slow on the time-scale of solvation events, the intermediate carbanion can achieve a symmetrical environment


substitution
R³W
protonation
HX
elimination
electron transfer
A
cleavage
addition
addition
HX
HX
Vinyl substitution
Knoevenagel reaction
Polymerization
Michael addition
Claisen, Dieckmann reactions
Darzens reaction
R² = H

SCHEME 3



a, X = H; **b**, X = NO_2

(**31**)

TABLE 30

Stereochemical Course of Carbanion Protonation

Expt.	*Compound*	*Solvent*	*Base*	*Temp* (°C)	k_e/k_α
1	(**31a**)	Bu^tOH	NH_3	200	>50
2			$Bu^tO^-K^+$	25	1.0
3		C_6H_6/C_6H_5OH (9 : 1)	$C_6H_5O^-K^+$	75	18
4			$C_6H_5O^-NMe_4^+$	75	1.0
5		CH_3OH	$CH_3O^-K^+$	25	0.69
6			$(C_3H_7)_3N$	75	0.65
7	(**31b**)	THF/1.5M Bu^tOH	$(C_3H_7)_3N$	—	0.1

[a] Taken from D. J. Cram, 'Fundamentals of Carbanion Chemistry', Academic, New York, 1965, chapter 3.

and racemization results (expt. 2). In more polar media and with the more acidic alcohols such as methanol and glycol, rapid protonation of the carbanion can occur and this is from the face opposite to that from which the base attacked (expts. 5 and 6). Isoracemization (*e.g.* expt. 7) can arise in two distinct ways. The first is by rotation of one component of the intermediate ion pair with respect to the other followed by reprotonation from the tertiary ammonium counter-ion. The second, so-called conducted tour mechanism, can occur if the carbanion has other basic sites in its structure to which the tertiary ammonium counter-ion can hydrogen bond; the carbanion centre thus achieves planarity without becoming free of the counter-ion which subsequently reprotonates the anion. As expected, cation-complexing agents, by drastically reducing the interaction of the cation and solvent molecules, inhibit protonation with retention and k_e/k_α values are usually in the range 0.5 to 1.

Some structural effects on carbanion reactivity in additions have been indicated in discussing carbanion formation. The overall reaction, however, depends upon the subsequent reaction of the product anion, whether it be protonation, attack on further unsaturated molecules as in anionic polymerization, or a cleavage or displacement reaction. Addition of carbanions to carbon dioxide, however, leads directly to a carboxylate ion, and this reaction has been used to investigate charge distribution in delocalized ions and the stereochemistry of carbanions.

Ion association plays an important part in these reactions and has been extensively studied in connection with anionic polymerization.[66] Table 31 gives reactivities of free (k_-) and paired ($k_\pm$) living polystyryl anions in propagating styrene polymerization in a variety of solvents. The solvent-separated ion pair and the free carbanion react at rather similar rates, but contact ion pairs show much lower reactivity and a complex variation with the counter-ion and the solvent. The stereochemistry of anionic polymerization is also affected. Thus methyl methacrylate is polymerized to an isotactic polymer by organolithium initiators in solvents of low dielectric constant such as toluene. Small additions of THF or dimethoxyethane at low temperatures lead to a predominantly syndiotactic polymer.

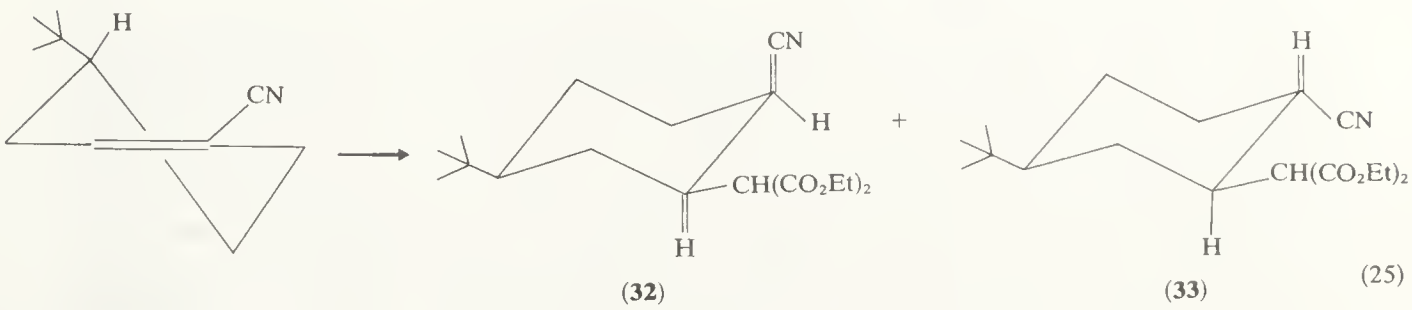
TABLE 31

Rate Constants for Propagation of Anionic Homopolymerization of Styrene at 25 °C.[a]

Solvent[b]	k_- ($l\,mol^{-1}\,s^{-1}$)	$k_\pm$ ($l\,mol^{-1}\,s^{-1}$)			
		Li	Na	K	Cs
Dioxan	—	0.9	3.4	20	24.6
THP	59000–72000	<10	14	73	53
2-MeTHF	27000–30000	57	11	7.5	22
THF	63000–65000	~160	80[c]	~100	25
DME	~40000	—	3600[c]	—	~150

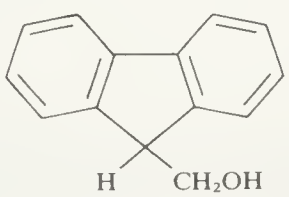
[a] Taken from M. Szwarc, 'Carbanions, Living polymers and Electron Transfer Processes', Wiley, New York, 1969, chapter 7. [b] THP = Tetrahydropyran; THF = tetrahydrofuran; DME = dimethoxyethane. [c] For solvent-separated ion pairs, $k_\pm$ is estimated to be ~20000 $l\,mol^{-1}\,s^{-1}$.

In Michael addition reactions the product carbanion differs from the reactant ion and makes the interpretation of results more complicated than in polymerization. The stereochemistry of the reaction is usually determined by the protonation of the product carbanion and is subject to the sort of influences already discussed. In many cases the product anion in Michael additions is stabilized by substituents containing carbonyl groups; protonation could thus occur most rapidly on oxygen, with the stereochemistry of the neutral Michael adduct determined thermodynamically in a subsequent prototropy. The addition of the sodium salt of diethyl malonate to 4-t-butyl-1-cyanocyclohexene (equation 25) under conditions of kinetically controlled protonation in ethanol leads predominantly to *trans* addition, giving (**32**); thermodynamic control gives the more stable *cis* adduct (**33**).[67]



(**32**) (**33**) (25)

When suitable leaving groups, usually halogen, are situated on the α- or β-carbon atoms of a carbanion, cleavage can occur giving a halide ion and a neutral product. α-Cleavage gives rise to carbenes or carbenoid species, the simplest example being the generation of dihalomethylenes from trihalomethyl anions. β-Cleavage yields olefins, this being one step in the *E*1cB mechanism of elimination. This pathway is able to compete with the much more common concerted *E*2 mechanism only if there are carbanion-stabilizing substituents on C-α and a relatively poor leaving group (*e.g.* OH, OPh) on C-β.[68] Examples of compounds giving olefins *via* the carbanion are (**34**) and (**35**).



(**34**)

$PhSO_2CH_2CH_2OPh$

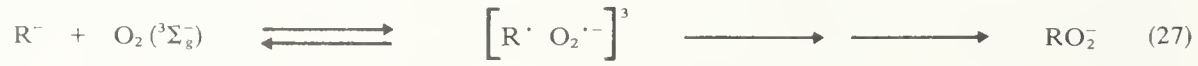
(**35**)

Alkylation of carbanions by reaction with alkyl halides is synthetically important. The reactivity of the halides is usually in the sequence iodides > bromides > chlorides. The commonest alkyl group is methyl; in other alkyl halides, β-elimination and proton transfer can often compete with nucleophilic displacement. Ion association can affect reactivity, free ions being more reactive than ion pairs in the case examined. Moreover, the counter-ion can influence regioselectivity in alkylation, the effect of thallium being particularly notable. Intramolecular alkylation is sometimes found. For example, intramolecular displacement of halide by a carbonyl-stabilized carbanion giving a cyclopropanone intermediate is a key step in the Favorskii rearrangement; the Ramberg–Bäcklund reaction involves an analogous alkylation by a sulphone-stabilized carbanion.

Another nucleophilic displacement at a saturated carbon atom by a carbanion is in ring-opening of epoxides (equation 26). The epoxide coordinates well with alkali-metal cations and this facilitates cleavage; thus the alkali-metal carbanide ion pair is often more reactive than the free carbanion.[64]

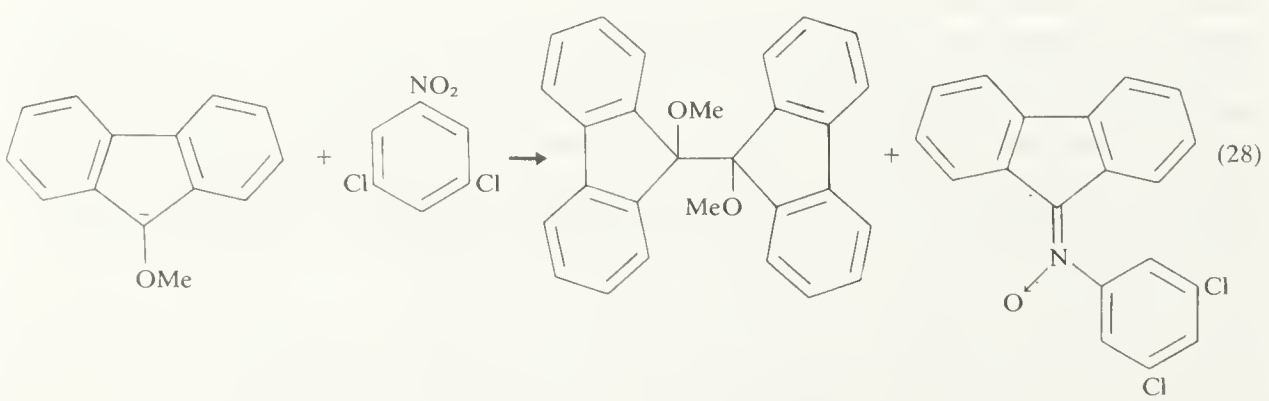
(26)

Comparison of the electron affinity of oxygen in its ground state (0.43 eV) with the redox potentials of carbanions (Table 29) indicates that many carbanions should be readily oxidized by molecular oxygen to give the corresponding radical and superoxide ion. Triplet–singlet mixing and collapse then yields the hydroperoxide (equation 27), and



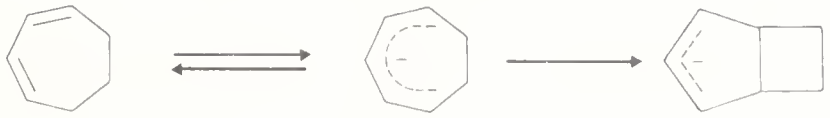
(27)

primary or secondary alkyl hydroperoxides usually eliminate water under the basic reaction conditions to give a carbonyl compound. In the base-induced autoxidation of fluorene, electron transfer from the intermediate fluorenyl anion is usually rate-limiting, but for triphenylmethane carbanion formation is the slow step, electron transfer from the less stable anion occurring very rapidly.[69] The slow electron transfer step for fluorenyl anions can be avoided by the use of singlet ($^1\Delta_g$) molecular oxygen with which they react very rapidly.[70] Aromatic nitro compounds can compete with oxygen as electron acceptors, the resultant radicals subsequently coupling, *e.g.* equation (28).[71] Radical dimer products are also formed on photochemical excitation of carbanions; thus cyclopentadienyl anion in t-butyl alcohol yields *meso*- and (±)-3-(3′-cyclopentenyl)cyclopentene.[72]



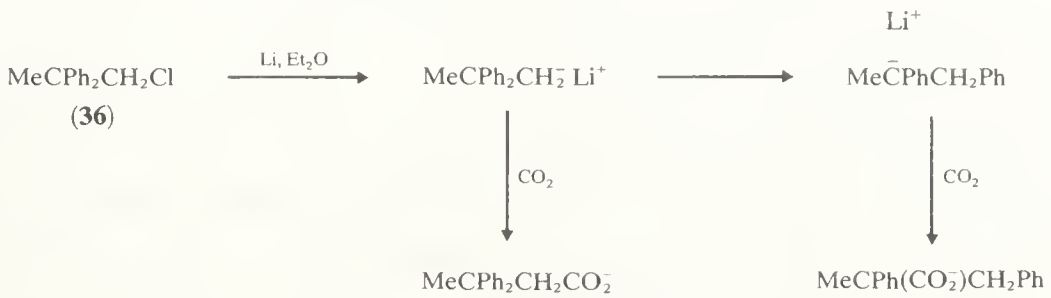
(28)

The pattern of carbanion rearrangements is somewhat different to that found with carbenium ions. Electrocyclic reactions of carbanions are observed, *e.g.* equation (29), and can be interpreted using orbital symmetry considerations,[47] but the transition state for a



(29)

suprafacial 1,2-shift of an alkyl group with retention is analogous to cyclopropenyl anion, a Hückel $4n$ π-electron anti-aromatic system, and is therefore thermally disallowed. Migration with inversion of the migrating group or an antarafacial 1,2-shift can be excluded for steric reasons. Ylides show 1,2-alkyl shifts with retention in the Stevens rearrangement for example, but a radical dissociation–recombination mechanism has been identified by the production of radical dimers in the reaction and the observation of chemically induced dynamic nuclear polarization in the rearrangement product.[58] Such a mechanism also probably operates in the Wittig rearrangement of α-alkoxycarbanions, $ArC\bar{H}—OR \rightarrow ArCHR—O^-$. For migration of allyl groups, an allowed, concerted [2,3]-sigmatropic pathway involving allylic inversion is available. Aryl groups undergo 1,2-shifts in compounds like (**36**), as shown in Scheme 4. The rearrangement is facilitated by



SCHEME 4

electron-withdrawing substituents in the aryl groups, and the reaction appears analogous to nucleophilic aromatic substitution.[73] Rearrangement can sometimes occur by a heterolytic cleavage–recombination mechanism, however (equation 30).

(30)

References

1. General references: (a) D. Bethell and V. Gold, 'Carbonium Ions. An Introduction', Academic, New York, 1967; (b) 'Carbonium Ions', ed. G. A. Olah and P. v. R. Schleyer, Wiley, New York, 1968–74, vols. 1–4.
2. (a) G. M. Kramer, *Adv. Phys. Org. Chem.*, 1975, **11,** 177; (b) G. A. Olah, *Accounts Chem. Res.*, 1976, **9,** 41.
3. C. D. Nenitzescu, in Ref. 1(b), vol. 1, p. 1.
4. J. F. Wolf, P. G. Harch, and R. W. Taft, *J. Amer. Chem. Soc.*, 1975, **97,** 2904; E. W. Bittner, E. M. Arnett, and M. Saunders, *ibid.*, 1976, **98,** 3734.
5. V. Gold, *J.C.S. Faraday I*, 1972, **68,** 1611.
6. G. A. Olah and M. W. Meyer, in 'Friedel-Crafts and Related Reactions', ed. G. A. Olah, Interscience, New York, 1963, vol. 1, p. 623.
7. L. Friedman, in Ref. 1(b), vol. 2, p. 655.
8. (a) F. Cacace, *Adv. Phys. Org. Chem.*, 1970, **8,** 79; P. Giacomello and F. Cacace, *J. Amer. Chem. Soc.*, 1976, **98,** 1823; (b) V. W. Jiang, K. A. Krohn, and M. J. Welch, *ibid.*, 1975, **97,** 6551.
9. (a) R. J. Gillespie and T. E. Peel, *Adv. Phys. Org. Chem.*, 1971, **9,** 1; (b) C. H. Rochester, 'Acidity Functions', Academic, New York, 1970.
10. G. A. Olah, 'Halonium Ions', Wiley, New York, 1975.
11. C. D. Nenitzescu, in Ref. 1(b), vol. 2, p. 463.
12. P. van Pelt and H. M. Buck, *J. Amer. Chem. Soc.*, 1976, **98,** 5864.
13. D. C. Nonhebel and J. C. Walton, 'Free Radical Chemistry', Cambridge University Press, 1974, chapter 10.
14. L. Eberson and K. Nyberg, *Adv. Phys. Org. Chem.*, 1976, **12,** 1.

15. (a) F. H. Field and D. P. Beggs, *J. Amer. Chem. Soc.*, 1971, **93,** 1585; (b) K. Hiraoka and P. Kebarle, *ibid.*, 1975, **97,** 4179; (c) 1976, **98,** 6119; (d) *J. Chem. Phys.*, 1975, **63,** 394, 1689.
16. (a) G. A. Olah, in 'Chemical Reactivity and Reaction Paths', ed. G. Klopman, Wiley, New York, 1974, chapter 5; (b) D. M. Brouwer and H. Hogeveen, *Prog. Phys. Org. Chem.*, 1972, **9,** 179; (c) C. J. Collins, *Chem. Rev.*, 1969, **69,** 543.
17. G. A. Olah and J. A. Olah, in Ref. 1(b), vol. 2, p. 715.
18. D. M. Brouwer, E. L. Mackor and C. MacLean, in Ref. 1(b), vol. 2, p. 837.
19. M. Cais, *Organometallic Chem. Rev.*, 1966, **1,** 435; D. Kaufman and R. Kupper, *J. Org. Chem.*, 1974, **39,** 1438.
20. H. C. Brown, *Tetrahedron*, 1976, **32,** 179; P. D. Bartlett, 'Non-classical Ions', Benjamin, New York, 1965.
21. H. Hogeveen and P. W. Kwant, *Accounts Chem. Res.*, 1975, **8,** 413.
22. G. A. Olah, C. U. Pittman and M. C. R. Symons, in Ref. 1(b), vol. 1, p. 153.
23. E. Heilbronner and H. Bock, 'The HMO Model and its Applications', Wiley, New York, 1976.
24. G. A. Olah and J. S. Staral, *J. Amer. Chem. Soc.*, 1976, **98,** 6290.
25. M. Saunders, R. Berger, A. Jaffe, J. M. McBride, J. O'Neill, R. Breslow, J. M. Hoffman, C. Perchonock, E. Wasserman, R. S. Hutton, and V. J. Kuck, *J. Amer. Chem. Soc.*, 1973, **95,** 3017.
26. W. C. Herndon, *Prog. Phys. Org. Chem.*, 1972, **9,** 99.
27. W. J. Hehre, *Accounts Chem. Res.*, 1976, **9,** 399; 1975, **8,** 369; W. A. Latham, L. A. Curtiss, W. J. Hehre, J. B. Lisle, and J. A. Pople, *Prog. Phys. Org. Chem.*, 1974, **11,** 175.
28. M. Bursey and F. W. McLafferty, in Ref. 1(b), vol. 1, p. 257.
29. J. L. Beauchamp, *Ann. Rev. Phys. Chem.*, 1971, **22,** 527; T. A. Lehman and M. M. Bursey, 'Ion Cyclotron Resonance Spectroscopy', Wiley, New York, 1976.
30. J. C. Evans, in Ref. 1(b), vol. 1, p. 223.
31. G. A. Olah, G. D. Mateescu, L. A. Wilson, and M. H. Gross, *J. Amer. Chem. Soc.*, 1970, **92,** 7231.
32. E. M. Kosower, *J. Org. Chem.*, 1964, **29,** 956.
33. G. Fraenkel and D. G. Farnum, in Ref. 1(b), vol. 1, p. 237.
34. (a) D. G. Farnum, *Adv. Phys. Org. Chem.*, 1975, **11,** 123; (b) D. A. Forsyth, R. J. Spear, and G. A. Olah, *J. Amer. Chem. Soc.*, 1976, **98,** 2512.
35. M. Cocivera and S. Winstein, *J. Amer. Chem. Soc.*, 1963, **85,** 1702.
36. R. A. Sneen, *Accounts Chem. Res.*, 1973, **6,** 46.
37. D. J. McLennan, *Accounts Chem. Res.*, 1976, **9,** 281.
38. S. Winstein, B. R. Appel, R. Baker and A. F. Diaz, in 'Organic Reaction Mechanisms', Special Publication No. 19, The Chemical Society, London, 1965, p. 109.
39. T. W. Bentley and P. v. R. Schleyer, *Adv. Phys. Org. Chem.*, 1977, **14,** 1.
40. L. M. Stock and H. C. Brown, *Adv. Phys. Org. Chem.*, 1963, **1,** 35.
41. *E.g.* A. Streitwieser, *J. Amer. Chem. Soc.*, 1956, **78,** 4935.
42. C. S. Foote, *J. Amer. Chem. Soc.*, 1964, **86,** 1853; P. v. R. Schleyer, *ibid.*, p. 1854.
43. L. M. Dorfman, R. J. Sujdak, and B. Bockrath, *Accounts Chem. Res.*, 1976, **9,** 352.
44. C. D. Ritchie, *Accounts Chem. Res.*, 1972, **5,** 348; *J. Amer. Chem. Soc.*, 1975, **97,** 1170.
45. A. Pross, *Adv. Phys. Org. Chem.*, 1977, **14,** 69; B. Giese, *Angew. Chem. Internat. Edn.*, 1977, **16,** 125.
46. R. B. Cundall, in 'The Chemistry of Cationic Polymerisation', ed. P. H. Plesch, Pergamon, Oxford, 1963, chapter 15.
47. R. B. Woodward and R. Hoffman, 'The Conservation of Orbital Symmetry', Verlag Chemie, Weinheim, 1970; T. L. Gilchrist and R. C. Storr, 'Organic Reactions and Orbital Symmetry', Cambridge University Press, 1972.
48. J. J. Beggs and M. B. Meyers, *J. Chem. Soc.* (*B*), 1970, 930.
49. T. M. Gund, P. v. R. Schleyer, P. H. Gund, and W. T. Wipke, *J. Amer. Chem. Soc.*, 1975, **97,** 743; T. S. Sorensen, *Accounts Chem. Res.*, 1976, **9,** 257.
50. P. W. Cabell-Whiting and H. Hogeveen, *Adv. Phys. Org. Chem.*, 1973, **10,** 129.
51. D. Bethell and P. N. Clare, *J.C.S. Perkin II*, 1972, 1464.
52. General references: D. J. Cram, 'Fundamentals of Carbanion Chemistry', Academic, New York, 1965; E. Buncel, 'Carbanions. Mechanistic and Isotopic Aspects', Elsevier, Amsterdam, 1975.
53. M. Schlosser, 'Struktur und Reaktivität Polarer Organometalle', Springer Verlag, Berlin, 1973.
54. J. R. Jones, 'The Ionisation of Carbon Acids', Academic, New York, 1973.
55. W. S. Matthews, J. E. Bares, J. E. Bartmess, F. G. Bordwell, F. J. Cornforth, G. E. Drucker, Z. Margolin, R. J. McCallum, G. J. McCollum, and N. R. Vanier, *J. Amer. Chem. Soc.*, 1975, **97,** 7006.
56. (a) E. M. Arnett, D. E. Johnston, L. E. Small, and D. Oancea, *Faraday Symp. Chem. Soc.*, 1975, **10,** 20; (b) F. G. Bordwell, *ibid.*, 1975, **10,** 100.
57. J. Miller, 'Nucleophilic Aromatic Substitution', Elsevier, Amsterdam, 1968.
58. 'Chemically Induced Magnetic Polarisation', ed. A. R. Lepley and G. L. Closs, Wiley, New York, 1973; D. Bethell and M. R. Brinkman, *Adv. Phys. Org. Chem.*, 1973, **10,** 53.
59. S. Wolfe, *Accounts Chem. Res.*, 1972, **5,** 102.
60. J. Smid, *Angew Chem. Internat. Edn.*, 1972, **11,** 112.
61. J. B. Grutzner, J. M. Lawlor, and L. M. Jackman, *J. Amer. Chem. Soc.*, 1972, **94,** 2306.
62. D. H. O'Brien, C. R. Russell, and A. J. Hart, *J. Amer. Chem. Soc.*, 1976, **98,** 7427.
63. J. A. Dixon, P. A. Gwinner, and D. C. Lini, *J. Amer. Chem. Soc.*, 1965, **87,** 1379; R. H. Cox, H. W. Terry, and L. W. Harrison, *ibid.*, 1971, **93,** 3297; M. M. Exner, R. Waack, and E. C. Steiner, *ibid.*, 1973, **95,** 7009.

64. T. E. Hogen Esch, *Adv. Phys. Org. Chem.*, 1977, **15,** 153.
65. F. Hibbert, in 'Comprehensive Chemical Kinetics, Vol. 8. Proton Transfer', ed. C. H. Bamford and C. F. H. Tipper, Elsevier, Amsterdam, 1977, chapter 2.
66. M. Szwarc, 'Carbanions, Living Polymers, and Electron Transfer Reactions', Wiley, New York, 1969.
67. R. A. Abramovitch and D. L. Struble, *Tetrahedron*, 1968, **24**, 357; R. A. Abramovitch, M. M. Rogić, S. S. Singer, and N. Ventkateswaran, *J. Amer. Chem. Soc.*, 1969, **91,** 1571.
68. W. H. Saunders and A. F. Cockerill, 'Mechanisms of Elimination Reactions', Wiley, New York, 1973.
69. G. A. Russell, A. G. Bemis, E. J. Geels, and E. G. Janzen, *Adv. Chem. Ser.*, 1968, **75,** 174; D. Bethell and R. J. E. Talbot, *J. Chem. Soc.* (*B*), 1968, 638.
70. D. Bethell and R. G. Wilkinson, *Chem. Comm.*, 1970, 1178.
71. R. D. Guthrie, D. P. Wesley, G. W. Pendygraft, and A. T. Young, *J. Amer. Chem. Soc.*, 1976, **98,** 5870.
72. E. E. van Tamelen, J. I. Brauman, and L. E. Ellis, *J. Amer. Chem. Soc.*, 1971, **93,** 6141, 6145.
73. J. A. Bertrand, E. Grovenstein, P.-C. Lu, and D. VanDerveer, *J. Amer. Chem. Soc.*, 1976, **98,** 7835.

2.8

Radicals, Carbenes, and Arynes

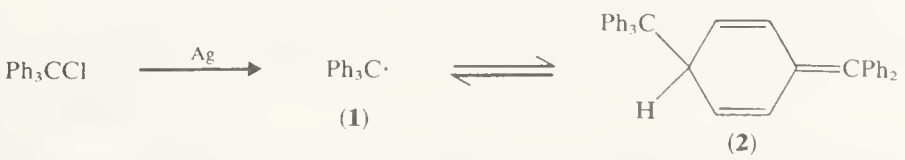
J. T. SHARP
University of Edinburgh

2.8.1 RADICALS 455
2.8.1.1 Structure, stability, and reactivity 456
2.8.1.2 Generation and reactions 458
2.8.2 CARBENES 467
2.8.2.1 Generation of carbenes and carbenoids 469
2.8.2.2 Reactions 473
2.8.3 ARYNES 477
2.8.3.1 Structure and spectra 478
2.8.3.2 Generation 479
2.8.3.3 Reactions 483

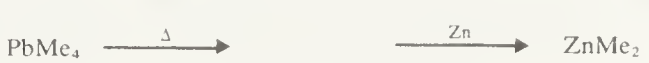
2.8.1 RADICALS[1]

A radical may be defined as an atom or molecule or complex which carries one or more unpaired electrons. Most of the radicals to be discussed here are electrically neutral but charged radicals, *e.g.* the benzene radical anion $[C_6H_6]^{\cdot-}$ and cation $[C_6H_6]^{\cdot+}$, are also well known and important intermediates.[2]

The chemistry of radicals in solution began in 1900 when Gomberg attempted to prepare hexaphenylethane (Ph_3CCPh_3) by reacting triphenylmethyl chloride with silver. Instead of the expected product, he observed an equilibrium (equation 1) between the long-lived triphenylmethyl radicals (**1**) and a dimer which he thought was hexaphenylethane but which was discovered many years later to be (**2**).[3] It was, however, in gas-phase reactions that short-lived radicals were first recognized as transient reaction intermediates; Paneth and Hofeditz in 1929 conclusively demonstrated that the pyrolysis of lead tetramethyl (equation 2) produced free methyl radicals which could subsequently either react with metal films or dimerize. The importance of transient radicals in solution



(1)

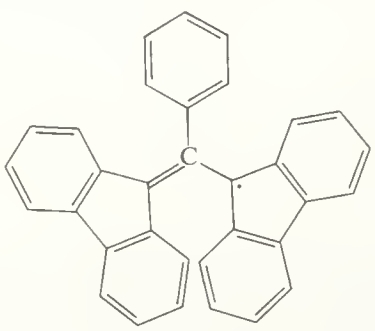


(2)

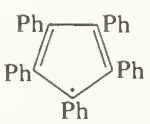
chemistry was firmly established in 1937 by the publication of three outstanding papers: (i) the review by Hey and Waters[4] which showed that a large number of previously inexplicable reactions could be rationalized in terms of radical intermediates; (ii) Kharasch's paper[5] which simultaneously advanced an explanation of 'abnormal' addition; and (iii) Flory's definitive analysis of the kinetics of addition polymerization.[6] The subsequent years have seen much progress both in the understanding of radical chemistry and in its applications to laboratory and industrial synthesis. Physical techniques, particularly electron spin resonance (e.s.r.) spectroscopy[7] and the nuclear magnetic resonance (n.m.r.) spectroscopy study of the chemically induced dynamic polarization of nuclei[8] (CIDNP), have allowed more direct observation of radicals and their properties, and a further unravelling of complex reaction mechanisms.

2.8.1.1 Structure, stability, and reactivity[9]

The stability and reactivity of radicals, as of carbenium ions and carbanions, is structure dependent and varies over a wide range. At one extreme lie the isolable species such as Koelsch's radical (**3**), and (**4**), followed by long-lived species of generally low reactivity such as triarylmethyl radicals, *e.g.* (**1**), and hindered tertiary alkyl radicals, *e.g.* (**5**),[10] while at the other end of the scale, radicals such as CH_3· and Ph· are so highly reactive to most organic substrates that their lifetimes are extremely short under normal reaction conditions. This last group are often called transient or 'short-life' radicals but, since radicals are usually destroyed in bimolecular processes, their lifetimes naturally depend on their environment and even a methyl radical would have an indefinite life if isolated in an inert matrix. However, it should be noted that certain types of radical are labile in the sense that they readily undergo unimolecular fragmentation or rearrangement processes (see p. 465).



(**3**)



(**4**)

$(Me_3C)_3C$·

(**5**)

While discussion of reactivity must necessarily be imprecise unless the reaction partners and conditions are specified, it is of value to note the three major factors which influence the reactivities and relative thermodynamic stabilities of radicals. (i) The degree of delocalization of the unpaired electron: the more it is delocalized, the lower the spin density at the radical centre and the lower its reactivity. (ii) Steric effects: large groups around the radical centre can severely reduce its reactivity by hindering the approach of reactant molecules or radicals. (iii) Shape: any structural constraints which prevent alkyl radicals attaining their preferred planar conformation tend to destabilize them. This effect is similar to that seen in carbenium ions but not so pronounced.

(**6**)

(**7**)

For alkyl radicals, the stability order is the same as for carbenium ions (tertiary > secondary > primary > $\dot{C}H_3$) owing to hyperconjugative delocalization of the unpaired electron. However, this effect is relatively small; e.s.r. measurements indicate only a *ca.* 8% spin density reduction by each methyl group attached to the radical centre.[9b] The

substantial differences in the bond dissociation energies for the alkanes (CH_3—H, 434; CH_3CH_2—H, 410; Me_2CH—H, 395; Me_3C—H, 381 kJ mol^{-1}) are thought to be due in large part to differences in ground state strain as well as to differences in the stabilities of the radicals produced.[9b] Other α-substituents stabilize the radical by resonance, *e.g.* (**6**) and (**7**). The percentage reduction of the spin density at the radical centre gives a qualitative measure of the stabilizing effect; for substituents X in $CH_3\dot{C}H$—X, the following values have been determined from β-C–H e.s.r. coupling constants: Ph (30%), CN (15%), OEt (17%), COEt (16%), OH (16%), CO_2R (7%), CH_2OH (8%).[9b] Benson has quantified radical stabilization energy as the difference between the strength of the appropriate primary, secondary, or tertiary alkane C—H bond and the C—H bond of the radical in question.[11] Thus, for example, the benzyl radical is stabilized by 54 kJ mol^{-1} since toluene has a benzylic C—H bond dissociation energy of 356 kJ mol^{-1}. Since stabilized radicals form weaker bonds to hydrogen and to other atoms, their reactions with substrate molecules are less thermodynamically favourable than similar reactions of non-stabilized radicals, but their reactions with other radicals (*ca.* zero activation energy) are still very fast. It is important to note that resonance stabilization will only accelerate the formation of a radical if the transition state comes late enough on the reaction coordinate for it to have significant radical character. The lowering of radical reactivity by resonance stabilization is illustrated by the differences between the reactions of benzyl and methyl radicals in benzene. The former fail to react with the solvent and give the dimer (**8**) as the major product while methyl radicals react so rapidly with benzene that few survive to dimerize. Triarylmethyl radicals, *e.g.* (**1**), are less reactive than benzyl radicals towards organic substrates and, being also more reluctant to dimerize, can exist in high concentration in benzene solution. However, although unreactive towards each other, they do react readily with small radicals and species containing unpaired electrons such as oxygen or nitric oxide. Their low reactivity is attributed not so much to more extensive spin delocalization, which is restricted by the twisting of the aryl rings, but to steric hindrance. The lifetimes of other types of radical, *e.g.* (**5**), can be extended similarly by steric hindrance; such radicals have recently been called 'persistent' rather than 'stable' to avoid ambiguity.[10a] Other groups of persistent radicals such as the hydrazyls, diarylamino radicals, and nitroxides are discussed elsewhere but it is interesting to note here that the longevity of the nitroxides has been exploited recently in the 'spin-trapping' e.s.r. technique. In this, reactive transient radicals are trapped by reaction with nitroso compounds or nitrones and their structures determined from the e.s.r. spectrum of the nitroxide, *e.g.* (**9**).

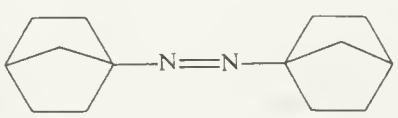
$$PhCH_2\cdot + PhCH_2\cdot \longrightarrow PhCH_2CH_2Ph$$

(**8**)

$$R\cdot + Bu^tN{=}O \longrightarrow \begin{matrix} & R & \\ & | & \\ & N\!-\!\!\cdot\!-O & \\ & | & \\ & Bu^t & \end{matrix}$$

(**9**)

Physical and chemical evidence point to a planar configuration at the radical centre for alkyl radicals but not for fluorinated derivatives such as $\dot{C}F_3$.[12] Alkyl radicals which cannot relax to a planar configuration are destabilized and tend to be less selective in their reactions than comparable planar radicals. They are also more difficult to form, *e.g.* (**10**) decomposes *ca.* 10^6 times more slowly than (**11**) (*cf.* the ease of formation of the comparable carbenium ions).



(**10**)

Me_3C—N=N—CMe_3

(**11**)

Although radicals are neutral species, polar effects do have an important influence on their reactions owing to charge separation in the transition state.[9b] For example, in the transition state (**12**) for the abstraction of hydrogen (equation 3) by radicals (X·) with a high electron affinity, *e.g.* Cl·, Bu^{t}O·, $CF_3^{\bullet}$, the electrons are drawn more towards X to give the charge separation shown. If the charges can be delocalized by adjacent substituents, then the transition state energy will be lowered and the reaction facilitated. Although solvent effects are generally less important than for ionic reactions, many radical reactions do show solvent dependence due to both free-volume and solvation effects.[13]

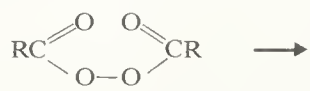
$$RH + X\cdot \longrightarrow \left[R\overset{\delta+}{\text{-----}}H\text{-----}\overset{\delta-}{X} \right]^{\ddagger} \longrightarrow R\cdot + XH \qquad (3)$$

(**12**)

2.8.1.2 Generation and reactions

Typical radical reactions such as alkane halogenation, addition to alkenes, vinyl polymerization, and homolytic aromatic substitution consist of a sequence of some or all of the elementary steps exemplified below (equations 4–11).

Initiation



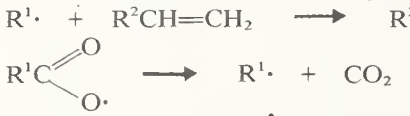
(**13**) (4)

Abstraction $R^1\cdot + PhCH_3 \longrightarrow R^1H + PhCH_2\cdot$ (5)

Substitution $R^1\cdot + PhSSPh \longrightarrow R^1SPh + PhS\cdot$ (6)

Addition $R^1\cdot + R^2CH{=}CH_2 \longrightarrow R^2\dot{C}HCH_2R^1$ (7)

Fragmentation



(8)

Rearrangement $Ph_3CO\cdot \longrightarrow Ph_2\dot{C}OPh$ (9)

Combination $2Cl_3C\cdot \xrightarrow{k_c} C_2Cl_6$ (10)

Disproportionation $2CH_3CH_2\cdot \xrightarrow{k_d} CH_2{=}CH_2 + CH_3{-}CH_3$ (11)

Reactions begin with the decomposition of some labile compound as a primary source of radicals (initiation), continue with a sequence of radical–molecule reactions (propagation), *e.g.* equations (5)–(7), which usually produce the reaction product, and conclude with the removal of the radicals by radical–radical reactions (termination), *e.g.* equations (10) and (11). Chain reactions[14] are more common in radical than in ionic chemistry: the new radical produced in an addition or abstraction reaction is often capable of reacting rapidly with a substrate molecule to produce another new radical which continues the sequence, *e.g.* equations (12) and (19), until the chain of reactions is terminated by a radical–radical interaction. The propagation of the chain depends on the high reactivity of the chain carrying radicals in their radical–molecule reactions. This keeps the radical concentration low and hence a low rate of radical–radical termination reactions.

$$\begin{aligned} &R\cdot + PhCH{=}CH_2 \longrightarrow PhCHCH_2R \\ &PhCHCH_2R + PhCH{=}CH_2 \longrightarrow PhCHCH_2CH(Ph)CH_2R \\ &PhCHCH_2[CH(Ph)CH_2]_{n+1}R \xleftarrow{n\,PhCH=CH_2} \end{aligned} \qquad (12)$$

There are two common methods of generating the particular radicals required for a reaction: (i) to construct a molecule containing the moiety required which will either homolyse, or can be converted to radicals *via* a redox reaction, or (ii) to decompose similarly a general purpose initiator to produce reactive radicals which then react with some organic substrate by abstraction or addition to give the desired radicals. In (ii), the nature of the initiator is unimportant provided it decomposes at a convenient temperature and gives radicals which are reactive enough for their intended purpose.

(*i*) *Primary production of radicals*

Bond homolysis is the most common method for the primary generation of radicals. Most bonds are thermally stable over the usual temperature range (25–150 °C) used in solution chemistry but there are a few (with bond energies less than *ca.* 160 kJ mol^{-1}), notably in peroxy (—O—O—) and azo (—N=N—) groups, which do cleave at convenient rates at these temperatures. Since the chemistry of peroxides and azo compounds[15,16] is discussed elsewhere, it will suffice here to note briefly their applications in radical reactions.

The transition state for azo compound thermolysis is thought to involve a considerable degree of bond breaking. The ease of the reaction is therefore related to the stability of the radicals being generated and has in fact been used as a measure of relative radical stability.[9b] Thus although dimethyldi-imide (MeN=NMe, $\Delta H^{\ddagger} = 220$ kJ mol^{-1}) is too stable to be used as an initiator, the dibenzyl analogue ($PhCH_2N{=}NCH_2Ph$, $\Delta H^{\ddagger} = 157$ kJ mol^{-1}) and azobisisobutyronitrile [$Me_2C(CN)N{=}N(CN)CMe_2$, $\Delta H^{\ddagger} = 131$ kJ mol^{-1}] decompose many hundreds of times faster. Such compounds, however, have limited value as general purpose initiators because the resonance-stabilized radicals they produce are not very reactive in abstraction reactions. The stabilization of only one of the derived radicals also much increases the decomposition rate; for example, although azobenzene is stable at 600 °C, phenylazotriphenylmethane (**14**) decomposes (equation 13) readily at 50 °C ($t_{\frac{1}{2}} = ca.$ 3 h). This compound is a useful source of phenyl radicals but also produces the persistent triphenylmethyl radicals which act as inhibitors. Although the thermal cleavage of simple aliphatic azo compounds is difficult, their photolysis provides a major route to alkyl radicals. Mixed alkylaryl azo compounds also photolyse to give radicals, *via* cleavage of their unstable *cis* isomers,[16] but aromatic azo compounds only undergo *cis–trans* isomerization.

$$\underset{\textbf{(14)}}{Ph_3C{-}N{=}N{-}Ph} \longrightarrow Ph_3C\cdot + Ph\cdot + N_2 \qquad (13)$$

Primary and secondary dialkyl peroxides are too unstable to find much use as initiators, but tertiary alkyl peroxides provide a valuable source of the reactive alkoxy and alkyl radicals (equation 14). Diacyl peroxides produce radicals in both thermal and photochemical decomposition (equation 4), but the latter is preferred for the generation of secondary and tertiary alkyl radicals as it avoids competing heterolytic reactions. When R^1 is an alkyl group, the intermediate carboxyl radicals fragment very rapidly (equation 8) and do not escape the solvent cage, but diaroyl peroxides, when decomposed in reactive substrates, often give products derived from aranoyl radicals (**13**; R = Ar). This detracts from their value as specific sources of aryl radicals but not as general purpose initiators. Peroxy esters decompose in a similar way, peroxalates and peroxydicarbonates being particularly useful as they decompose at convenient rates at 40–50 °C to produce much more reactive radicals than azo compounds, *e.g.* azobisisobutyronitrile, which decompose in the same temperature range. The thermal decomposition of peroxides is not always first order; in many systems they are also consumed in bimolecular radical-induced reactions.

$$Me_3C{-}O{-}O{-}CMe_3 \longrightarrow 2Me_3CO\cdot \longrightarrow Me_2CO + Me\cdot \qquad (14)$$

Aryl radicals are usually generated directly; diaroyl peroxides provide one source but several methods are also available using the readily available aromatic amines or their derivatives as precursors. These methods depend on the one-electron transfer reduction of diazonium ions (ArN_2^+) to the very labile diazenyl radicals ($ArN_2\cdot$) which rapidly lose nitrogen, *e.g.* equation (15).[17] The Gomberg reaction (equation 16) and the decomposition of acylarylnitrosamines (equation 17) apply particularly to homolytic aromatic substitution and involve chain reactions.[18] The most convenient and versatile routes to aryl radicals are *via* the aprotic diazotization of aryl amines with organic nitrites[19a–e] (equation 8) and by the reactions of arenediazonium tetrafluoroborates with potassium

acetate in the presence of the phase-transfer reagent 18-crown-6.[19f] Organic nitrites also react with 1,3-diaryltriazenes to give aryl radicals in high yield.[20]

$$ArN_2^+X^- \xrightarrow[H_2O,\ Me_2CO]{Cu\ or\ CuCl} Ar\cdot + N_2 \quad (15)$$

$$ArN_2^+X^- + PhH \xrightarrow[aqueous]{OH} Ar—Ph \quad (16)$$

$$ArN(NO)COR + PhH \longrightarrow Ar—Ph \quad (17)$$

$$ArNH_2 \xrightarrow{RONO} Ar\cdot + N_2 \quad (18)$$

The photolytic cleavage of halogens, polyhalomethanes, aryl iodides, alkyl and aryl nitrites,[21] ketones, and organomercury compounds is also important in radical generation. Higher energy radiation, X- and γ-rays, and fast electrons will induce homolytic cleavage of many classes of compound.[22]

(*ii*) *Abstractions*

The generation of new radicals by abstraction (equation 5) occurs as an elementary step in most free radical reactions. Hydrogen can be abstracted by many types of atoms and radicals *via* a more or less linear transition state, the ease of the reaction depending on the reactivity of the abstracting radical and the chemical environment of the hydrogen.[23] In the latter, the strength of the C—H bond, polar factors, and non-bonded interactions are all important. All radicals show the same gross reactivity order, $CH_3—H < RCH_3 < R_2CH_2 < R_3CH$, but the selectivity varies widely and depends mainly on the reactivity of the attacking radical (Table 1). Highly reactive radicals, those forming strong bonds to hydrogen such as F·, show very low selectivity while those of low reactivity, *e.g.* Br·, discriminate strongly. Note that the radicals produced by most initiators, alkyl, aryl, and alkoxy radicals, are only moderately selective. In terms of Hammond's postulate, for reactive radicals the transition state comes early on the reaction coordinate and will involve little C—H bond breaking, *e.g.* (**15**), so differences in the C—H bond strength or the stability of the incipient radical do not have much effect on the rate. With less reactive radicals there is much more C—H bond breaking in the transition state, *e.g.* (**16**), so the bond strength is more important and the transition state energy will be lowered by any factors which stabilize the incipient radical. The last point is illustrated by the relative reactivities of the indicated hydrogens in (**17**) and (**18**) to abstraction by Cl·, Ph·, and Br· radicals; both have similar reactivity to Cl·, but for abstraction by Br·, where the transition state more resembles the incipient radical, compound (**17**) is 800 times more reactive than (**18**) owing to the greater radical stabilizing capacity of the phenyl group. For abstraction

TABLE 1

Relative Rates of Hydrogen Abstraction from Alkanes[a]

Radical X·	*Relative reactivity per hydrogen* CH_4	RCH_3	R_2CH_2	R_3CH	*D*(X—H) (kJ mol^{-1})
F·	0.5	1	1.2	1.4	562
Cl·	0.004	1	4.3	7.0	428
Br·	0.002	1	80	1700	362
Ph·	—	1	9	44	431
Bu^tO·	—	1	12	44	424
·CH_3	—	1	10	80	433

[a] See Ref. 23.

TABLE 2

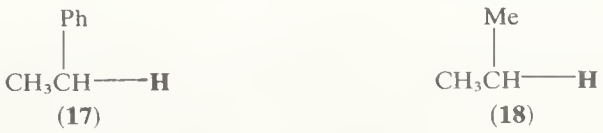
Relative Reactivity of Substituted Methanes (CH_3Y) to Hydrogen Abstraction by Phenyl Radicals[a]

Y	CH_3	Ph	CH_2=CH	CO_2Me	CN	Cl	MeS	Me_2N	NO_2
Relative reactivity	1.0	9.0	10–15	2.9	2.6	3.1	17	33	1.6

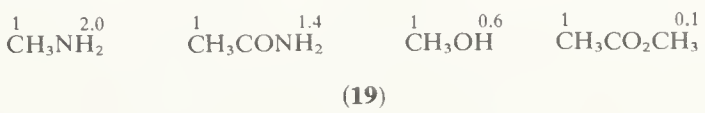
[a] See Ref. 23.

by Ph·, compound (**17**) is *ca.* 5 times more reactive. The effects of some other α-substituents on the rates of hydrogen abstraction by phenyl radicals are given in Table 2.[23] Note particularly the big rate enhancement by the vinyl group which relates to the ease of allylic substitution in such compounds.[24] Some relative reactivities per hydrogen of O—H and N—H bonds to abstraction by methyl radicals are given in (**19**).[1a]

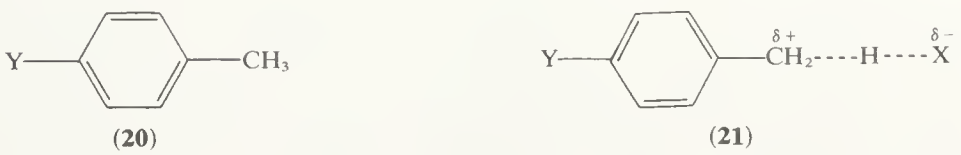
(**15**) (**16**)



(**17**) (**18**)



(**19**)



(**20**) (**21**)

The important influence of polar effects on the rates of abstraction reactions was outlined in Section 2.8.8.1. For example, the rate of hydrogen abstraction from the methyl group of substituted toluenes (**20**) is reduced by electron-withdrawing groups (Y) which destabilize the transition state (**21**). A Hammett treatment of these reactions gives a low ρ value (−0.1) for abstraction by H·, Me·, and Ph·, indicating only a small dependence of the rate on polar effects, but higher ρ values for radicals with greater electron-affinity, *e.g.* $Bu^tO\cdot$ (−0.4), Cl· (−0.7), p-$NO_2C_6H_4\cdot$ (−0.6), Br· (−1.4), $\cdot CCl_3$ (−1.5). Similar polar effects are observed in wholly aliphatic systems: note how the inductive effects of the CN and Bu^t substituents (Table 3) affect the reactivity of the α and β C—H bonds to

TABLE 3

Relative Selectivity in Hydrogen Abstraction from Substituted Butanes[a] in the Gas Phase

Abstracting radical	$X-\overset{\alpha}{C}H_2-\overset{\beta}{C}H_2-CH_2-CH_3$				
Cl·	H	1	3.6	3.6	1
Cl·	CN	0.2	1.7	3.9	1
Cl·	Bu^t	2.9	3.7	5.3	1
Br·	H	1	80	80	1
Br·	CN	20	8	80	1

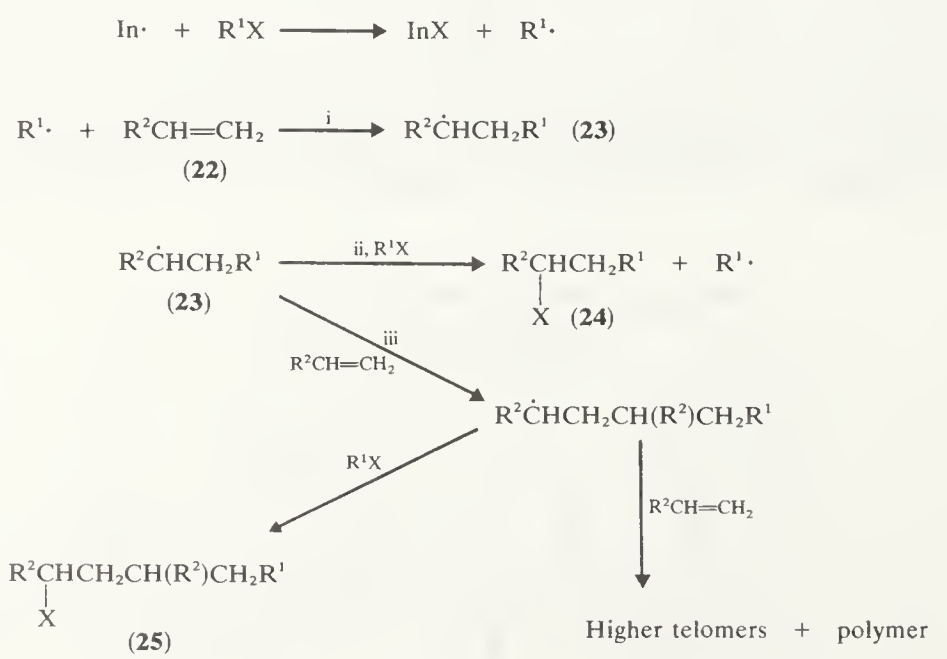
[a] See Ref. 1a.

abstraction by Cl· radicals. The results for abstraction by Br· radicals differ because there is more bond breaking in the transition state: the increase in reactivity at the α position shows that the resonance stabilization of the incipient radical by the cyano group outweighs its polar deactivating effect; however, the β-position is still deactivated by the polar effect.[1a] Halogens are also abstracted by many radicals, the reactivity order I > Br ≈ H > Cl > F following bond strength except for H. Polar repulsion between the filled orbitals of the halogen and the approaching radical is thought to retard halogen abstraction relative to that of hydrogen and to account for its anomalous position. Rate studies on iodine abstraction indicate a transition state polarization opposite to that in (**21**). The abstraction of halogens and hydrogen by aryl radicals generated from arylamines provides a useful alternative to the Sandmeyer reaction.[19]

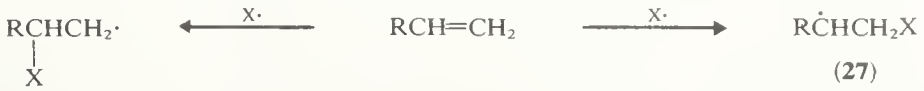
Homolytic displacements of all types have been recently reviewed.[25]

(*iii*) *Additions*

Radicals of many types undergo addition (equation 7) to alkenes, dienes, arenes, alkynes, and other unsaturated bonds.[26] In reactions with alkenes, this addition step is usually part of a chain process (equation 19) which can lead to 1 : 1 adducts (**24**), telomers, *e.g.* (**25**), or high polymers. The importance of radical polymerization hardly has to be stated but the formation of 1 : 1 adducts is also a valuable synthetic reaction[27] applicable to a wide range of addenda, for example polyhalomethanes, carboxylic acids, esters, nitriles, alcohols, amines, and a variety of heteroatom-centred radicals. Whether the reaction gives a high yield of the adduct or of polymer is determined by competition between steps (ii) and (iii) in equation (19) and, although this depends largely on the nature of the reactants, considerable control is possible by manipulation of the reaction conditions. Alkenes which give stabilized chain-carrying radicals (**23**), tend to give polymers, *e.g.* styrene (**22**; R^2 = Ph) will readily undergo the addition steps but the resonance-stabilized radical so formed will have low reactivity in the chain-transfer step (ii) and will react preferentially with another molecule of styrene. Such alkenes tend to give polymers except in cases where the addendum has a weak enough bond to make the transfer step (ii) competitive with further addition (iii). Conversely, the less-stabilized chain-carrying radicals from alkenes such as (**22**; R^2 = alkyl) are more reactive in step (ii) and will tend to give higher adduct yields. High adduct yields can be encouraged by having a high concentration of the addendum and a low concentration of the alkene, so



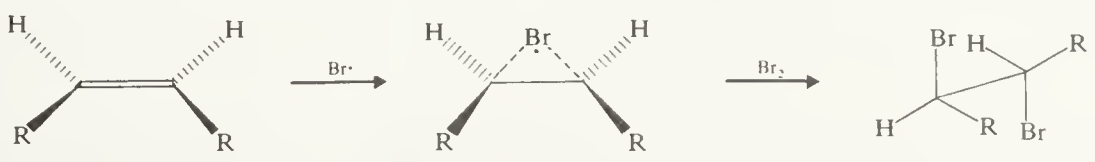
promoting step (ii) at the expense of step (iii); this is particularly important for addenda in which a strong bond has to be broken in the transfer step. The addition of simple alkyl radicals is exothermic and not reversible under normal solution reaction conditions; however, additions giving weaker bonds are appreciably reversible, *e.g.* with Br·, I·, and many radicals centred on heteroatoms. The rate of the addition step (i) is affected by both polar and steric factors. For example, the rate of addition of radicals $\cdot CF_3$ and $\cdot CCl_3$, both considered to be electrophilic in character, to substituted ethenes is increased by electron-donating substituents and decreased by electron-withdrawing substituents. Unsubstituted alkyl radicals, *e.g.* $\cdot CH_3$, which are slightly nucleophilic show the opposite effect; the reactivity of the alkene decreases sharply as the number of methyl substituents goes up owing to both polar and steric factors. The activation energies for the addition of $\cdot CCl_3$ radicals to both ends of a number of alkenes of type $CH_2{=}CXY$ have been measured. For addition to the $CH_2{=}$ end, giving $Cl_3CCH_2\dot{C}XY$, the activation energy varies little with the nature of X and Y. Hence, for this system at least, the rate of the addition step seems to be little influenced by the degree of resonance stabilization of the radical produced.[28]



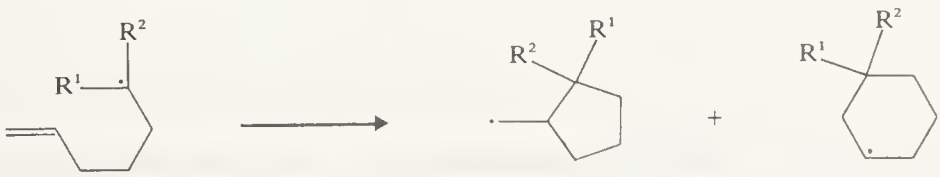
(**26**) (**27**)

In principle, the addendum radical can add to either end of the alkene to give radicals (**26**) and (**27**). For terminal alkenes $RCH{=}CH_2$ the product from (**27**) is generally formed almost exclusively, thus enhancing the synthetic utility of the reaction. The orientation of addition can almost always be predicted using the simple rule that radical attack will occur predominantly at the least-substituted carbon of the double bond. The usual explanation is that addition proceeds *via* the 'more stable' of the two possible radicals; usually, this can be judged by resonance delocalization. Tedder has argued that simple resonance considerations are inadequate and that it is more correct to differentiate between the two orientations on the basis of the strength of the new bond formed.[29] Tedder and Walton in a recent review of the orientation problem have also emphasized the importance of steric and polar effects.[30] For example, polar effects play a significant role in determining the orientation of addition to $CF_2{=}CHF$; electrophilic radicals, *e.g.* $\cdot CF_3$, add predominantly to the CHF= end, but with $CH_3\cdot$ radicals the orientation is reversed and it adds mainly to the $=CF_2$ end.

Reactions taking place *via* the addition of Br· radicals are notable in that they are stereospecifically *trans*; this has frequently been adduced as evidence for a bridged intermediate (**28**).[31] Thiol addition also shows a strong *trans* preference but is less specific. Intramolecular addition has been much studied in recent years.[32] Hex-5-en-1-yl radicals (**29**; $R^1 = R^2 = H$) are particularly interesting in that stereoelectronic factors direct the cyclization to give the less-stable radical (**30**). With more stabilized radicals (**29**; $R^1 = CN$, $R^2 = CO_2R$), both (**30**) and (**31**) are produced.



(**28**)

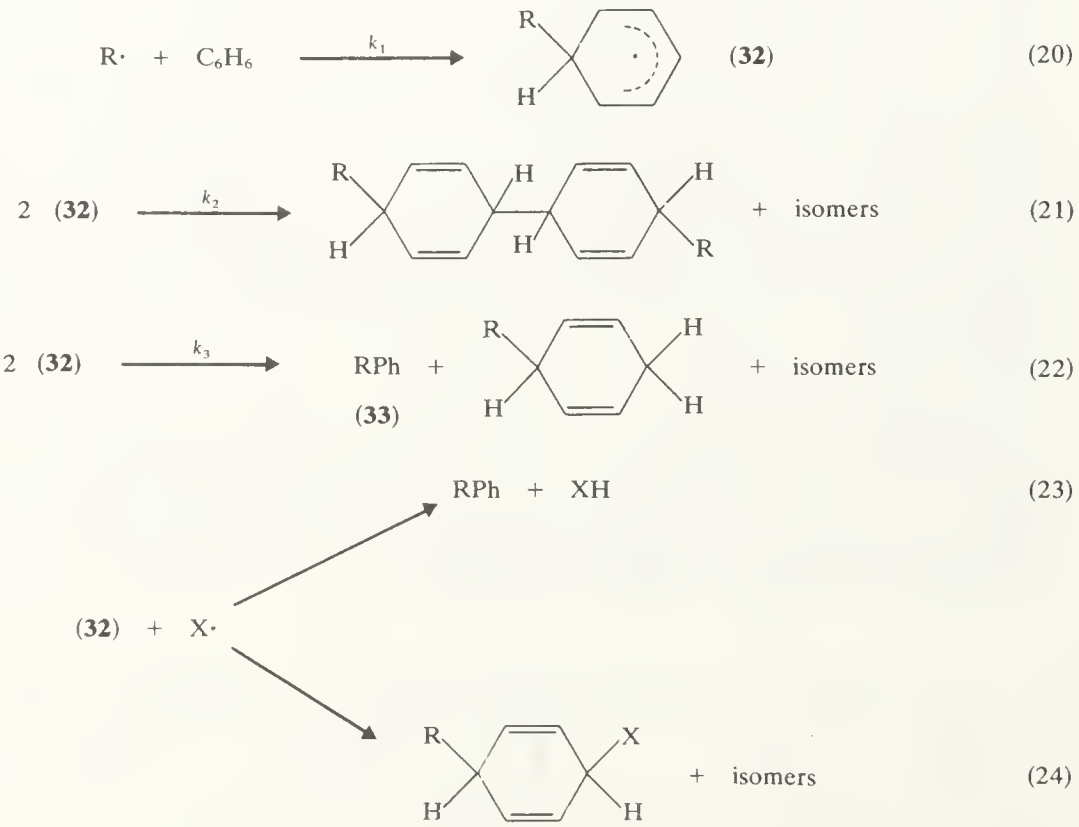


(**29**) (**30**) (**31**)

Addition to conjugated dienes generally gives predominantly the 1,4-adduct provided there are no structural features inhibiting conjugation. Most radicals attack the terminal position in allenes but some, *e.g.* Br·, ·PH_2, and F·, add to the centre carbon. Radical addition to acetylenes produces reactive vinyl radicals which usually react rapidly in chain transfer to give the alkene; hydrogen bromide adds stereospecifically but most other addenda give both stereoisomers.

(*iv*) *Aromatic substitution*[33]

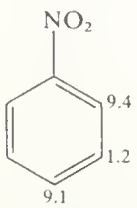
The involvement of radicals in aromatic substitution reactions was first recognized in 1934 in a classic paper by Grieve and Hey. The detailed mechanism and synthetic scope of the reaction have been under constant investigation ever since. The reaction is versatile; aryl and many other radical types react with arenes and hetarenes[34] by the general mechanism in equations (20)–(24). Intramolecular arylation is also well known.[35] Most of the work on the mechanism of the reaction has been done with aryl radicals generated from aroyl peroxides. The addition step to give radical (**32**) in equation (20) is rate-determining; for a phenyl radical, it is exothermic by *ca.* 75 kJ mol^{-1} and is not appreciably reversible under normal conditions. The resonance-stabilized cyclohexadienyl radical (**32**) so formed does not react with the substrate, nor does it spontaneously lose a hydrogen atom to give the substitution product (**33**), but it undergoes fast radical–radical reactions (equations 21–24). It has been estimated that, for the reaction of benzoyl peroxide with benzene at 80 °C, $k_1 = 2 \times 10^3$, $k_3 = 4.5 \times 10^6$, $k_2 = 10.5 \times 10^6$ l mol^{-1} s^{-1}. In this reaction the benzoyl peroxide also undergoes induced decomposition by reaction with phenylcyclohexadienyl radicals.



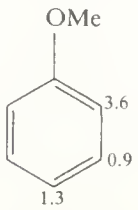
Polycyclic aromatic hydrocarbons and some heterocyclic systems are very much more reactive than benzene; anthracene, for example, reacts *ca.* 250 times faster with phenyl radicals and also reacts with less-reactive radicals such as $PhCH_2$·, $Me_2\dot{C}CN$, $Ph\dot{C}O$, and RS· which do not attack benzene.

Substituents in the aromatic ring of the substrate have relatively little effect on the rate compared with their effect in analogous electrophilic substitution reactions; some partial

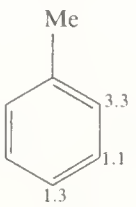
rate factors are given in (**34**)–(**36**) for substitution by phenyl radicals. The higher reactivity at the *ortho* and *para* positions may be due to the ability of the substituent (X) to delocalize the unpaired electron in (**37**), but it has been argued that the cyclohexadienyl radical is a poor transition state model for the exothermic addition of reactive radicals like Me· or Ph· where little transition state bond formation might be expected. The orientation data for a variety of substrates have been correlated with calculated localization energies.[33a] Substituents in the aryl radical have a secondary effect both on its reactivity to the substrate and the isomer distribution due to polar effects, *e.g.* p-$NO_2C_6H_4$· reacts more slowly than p-$CH_3C_6H_4$· with nitrobenzene. Hammett ρ values have been calculated for substitution by a large number of substituted aryl and other radicals.[33a]



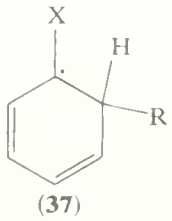
(**34**)



(**35**)



(**36**)



(**37**)

The presence of persistent radicals or other oxidants has a marked effect on the course of the reaction, *e.g.* in the decomposition of phenylazotriphenylmethane (**14**) the cyclohexadienyl racical (**32**) is scavenged by the Ph_3C· radical *via* both equations (23) and (24).

(*v*) *Combination and disproportionation reactions*

These occur as the termination steps in radical reactions. Combination reactions (equation 10) have very low or zero activation energy and thus are very fast compared with radical–molecule reactions.[36] Carbon-centred radicals usually have dimerization rate constants in the range 10^8–10^{10} l mol^{-1} s^{-1} (*cf. ca.* 10^3 l mol^{-1} s^{-1} for radical addition to alkenes) for liquid-phase reactions, which is close to the diffusion-controlled limit. Notably, the combination rate for resonance-stabilized species such as $PhCH_2$· and $Me_2\dot{C}CN$ radicals is not lower than for less-stabilized species but dimerization is inhibited by bulk effects such as already noted for species such as (**1**) and (**5**). The lower dimerization rate of $^{\delta+}\cdot Cl_3^{\delta-}$ compared with $\cdot CH_3$ radicals may be due to polar repulsion. Disproportionation reactions (equation 11) occur at a similar rate to combinations and thus cannot involve a normal hydrogen abstraction since, in radical–molecule reactions, this has an activation energy of *ca.* 30 kJ mol^{-1}. The k_d/k_c ratios per β hydrogen are 0.03, 0.1, and 0.4 for primary, secondary, and tertiary alkyl radicals; this ratio is reduced for resonance-stabilized radicals, *e.g.* it is 0.005 for $Ph\dot{C}Me_2$. In addition to diffusion-controlled encounters, both of these processes can also take place within a solvent cage.[37] In cases where the radical pairs are generated close together, as in the decomposition of azo compounds or peroxides, some undergo geminate combination within the solvent cage before they can diffuse apart to react with substrate molecules or other radicals. The extent of caged recombination goes up with solvent viscosity and can considerably reduce the efficiency of initiators.

Combination reactions can be used synthetically, for example in the preparation of dimers such as $PhCH_2CH_2Ph$, Cl_3CCCl_3 and $(CH_2CO_2R)_2$ and in the oxidative coupling of phenols (p. 746). Persistent radicals are also used as small radical scavengers, frequently to inhibit chain reactions.

(*vi*) *Fragmentation and rearrangement*[32b]

Some examples of homolytic radical fragmentation are given in equations (8), (14), and (25)–(27). Fragmentations which are the reversal of radical addition to alkenes (equation

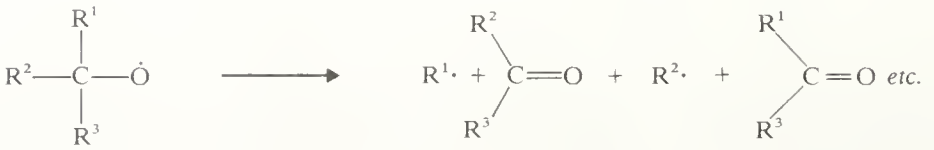
7) are common for $R^1 = I$, Br, or R^2S but occur for $R^1 = R_3^2C$ only when a weak or highly strained bond is involved. Intramolecular examples are the cyclopropyl–homoallyl rearrangement (**38**; $Y = CH_2$) and the analogous ring opening of oxirans (**38**; Y = O). The fragmentation of alkoxy radicals, *e.g.* (**39**), favours the most stable radical and has been used to estimate relative radical stabilities. Heterolytic fragmentations, *e.g.* equation (28), also occur.

$$ArCHOR \longrightarrow ArCHO + R\cdot \qquad (25)$$

$$R\dot{C}O \longrightarrow R\cdot + CO$$

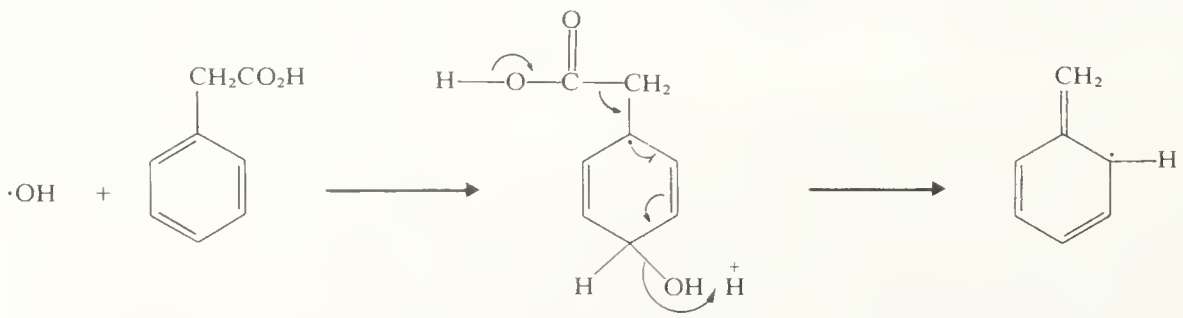
(38)

(26)



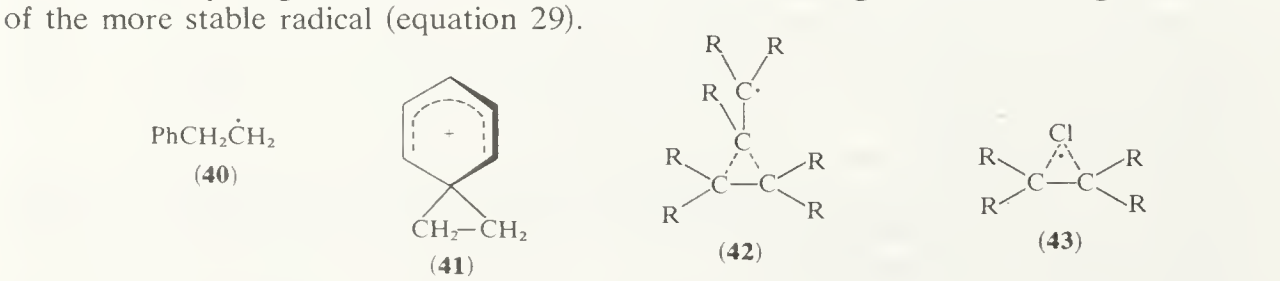
(39)

(27)

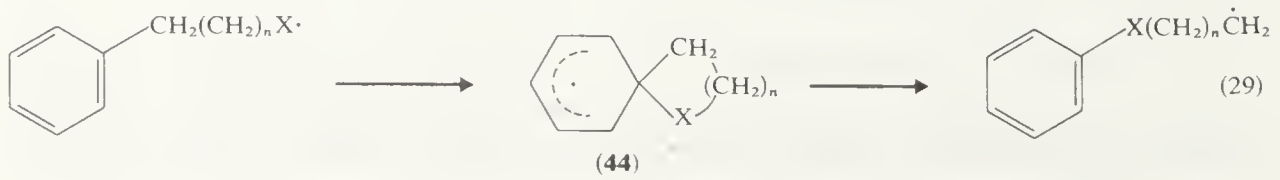


(28)

Radical rearrangements are far fewer than those of carbenium ions, in part as a consequence of the relatively smaller stability differences between primary, secondary, and tertiary radicals and possibly also because of orbital-symmetry restrictions. Evidence for the radical analogues of non-classical carbenium ions is lacking, for example the e.s.r. spectrum of (**40**) shows that it does not have a bridged structure analogous to (**41**). The most marked contrast with carbenium ions is the absence of 1,2-shifts of hydrogen and alkyl groups; however, aryl, vinyl, acyl, and acyloxy groups and chlorine do migrate. Bridged species such as (**42**) and (**43**) are probably involved as transition states or short-lived intermediates. Longer range migrations also occur; 1,3- and 1,4-hydrogen shifts are rare but 1,5-migration, in effect intramolecular abstraction, to both C and O is common.[21] Aryl migrations involve addition to the arene ring (**44**) and cleavage in favour of the more stable radical (equation 29).



(40) (41) (42) (43)



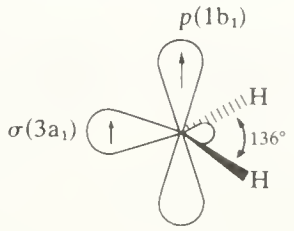
(44)

(29)

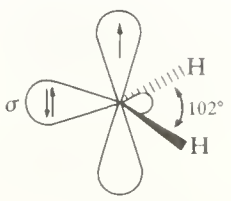
These fragmentation and rearrangement processes occur in competition with intermolecular reactions of the radicals concerned and the extent to which they occur depends therefore on the temperature, and the nature of the substrate.

2.8.2 CARBENES

Carbenes are highly reactive neutral species (R_2C:) in which carbon is attached to two groups by covalent bonds and has two non-bonding electrons. They are true intermediates with characteristic reactivity and selectivity which is independent of the mode of generation but does depend on the nature of the substituents (R) and on the electronic state of the species at the time of reaction. The latter is important since the reactions of singlet carbenes in which the two non-bonding electrons are paired, *e.g.* (**46**), are quite different in character from those of the triplet species (**45**) in which the electrons occupy different orbitals with parallel spins (see Section 2.8.2.2).[38] Much theoretical work has been done to predict the electronic structure and geometry of carbenes.[38] For methylene itself the ground state is the bent triplet (**45**) in which one of the non-bonding electrons occupies a σ orbital which has much p character while the other electron occupies a p orbital perpendicular to the molecular plane.



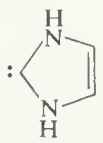
$^3B_1$ (**45**)



$^1A_1$ (**46**)

The first excited state is predicted to be the singlet (**46**), which has a smaller bond angle than the triplet. Thus for methylene and many other carbenes the energy difference between the σ and p orbitals is small enough for the triplet σp state to be of lower energy than the singlet because of the higher electron–electron repulsion energy in the latter. Current estimates indicate an energy difference of *ca.* 45 kJ mol^{-1} between the two states. It has been calculated, however, that a bigger σ–p splitting which would stabilize a singlet ground state can be achieved either by reducing the bond angle or by the interaction of one of the carbene's non-bonding orbitals with orbitals on a substituent, allowing either electron donation or acceptance by the carbene.[38–40] Examples of this type are (**47**), (**48**), and the halocarbenes (**49**).[41] Singlet ground states for these and for alkoxycarbonyl- and acyl-carbenes are also supported by experimental evidence.

(**47**)

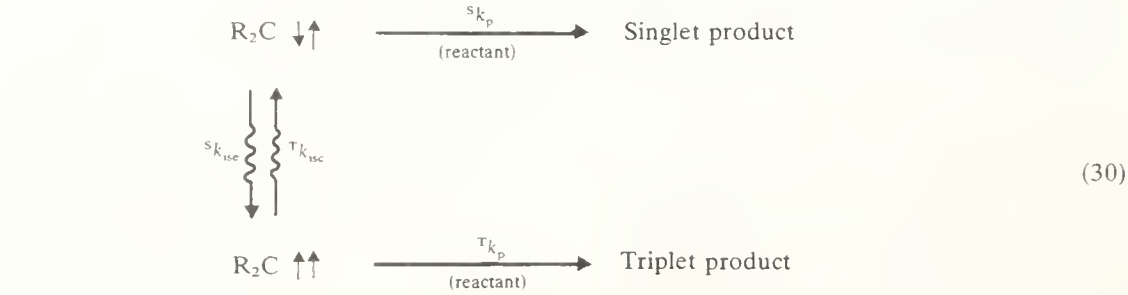


(**48**)

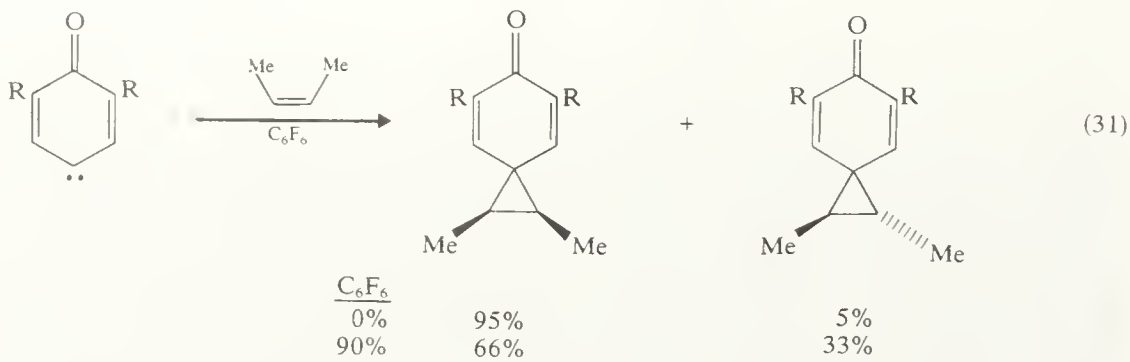
(**49**)

The proximity of the singlet and triplet states and the possibility of interconversions between them provide much of the fascination of carbene chemistry.[42] The spin state of the carbene at the instant of its reaction depends not only on the state in which it was formed or on the nature of its ground state, but also on the relative rates of the intersystem crossing processes (k_{isc}) (equation 30) and the product-forming reactions (k_p). Thus, for example, many carbenes with triplet ground states (*e.g.* :CH_2) when generated in solution as singlets (see Section 2.8.2.1) react so rapidly with most substrates in that state that they have no time to cross to their ground state ($^sk_p \gg {}^sk_{isc}$). In such cases, several techniques are available which allow the reactions of the other spin state to be observed.[38]

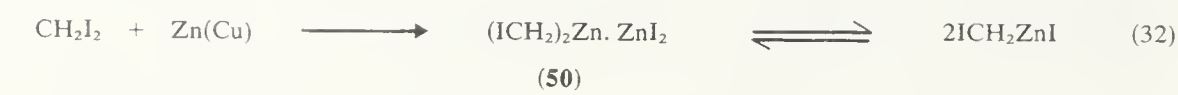
The usual method is to prolong the lifetime of the carbene to allow more intersystem crossing before reaction either by diluting the reaction mixture with an inert moderator, or, less commonly, by generating the carbene frozen in a matrix.[43] The effect of dilution can be seen, for example, in equation (31), where it causes a decrease in the stereospecificity of the reaction, so indicating an increase in the proportion of product formed by the triplet (ground-state) carbene.[44] Moderators do not always achieve this effect, however; for example, in the addition of diphenylmethylene (Ph_2C:), the *cis*-to-*trans* product ratio is unaffected by dilution with cyclohexane. In this case the energies of the singlet and triplet species are so close that they are in rapid thermal equilibrium which is fast compared with the rate of addition of either species to the alkene. In such cases, although the multiplicity of the carbene at its inception cannot be determined by dilution experiments, it can be inferred from the changes in stereospecificity induced by added scavengers.[45] Another method of increasing the amount of intersystem crossing before reaction is to increase the rate of the process either by using heavy-atom solvents or by incorporating a heavy atom such as mercury or a halogen into the carbene itself.[46] Thus, for example, $CH_3HgC\ddot{C}N$ undergoes intersystem crossing faster than the analogous $CH_3\ddot{C}CN$.



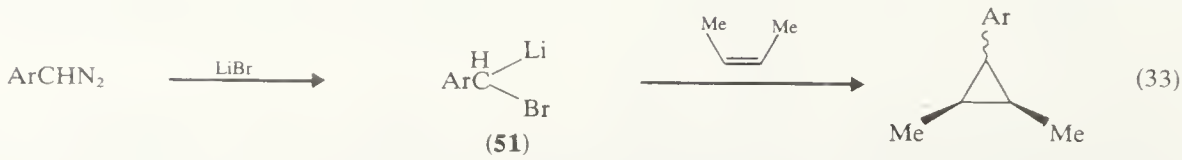
(30)



(31)



(**50**) (32)

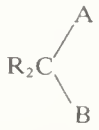


(**51**) (33)

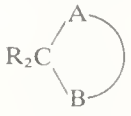
The free carbenes discussed above form a well-defined group of reactive intermediates, but there are also a number of other reagents known as 'carbenoids', *e.g.* (**50**) and (**51**) in equations (32) and (33), respectively, which, although they qualitatively mimic some carbene reactions, do not involve *free* divalent species.[47] Some of these are extremely useful cyclopropanation reagents but their alkene selectivity varies to such an extent that they can be differentiated experimentally from true carbenes by competition experiments with pairs of alkenes.[48]

2.8.2.1 Generation of carbenes and carbenoids

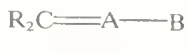
This requires the cleavage of two bonds to carbon, *e.g.* in precursors (**52**)–(**54**); the bonds can be broken in concert by heat or irradiation or stepwise *via* some metastable intermediate such as the metallated carbanion (**55**) in equation (34), which may also function as a carbenoid reagent. This review will outline only the major 'synthetic' routes with emphasis on carbenes rather than carbenoids.



(**52**)



(**53**)



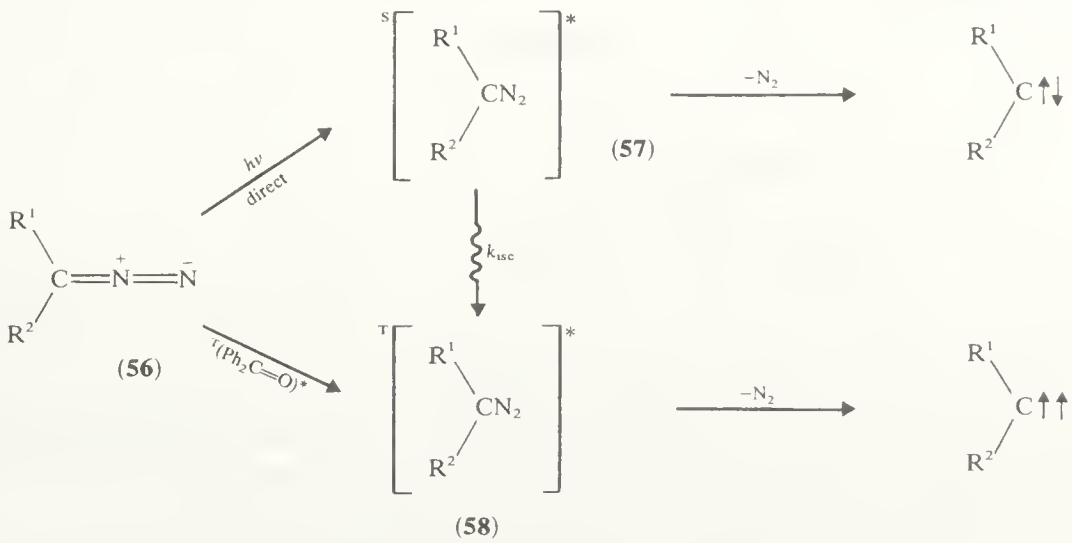
(**54**)

(**55**)

(34)

(*i*) *From diazo compounds*

The thermal or photolytic elimination of nitrogen from diazo compounds (**56**) provides one of the major routes to carbenes.[49] They may also be decomposed with a variety of catalysts *via* carbenoids.



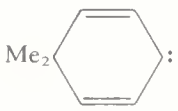
(**56**)

(**57**)

(**58**)

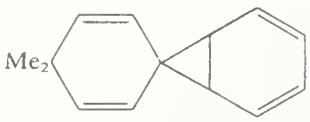
(35)

Photolytic decomposition (equation 35) can give both the singlet and triplet species.[50] Direct photolysis usually produces the singlet carbene *via* the first-formed excited singlet diazo compound (**57**), but in some cases the latter may cross to the triplet (**58**) at a rate which competes with nitrogen loss, so leading to the formation of the triplet carbene as well. In the presence of triplet sensitizers such as benzophenone, the light is absorbed by the sensitizer and energy is then transferred from the excited triplet sensitizer to the diazo compound to give (**58**) and thence the triplet carbene. Since (**58**) is lower in energy than (**57**), intersystem crossing to the singlet is not usually competitive with nitrogen loss and sensitized decomposition produces only the triplet carbene, provided all the radiation is absorbed by the sensitizer. The direct gas-phase photolysis of diazomethane is complicated by the fact that the generated methylene carries excess of energy and on addition to alkenes produces 'hot' or vibrationally excited cyclopropanes which undergo unimolecular rearrangement before collisional deactivation. In solution, however, this excess of energy is rapidly lost and it is clear from the high stereospecificity of cyclopropanation that only singlet methylene is produced.



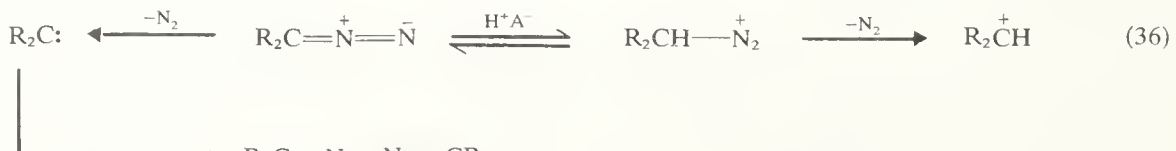
(59)

(60)



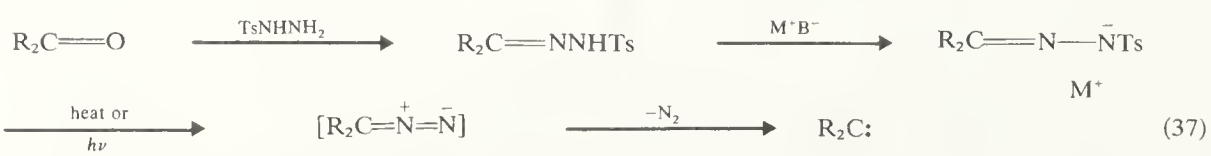
(61)

One of the uncertainties in this route to carbenes is that some of the product(s) may be formed directly by reactions of the excited diazo compound rather than *via* the carbene. This is difficult to rule out but can be checked in some cases by careful study of the quantum yield of the reaction or by comparing the properties of the carbene with those of the same carbene prepared by an alternative route, *e.g.* (**59**) produced from both (**60**) and (**61**) showed identical selectivity in competition reactions with pairs of alkenes.[51] This slight complication is absent in the production of carbenes by the thermolysis of diazo compounds, but there are three common side-reactions of the ground-state diazo compound which interfere with carbene generation. Diazo compounds can trap the generated carbene to give azines (**62**); they are also susceptible to protonation and carbenium ion production (equation 36). In addition, they can add as 1,3-dipoles to any alkenes or alkynes present to give pyrazolines or pyrazoles which may subsequently extrude nitrogen to give what are apparently carbene-derived products. These reactions are more likely to be important at the higher temperatures of the thermal decompositions than in the photolytic reactions which are usually carried out at room temperature or below. Because of equation (36), to be certain that the reactive intermediate is a carbene and not a carbenium ion it is vital that diazo compound thermolysis is carried out under rigidly aprotic conditions.



(62)

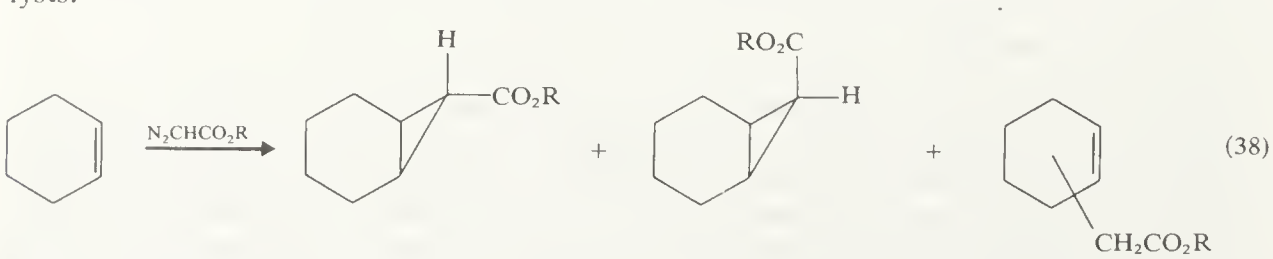
(36)



(37)

Diazo compounds can be prepared by a variety of methods but it is often more convenient to generate them *in situ*. There are several methods of doing this[47], but the most widely used is the Bamford–Stevens reaction (equation 37).[52,53]

Catalytic decomposition of diazo compounds proceeds *via* carbenoids, *e.g.* equation (38), which shows the different product distributions obtained with the copper carbenoid and the free carbene; note that the latter also gives a C—H insertion product. Copper and its salts, a variety of metal halides and other Lewis acids, and tetraphenylethane all serve as catalysts. That the catalyst is involved in the cyclopropanation transition state is shown by the asymmetric induction obtained when chiral copper complexes are used as catalysts.[54]



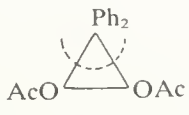
hν	31%	16%	21%
Cu	69%	4%	0%

(38)

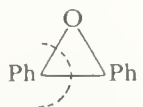
The photolysis of keten, $CH_2{=}C{=}O$, which is isoelectronic with diazomethane, is often used to generate methylene, but the higher ketens are not much used as carbene sources.

(*ii*) *Cycloeliminations*

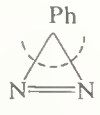
Thermal and photochemical cycloeliminations[55–57] also provide several useful routes to carbenes. Three membered rings, *e.g.* (**63**)–(**65**), fragment relatively easily. Simple cyclopropanes do not generally give high conversions to carbenes but the yields are better from norcaradienes, *e.g.* (**61**) and (**66**); the latter has been recommended as a 'shelf-stable' methylene source (>90%). The photofragmentation of oxirans, *e.g.* (**64**), is a much more synthetically useful reaction. Among larger rings, norbornadienes (**67**) eliminate dialkoxy- or difluoro-carbenes under relatively mild conditions and 1,3-dioxolans and cyclic carbonates undergo cycloeliminations, *e.g.* (**68**) and (**69**).



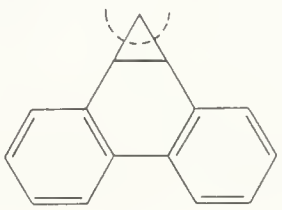
(**63**)



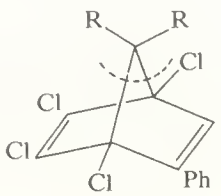
(**64**)



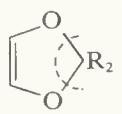
(**65**)



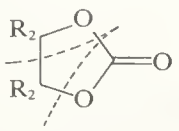
(**66**)



(**67**)



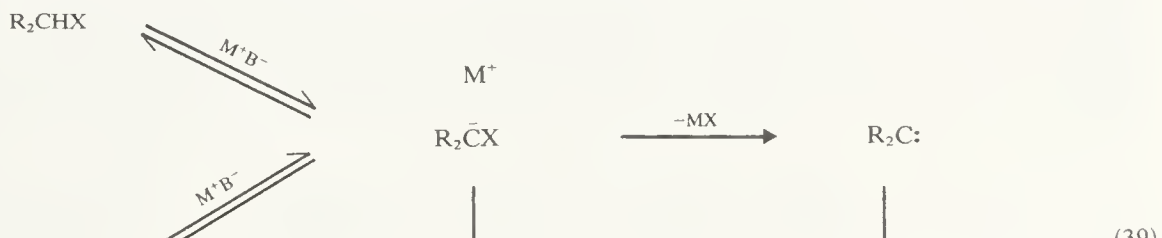
(**68**)



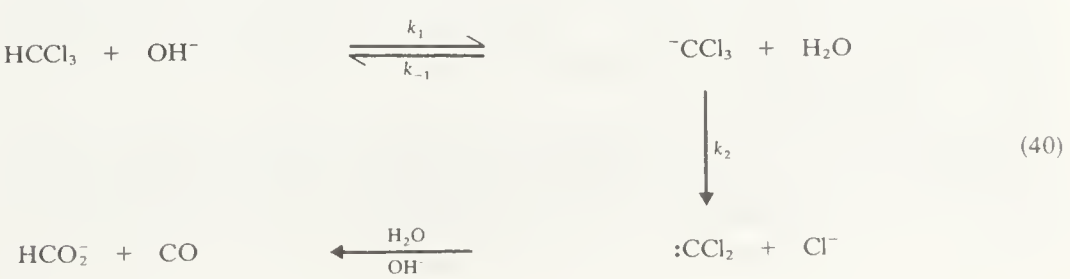
(**69**)

(*iii*) *Base-induced α-eliminations*

These reactions of halides or *gem*-dihalides (equation 39) provide a major route to either free carbenes or give reactions *via* ill-defined carbenoids, depending on the nature of the substrate and the reaction conditions.



(39)



(40)

Hine's classic studies on the hydrolysis of haloforms showed that in most cases the reaction followed equation (40), generating free halocarbenes.[41] This work, followed by that of Doering and Hoffman, who showed that under aprotic conditions the carbene could survive to be trapped by alkenes, stands at the foundation of modern carbene chemistry. Recently, however, this reaction has provided a most impressive example of the benefits of phase-transfer catalysis[58,59] and the preferred technique now is to generate the carbene from the haloform using aqueous sodium hydroxide solution in the presence of a quaternary ammonium salt (usually benzyltriethylammonium chloride) or a trialkylamine as catalyst. Thus a wide range of halocarbenes can be produced and the yields of halocyclopropanes are high even for unreactive alkenes. A triphase technique in which the catalyst is bonded to polystyrene resin beads offers the work-up advantage that the catalyst can be simply removed by filtration.[60]

Trihalomethyl anions produced by other methods[47] also give free carbenes. Vinylidenecarbenes can also be produced by hydrogen halide elimination but many organic halides react with bases, particularly with lithium alkyls, to give carbenoids[61] which are stable at low temperatures and which can react directly with alkenes to give cyclopropanes. The situation is complex and, although most such reactions, *e.g.* CH_2X_2/RLi, go wholly or at least partly *via* carbenoid addition, others, *e.g.* $LiCCl_3$ (above −80 °C), show the same selectivity as the free carbene and the reaction then most likely involves the equilibrium shown in equation (41) with rate-determining addition of the carbene to the alkene. In an important recent development it has been shown that reactions known to go *via* carbenoids, *e.g.* $PhCHBr_2$/$KOBu^t$/alkene, can be modified to produce the free carbene by the presence of reagents which complex the cation, *e.g.* 18-crown-6.[62] This makes possible the generation of free carbenes by α-elimination when diazo precursors are not accessible.

$$HCCl_3 + BuLi \longrightarrow LiCCl_3 \rightleftharpoons LiCl + :CCl_2 \xrightarrow[\text{slow}]{\text{alkene}} \text{Cyclopropane} \quad (41)$$

(*iv*) *From organometallic reagents*

Seyferth and his group have developed a wide range of organomercury reagents ($PhHgCX_3$) which function as highly effective methylene transfer reagents at convenient temperatures, *e.g.* $PhHgCCl_2Br$ (equation 42) which gives the norcarane in high yield in *ca.* 2 h at 80 °C, and $PhHgCCl_2I$ which requires *ca.* 24 h at room temperature.[63] Methylenes of many types, *e.g.* CX_2, CXY, CHX, CRX, and ROCOCX, can be transferred in addition and insertion reactions *via* similar reagents. The cyclopropanation of alkenes with $PhHgCCl_2Br$, and probably with most of the other $PhHgCCl_nBr_{3-n}$ ($n = 0$–3) reagents, involves free carbenes (equation 42), but reactions with substrates containing atoms with lone pair electrons may be *via* direct interaction with the organomercury reagent.

$$PhHgCCl_2Br \rightleftharpoons PhHgBr + :CCl_2 \longrightarrow \text{Cl}_2 \quad (42)$$

The Simmons–Smith reaction of methylene iodide with a zinc–copper couple produces an organozinc carbenoid usually formulated as (**50**), which is a powerful and extensively used cyclopropanation reagent.[64] The diethylzinc–methylene iodide system ($EtZnCH_2I$) is an alternative capable of extension, for example, to the synthesis of methylcyclopropanes from 1,1-di-iodoethane.[65]

A variety of other organometallic reagents, *e.g.* (**70**)–(**72**), also function as carbene or carbenoid sources, but they are less used synthetically than those above.

R_2CXSiX_3	R_2CXGeX_3	R_3SnCX_3
(**70**)	(**71**)	(**72**)

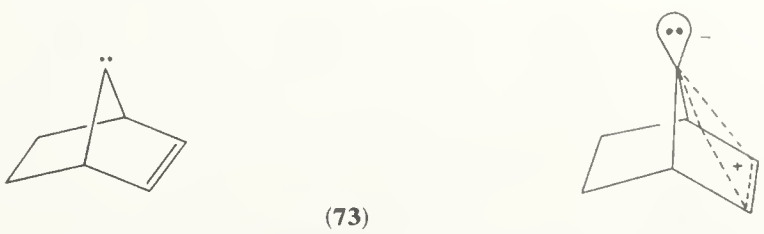
2.8.2.2 Reactions

Our understanding of carbene chemistry owes much to the application of physical techniques such as chemically induced dynamic nuclear polarization (CIDNP), electron paramagnetic resonance and, more recently flash photolysis studies of carbene reactions in solution.[66] Coverage of these topics is beyond the scope of this article and attention is drawn to the excellent reviews now available.[67,68]

(*i*) *Cycloaddition*

The addition of carbenes to alkenes to give cyclopropanes (equations 31, 38, and 42), is one of their most characteristic and synthetically useful reactions.[69] Intramolecular variations of the same reaction, *e.g.* equation (43), are often useful but are frequently low yielding and accompanied by hydrogen shifts and other competing reactions. In cases such as (**73**), where the stereochemistry of the molecule makes intramolecular cyclopropane formation impossible, calculations indicate that there can still be sufficient electronic interaction with the double bond to stabilize the singlet ground state of the carbene. Such carbenes are known as 'foiled' methylenes and much work has been done to probe experimentally the effects of this non-classical stabilization on the properties of the carbene.[69]

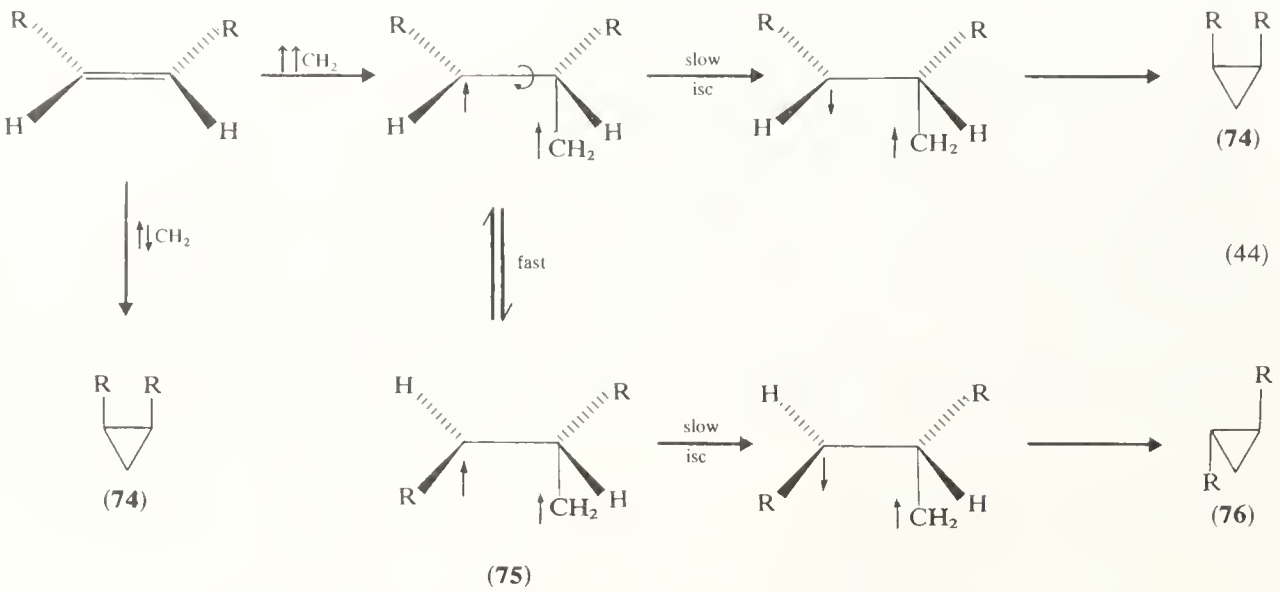
(10%) (43)



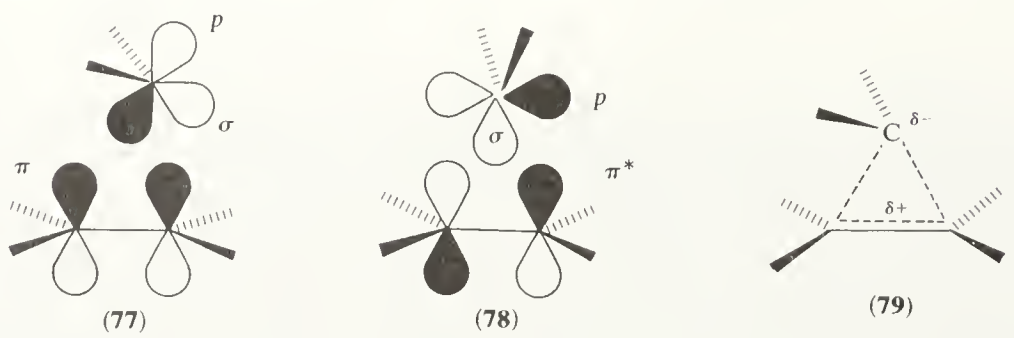
(**73**)

The mechanism of the intermolecular addition of carbenes to alkenes has been the subject of much debate over many years. With impressive chemical insight, Skell proposed in 1956 that the mechanism and stereochemistry of the reaction depended on the spin state of the carbene. He argued that singlet carbenes would add *via* the concerted formation of both new σ-bonds to give only (**74**), so preserving the sterochemistry of the alkene, while triplet carbenes would add in a radical-like two-step process giving first the diradical (**75**) in which bond rotation could occur before spin inversion and ring closure, so leading to both diastereoisomers (**74**) and (**76**). Although there has been much discussion about its theoretical validity, Skell's rule has been enormously successful in rationalizing much of the experimental data on these additions. However, caution should attend its application, since it depends on certain assumptions about the relative rates of the steps in equation (44) which may not hold in all cases.[38] Thus before particular reactivity can be unambiguously ascribed to one spin state of a carbene the properties of both should be determined. In a number of cases where this has been done rigorously, *e.g.* with methylene itself, bismethoxycarbonylcarbene, fluorenylidene, and others, the results have all been in accord with the Skell predictions. Calculations on the potential energy surface for the addition of singlet methylene to ethylene[40,70] support the idea of a concerted reaction and suggest that it goes *via* the non-least-motion, orbital-symmetry-allowed approach (**77**) in which the empty *p*-orbital (LUMO) of the carbene interacts with the filled π-molecular orbital of the alkene, the carbene being tilted to maximize overlap while minimizing steric interactions. The more symmetrical approach (**78**) with the carbene's filled σ-orbital interacting with the π-system is orbital symmetry forbidden and calculated to be at a higher energy than (**77**). For (**77**) the calculations show charge transfer from $\pi \rightarrow p$ in the

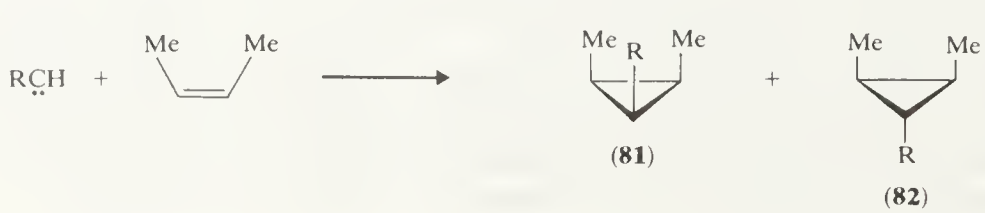
transition state (**79**), which fits with the experimental observation that for most carbenes the addition is accelerated by electron-donating substituents on the alkene and is thus an electrophilic attack by the carbene. The many relative reactivity studies done to determine the steric and electronic effects of various alkene and carbene substituents have been critically assessed by Moss,[48] who has also recently shown that the olefinic selectivity of many carbenes :CXY can be correlated using both resonance and inductive parameters of X and Y.[71] Most carbenes, even the strongly π-stabilized :CF_2 (**49**), exhibit typical electrophilic behaviour, but 'aromatic' carbenes such as (**80**) and (**47**) show nucleophilic properties, *e.g.* (**80**) adds *via* a transition state of opposite polarization to (**79**).[72] This is thought to be due to the incorporation of the carbene *p*-orbital into the $(4n+2)$ π-electron system of the cycloalkene ring.



(44)

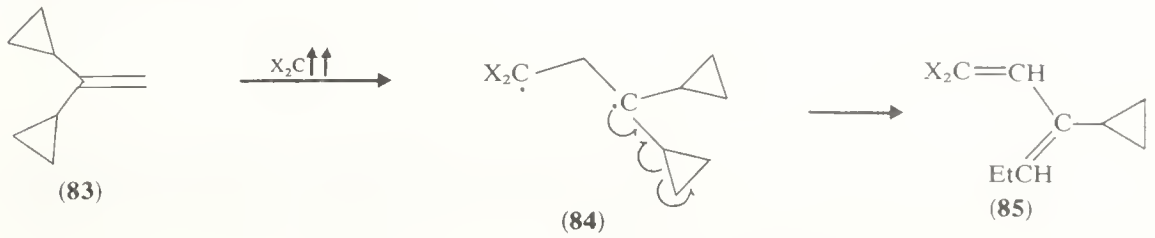


In addition to *cis*-alkenes (equation 45), unsymmetric carbenes show a remarkable contra-thermodynamic stereoselectivity, giving higher yields of (**81**) than (**82**).[73] This results at least partly from steric attraction due to secondary orbital interactions in the transition state.[74]



(45)

In the addition of triplet methylene to ethylene, calculations indicate an initially σ-like approach, with the carbene then bending to one side to form the triplet trimethylene biradical.[50] Triplet carbenes generally react more slowly than the singlet species with alkenes, but the converse is true for dienes. The alkene (**83**) provides a useful probe for carbene multiplicity since singlet carbenes add without rearrangement, whereas triplet addition gives (**84**) which undergoes fast rearrangement, and thence gives (**85**)[50] as shown in equation (46).



(**83**) (**84**) (**85**) (46)

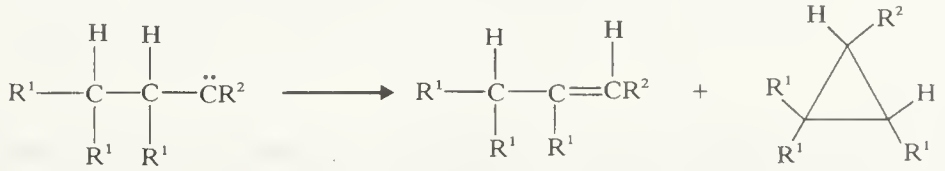
In addition to conjugated dienes, both 1,2- and 1,4-addition are orbital symmetry allowed, but the latter is discriminated against by closed-shell repulsions and is very rarely observed.[75] Cyclopropenylidene, however, does add 1,4- to tetracyclones and difluorocarbene undergoes homo-1,4-addition to norbornadiene.[76]

Carbenes also add to alkynes, arenes, hetarenes, and various other unsaturated groups such as C=O, C=S, C=N, C=P, and N=N.[69]

(*ii*) *Insertion and abstraction reactions*

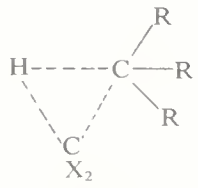
The characteristic bond insertion reaction, *e.g.* equations (47) and (48), is undergone by most carbenes and many bond types, *e.g.* C—H, C—halogen, Si—H, Si—C, Ge—H, N—H, O—H, and S—H in both inter- and intra-molecular reactions.[47] For insertions into C—H bonds, methylene itself shows virtually no discrimination between primary, secondary, and tertiary bonds in solution, and not much in gas phase reactions, *e.g.* for isopentane (primary, 1.0; secondary, 1.2; tertiary, 1.4). The selectivity is increased by aryl groups, halogens, and electron-withdrawing substituents on the carbene. In reactions with alkenes the double bond addition is the major reaction, with C—H bond insertion competing poorly and then only with the more reactive carbenes.

$$CH_3CH_2CH_3 \xrightarrow{:CH_2} CH_3CH_2CH_2CH_3 + (CH_3)_2CHCH_3 \qquad (47)$$

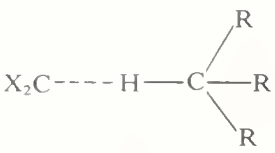


(48)

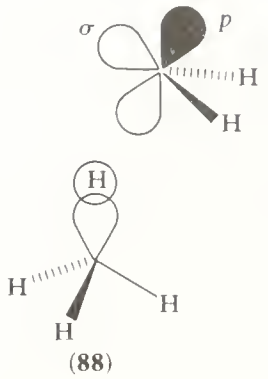
As with the addition reaction, either one-step concerted or two-step mechanisms are possible.[38] It is well established that singlet methylene inserts into C—H and Si—H bonds by the concerted process as shown, for example, by reactions at chiral centres when the configuration is retained. Two types of transition state for C—H insertion have been suggested, one involving a triangular approach (**86**) and the other an end-on attack along the line of the C—H bond (**87**). Calculations on the methylene/methane reaction indicate an electrophilic attack by the carbene with its empty *p*-orbital impinging on the hydrogen atom with slightly off-linear geometry (**88**) followed at *ca.* 300 pm by the methylene moving to one side, hydrogen transfer, and collapse to ethane geometry.[77] Intramolecular insertions, however, seem to favour those C—H bonds which can most easily attain a triangular-like transition state.



(86)



(87)



(88)

Although singlet carbenes react with C—H bonds by concerted insertion, it is now clear that they react with C—halogen bonds by abstraction, *e.g.* equation (49).[68] The singlet radical pair, which may be formed *via* an ylide, then couples to give the 'insertion' product, although it can also disproportionate.

$$R_2C\uparrow\downarrow \xrightarrow{CHCl_3} {}^{1}\overline{R_2\dot{C}Cl \qquad H\dot{C}Cl_2} \longrightarrow R_2ClCCHCl_2 \qquad (49)$$

$$R_2C\uparrow\uparrow \xrightarrow{CHCl_3} {}^{3}\overline{R_2\dot{C}H \qquad \dot{C}Cl_3} \longrightarrow R_2HCCCl_3 \qquad (50)$$

Triplet carbenes invariably insert by the abstraction–recombination mechanism (equation 50), as has been elegantly demonstrated by CIDNP studies[67,68] and by reactions with chiral compounds which give racemic products.[78] In general with halogen containing substrates, singlet carbenes react preferentially by halogen rather than by hydrogen abstraction, while the converse is true for triplets.

(*iii*) *Reactions with nucleophiles*

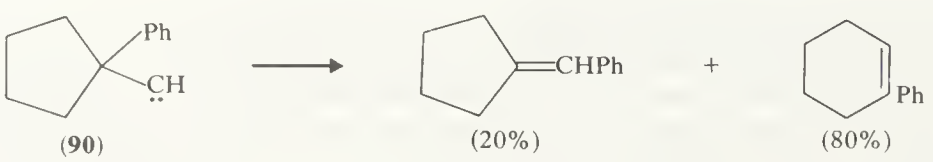
As expected for electron-deficient species, most carbenes react readily with heteroatoms carrying lone pair electrons to give ylides which may be isolable or may convert to products *via* the usual rearrangement, elimination, and cleavage reactions. Polarizable nucleophiles react very readily; for example, (**89**) reacts seven times faster with dimethyl sulphide than it does with cyclohexene (equation 51). Other examples of reactions involving ylides are given in references 47 and 79.

$$:C(CO_2Me)_2 \xrightarrow{Me_2S} Me_2\overset{+}{S}-\bar{C}(CO_2Me)_2 \qquad (51)$$

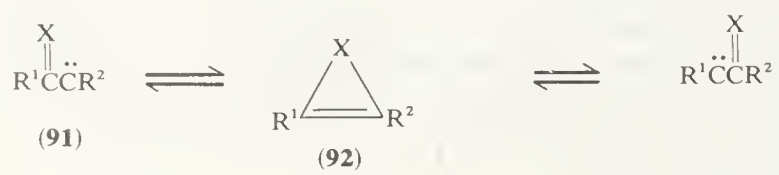
(**89**)

(*iv*) *Rearrangements*

1,2-Shifts in singlet carbenes are very common.[80–82] Hydrogen migrates very readily (equation 48) but alkyl and aryl groups, *e.g.* in (**90**) (equation 52), and RS and F also migrate. The reaction has been used in the synthesis of anti-Bredt alkenes.[83]

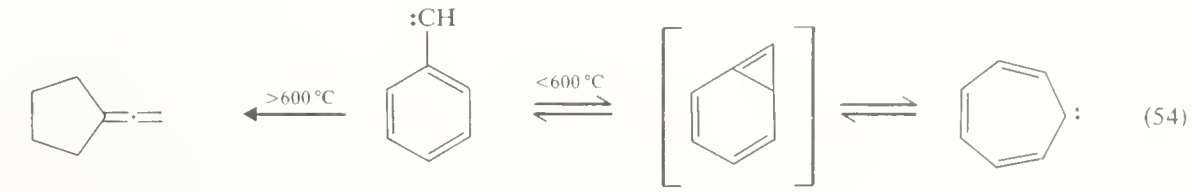


(**90**) (20%) (80%) (52)



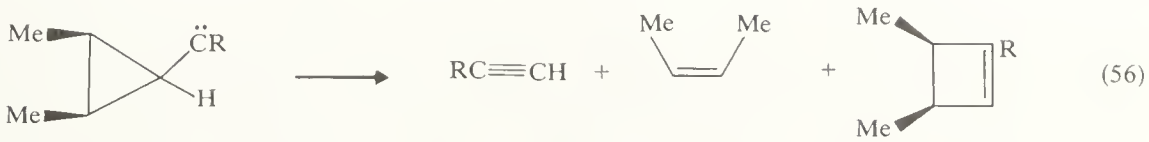
(**91**) (**92**) (53)

Carbenes with α,β-unsaturation, *e.g.* (**91**; X = O, NR, CR_2), can undergo carbene–carbene rearrangements *via* (**92**) under appropriate conditions (equation 53). When X = O the interconversion precedes the Wolff rearrangement for photolytically generated ketocarbenes.[84] Arylcarbenes also fall within this group and although they do not normally rearrange in solution, when subjected to flash vacuum pyrolysis at below 600 °C, they interconvert with aromatic carbenes (equation 54), and at higher temperatures they also ring contract, for example, to vinylidenecyclopentadiene.[83,85–88] Arylnitrenes undergo a superficially similar series of rearrangements (Chapter 6.6).



(54)

(55)

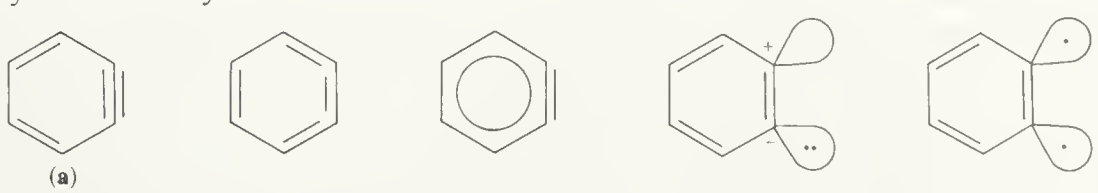


(56)

Other characteristic carbene rearrangements and fragmentations are the conversions of cyclopropenylidene to allene, cyclobutylidene to methylenecyclopropane,[47] and those exemplified in equations (55)[83] and (56).

2.8.3 ARYNES

Arynes are short-lived, highly reactive bifunctional intermediates formally derived by the removal of two *ortho* hydrogen atoms from an aromatic ring. Benzyne itself has been represented by various formulae (**93**), the most common being (**93a**), from which the 'yne' nomenclature is derived. Although the molecule does not contain the full triple bond shown in (**93a**), the name is appropriate since its chemistry is in many respects like that of a highly reactive alkyne.

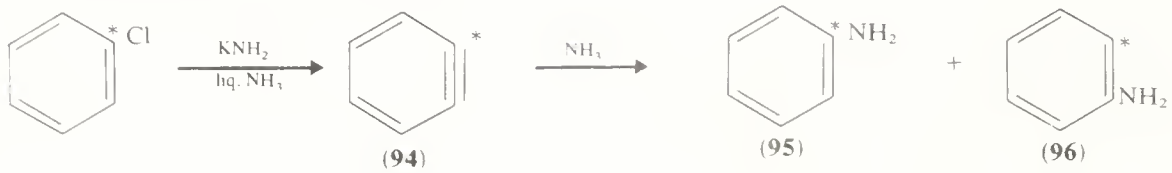


(**a**)

(**93**)

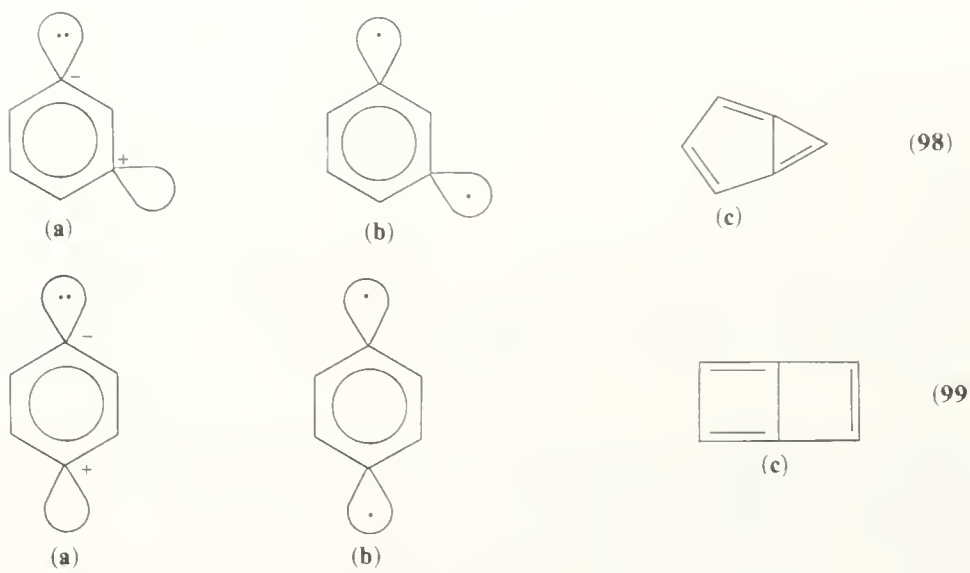
Although chemical reactions involving arynes had been carried out for over 100 years and there had been sporadic suggestions of the possibility of such intermediates, it was not until 1953 that conclusive proof for the existence of benzyne was obtained. At that time, J. D. Roberts solved the long-standing mechanistic puzzle of cine substitution in the reactions of aryl halides with metallic amides by using ^{14}C labelling to show that reaction occurred by an 'elimination–addition' mechanism (equation 57) involving first the formation of benzyne (**94**) and then addition of ammonia to give equal amounts of (**95**) and (**96**). Soon afterwards, Huisgen presented evidence for 1,2-naphthalyne and Wittig

showed that benzyne generated from fluorobromobenzene and lithium amalgam could be trapped by reaction with dienes such as furan (equation 58) to give the endoxide (**97**). These landmark publications initiated 20 years of extensive investigation into the formation and synthetic use of arynes.[89]



(94) (95) (96) (57)

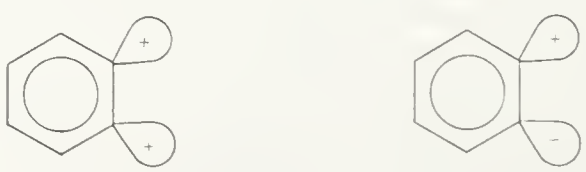
(97) (58)



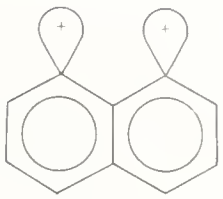
In contrast, the isomeric 1,3- and 1,4-dehydrobenzenes (**98**) and (**99**) have received comparatively little attention; although promising interesting chemistry, they have so far proved difficult to generate and have found little synthetic application. Although these species have often been called *m*- and *p*-benzyne, the nomenclature is hardly justified since they have no pretensions to either 'yne' structure or reactivity.

2.8.3.1 Structure and spectra

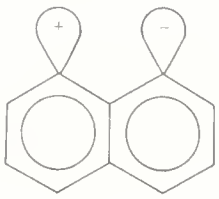
Benzyne can be pictured as having a weak, easily polarized third bond produced by overlap of the adjacent σ-hybrid orbitals at the dehydro-carbons. This interaction, which gives rise to a high-lying occupied S level (**100**) and a low-lying empty A level (**101**), is relatively inefficient but enough to ensure a singlet ground state. The configurations $(S)^2$ and $(A)^2$ mix strongly by configuration interaction and the singlet ground state has the form $C_1(S)^2+C_2(A)^2$ with $C_1>C_2$ so that it is primarily $(S)^2$ in character.[90] Recent calculations (MINDO/3) of its heat of formation agree well with the experimental value



(**100**) S- (**101**) A-



S-



A-

(102)

(491 ± 20 kJ mol^{-1}) and the molecule is predicted to have a short (acetylenic) C-1—C-2 bond and large 123 and 612 bond angles.[91] These results are supported by reactivity data and by the i.r. spectrum, which shows a —C≡C— absorption at 2085 cm^{-1}.[92]

Calculations suggest that 1,3-dehydrobenzene should also have strong bonding between the dehydro-carbons so that it is closer in structure to (**98c**) than to (**98b**) and that it should have a singlet ground state and stability comparable to benzyne.[91] In contrast to benzyne, the 1,3-dehydro species (**102**) is predicted[90] to have the A combination at lower energy than the S, which has important consequences on the stereochemistry of its cycloadditions (see Section 2.8.3.3). 1,4-Dehydrobenzene is predicted to have two energy minima corresponding to (**99b**) and (**99c**) separated by an energy barrier of 19 kJ mol^{-1}, with (**99b**) being *ca.* 79 kJ mol^{-1} more stable.[91]

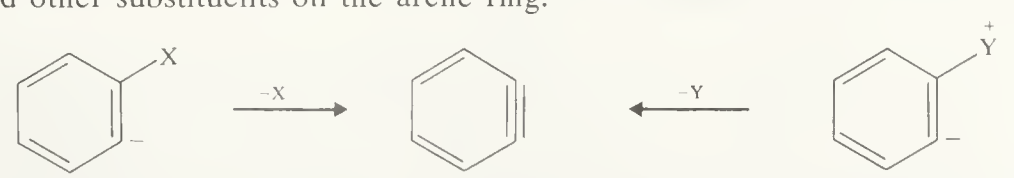
2.8.3.2 Generation

Much of the early work on aryne chemistry utilized the aryl halide–strong base route outlined above, but this imposed severe limitations on the reactions which could be studied since the generated aryne was often consumed rapidly by reaction with the base rather than reacting with any added reagent. Consequently, much effort has been expended on the development of aryne syntheses requiring non-basic, mild reaction conditions.

Routes to arynes fall into two main categories: (i) from aryl anions with an adjacent leaving group, and (ii) by the fragmentation of a cyclic system *ortho*-fused to the arene ring.

(*i*) *From aryl anions*

Aryne formation (equation 59) can occur by the loss of either an anion (**103**) or a neutral molecule (**104**). The most widely used anionic leaving groups are the halides; with the formation of the anion (**105**) by the reaction of a halogenoarene precursor with strong base (equation 60). This reaction is subject to competition from both direct nucleophilic substitution and from metal–halogen interconversion and, since both the metallation step (k_1) and halogen loss (k_2) are reversible, the partitioning between the various routes depends on many factors including the nature of the halogen and base, temperature, solvent, and other substituents on the arene ring.[89]



(59)

(103)

X = Halogen, OPh, OTs, ClO_3

(104)

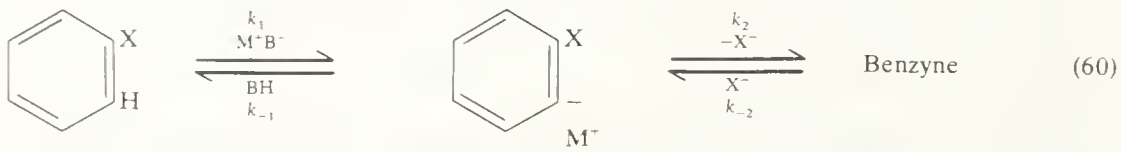
Y = N_2, NR_3, SR_2, IR

The metallation step (k_1) can be accomplished by a variety of bases; the weaker the base the higher is the temperature required. For example, the conversion of chlorobenzene to phenol using aqueous sodium hydroxide requires *ca.* 250 °C; the stronger potassium t-butoxide[93] is effective at *ca.* 150 °C while the powerful metal alkyls and aryls

are usually used at between −70 and 35 °C. The bases most often used, however, are the metallic amides, *e.g.* sodamide or lithium piperidide; these are adequately strong, convenient to prepare, and can be used either in inert solvents or in an excess of the parent amine, so a wide temperature range is available. Free amines, for example piperidine and *N,N,N′,N′*-tetramethylethylenediamine, also catalyse the reaction by increasing the cation solvation.[94] 'Complex bases' containing sodamide and an activating compound such as a sodium t-alkoxide are reported to have many advantages for the generation of arynes in inert solvents like THF.[95] The use of the highly hindered base lithium tetramethylpiperidide, which is less reactive to the generated aryne, results in better yields of products in both aryne–diene and aryne–nucleophile reactions.[96]

The rate of metallation (k_1) depends not only on base strength but also on the acidity of the hydrogen to be abstracted and thus on substituent inductive effects both of the adjacent halogen and of other ring substituents. The effect of the nature of the halogen is seen, for example, in the far faster metallation of fluorobenzene than of the other halobenzenes.

The rate of halide loss from (**105**) (k_2) also depends on many factors, particularly on the nature of the halogen, the metal, the solvent, and other ring substituents (equation 60). The dependence on the halides is as found in S_N1 and $E1$ reactions, I>Br>Cl>F; however, the same order also holds for the reverse (k_{-2}) reaction with the net effect that the k_2/k_{-2} equilibrium lies *ca.* three times further to the right for bromide than for iodide and chloride. The nature of the metal is also important; for example, when it is magnesium the intermediate is not only much more stable but fluoride is lost faster than the other halides owing to its better coordination to the magnesium. Substituent effects are as expected, those stabilizing the anion reduce k_2 and *vice versa.*

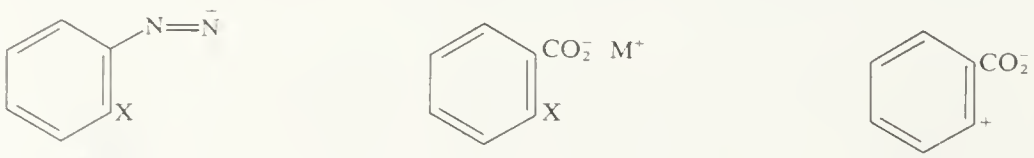


(60)

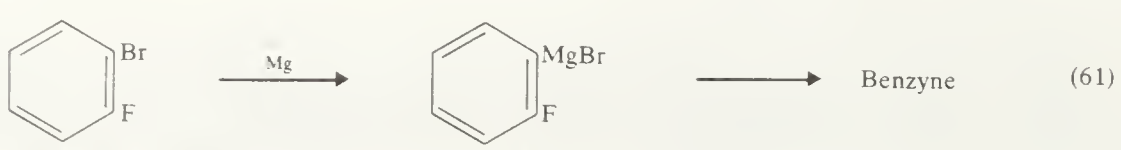
(**105**)

The nature of the solvent can be critical. If, for example, metallic amides are used as bases in the presence of an excess of the amine, then the rate of reprotonation is increased ($\propto$[BH]) and may become fast compared with halide elimination. Thus KNH_2/NH_3 is unsuitable for benzyne generation from fluorobenzene, although phenyl-lithium in an inert solvent works well. In ether solvents there is evidence that the benzyne is formed by a concerted β-elimination of lithium halide from a complex of the metallated aryl halide with the ether.[97]

There are several other routes to aryl anions which are applicable in aryne synthesis, *e.g. via* the di-imide (**106**) which can be generated from a number of precursors under relatively mild basic conditions. Decarboxylation of 2-halogenobenzoates (**107**) also leads to arynes but requires high temperatures; the potassium salt may decompose *via* (**108**) while the silver salts decompose by a radical route.



(**106**) (**107**) (**108**)



(61)

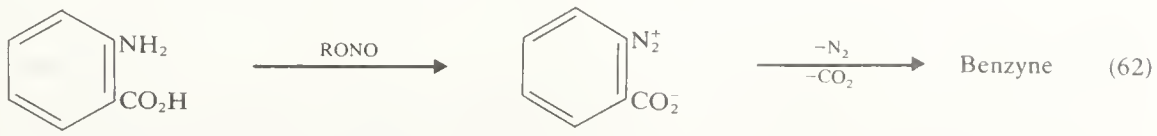
(**109**)

An important mild route to benzyne developed by Wittig involves aryl anion formation by metal–halogen exchange in the reactions of *o*-dihalogenobenzenes (**109**) with either lithium amalgam or magnesium (equation 61).

Some anionic leaving groups, other than halides, are listed in equation (59), but none have found much synthetic use because their leaving group ability is no better than bromide and the aryl halides are more readily available.

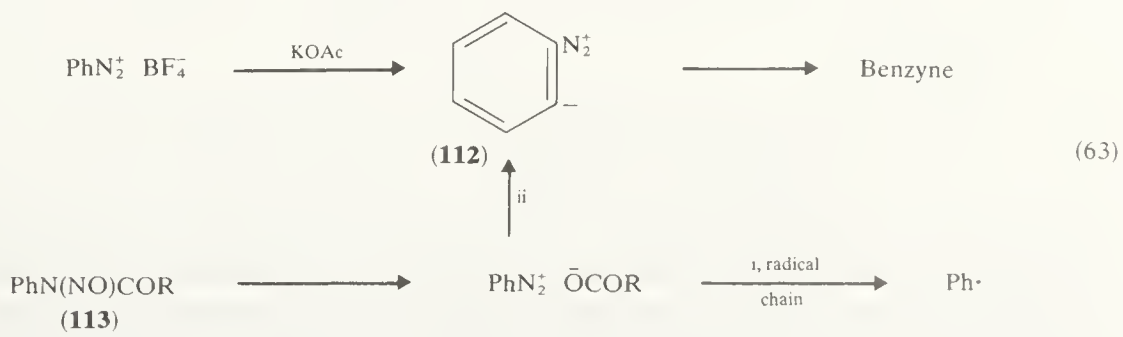
A number of neutral leaving groups are shown in (**104**) in equation (59). The most important is nitrogen. The adjacent anion is usually created by either proton abstraction or decarboxylation.

One of the major synthetic routes to benzyne has been developed from Stiles' discovery in 1960 that benzenediazonium-2-carboxylate (**111**) decomposes under mild conditions in the presence of benzyne traps to give adducts in high yield (equation 62).[98] The only drawback to this route, the extreme instability of (**111**) which made large-scale work inadvisable, was overcome by Friedman who used the *in situ* diazotization of anthranilic acid (**110**) with pentyl nitrite to generate the same intermediate safely.[99,100] For the synthesis of benzyne itself, for reaction with reagents other than strong nucleophiles, this is usually the method of choice but, for substituted arynes, the need to synthesize the substituted anthranilic acid makes the route less attractive.



(**110**) (**111**) (62)

The betaine (**112**) can be generated from diazonium salts by proton abstraction and since the diazonium group is so strongly activating, only mild bases such as potassium acetate are required.[101] Much work has been reported on the formation of arynes from diazonium carboxylates derived by rearrangement of *N*-nitrosoacylarylamines (equation 63).[102] The latter, *e.g.* (**113**), have been well known since the 1930s as sources of aryl radicals, but it was not discovered until the 1960s that they also form arynes in a competing heterolytic process. In aromatic solvents alone the reaction follows path (i) in which phenyl radicals are generated in a radical chain process and so phenylate the solvent to give the biaryl in yields up to 60%. However, the same reaction carried out in the presence of aryne traps gives adducts (path ii) in yields up to 80%, depending on the diene used. This diversion from path (i) → (ii) is specific to aryne traps which also function as radical chain inhibitors and so fulfil the dual role of suppressing the chain sequence (i), leaving (ii) as the main decomposition route.



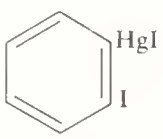
(63)

The addition of other radical traps, *e.g.* 1,1-diphenylethene, similarly promotes benzyne formation.[103] Since the precursor (**113**) can be prepared by *in situ* nitrosation with organic nitrites, this provides a convenient 'one-pot' route to benzyne and substituted arynes from the readily available aromatic amines.[104]

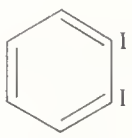
Of the other neutral leaving groups, iodobenzene is the most effective; for example, (**114**) heated at 160 °C in the presence of tetracyclone gives the benzyne adduct in 70% yield.

Suitable *o*-disubstituted benzenes, *e.g.* (**115**) and (**116**), can also lead to benzyne *via* radical rather than ionic routes.

(**114**)



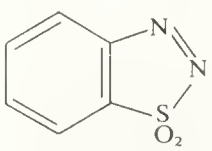
(**115**)



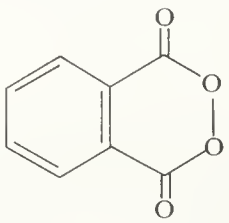
(**116**)

(ii) Fragmentation of cyclic systems

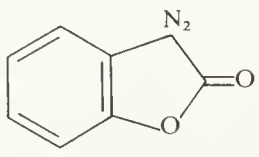
The disruption of ring systems *ortho*-fused to arenes can be accomplished either photochemically or thermally, the severity of the conditions ranging from sub-room temperature to flash vacuum pyrolysis at 1000 °C and obviously depending on the fragility of the precursor. Several such routes are suitable for the formation and synthetic use of benzyne in solution; for example, (**117**) decomposes thermally at *ca.* 20 °C or photochemically at −50 °C.[105] Phthaloyl peroxide (**118**) does not give benzyne on thermolysis but does on photolysis; triplet sensitization of this reaction still produces benzyne with characteristic ground-state singlet reactivity.[106] Compounds (**118**), (**119**), and (**120**) have all been used for the photochemical production of benzyne in matrices at low temperatures.[92,107] Obviously, ring systems which fragment easily, although ideal for benzyne generation, do present problems in synthesis and storage. This can be avoided by utilizing a relatively stable heterocyclic system with a chemical 'fuse' attached, *e.g.* 1-aminobenzotriazole (**121**), whose decomposition to benzyne is triggered by the oxidation of the amino group even at −80 °C (equation 64).[108] This reaction has been extended to the generation of substituted arynes, naphthalynes, phenanthryne, and dehydrobenzoquinone in excellent yields. Alternative fuses (**122**) avoid the use of oxidizing agents.[109,110]



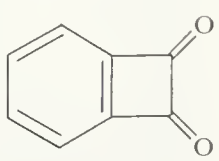
(**117**)



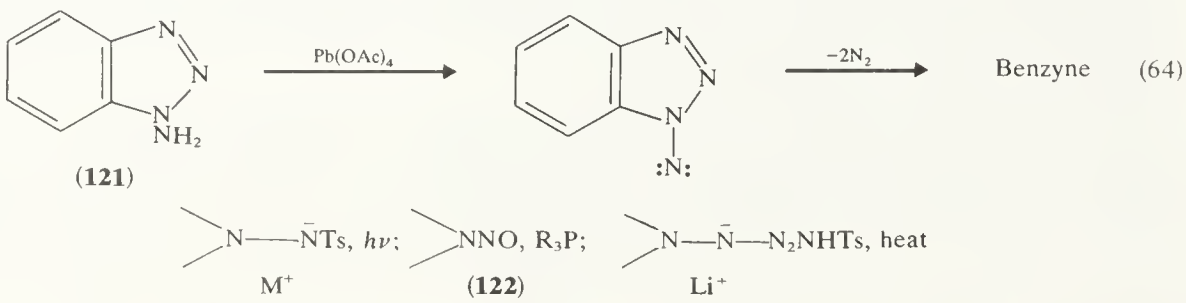
(**118**)



(**119**)



(**120**)

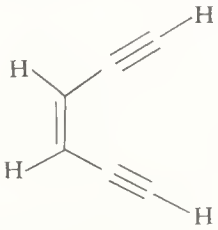


A large number of more stable ring systems, *e.g.* phthalic anhydride[111] and indane-1,2,3-trione,[112] give arynes on pyrolysis, usually flash vacuum pyrolysis, at high temperatures.

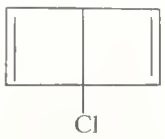
In contrast to the many routes now available to arynes, there are few to 1,3- and 1,4-dehydroarenes. By analogy with the efficient production of benzyne from (**111**), it might be expected that 1,3- and 1,4-benzenediazonium carboxylates would yield (**98**) and (**99**), but, although there is good mass spectrometric evidence that such species are produced by flash photolysis,[113] they do not appear to be formed in a major reaction path in the thermolysis of the related diazonium salts.[114]

However, there is good evidence for the intermediacy of 1,4-dehydrobenzene in the thermally induced reactions of (**123**); at 200 °C it apparently rearranges to (**99b**), which

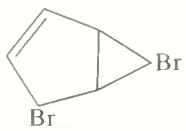
abstracts hydrogen or chlorine atoms from the solvent to give benzene or 1,4-dichlorobenzene.[115] This 1,4-benzenediyl is one of the two energy minima predicted by Dewar for 1,4-dehydrobenzene. The alternative, higher-energy, butalene form (**99c**), produced by the dehydrochlorination of (**124**), adds dimethylamine to give *N,N*-dimethylaniline.[116]



(**123**)



(**124**)

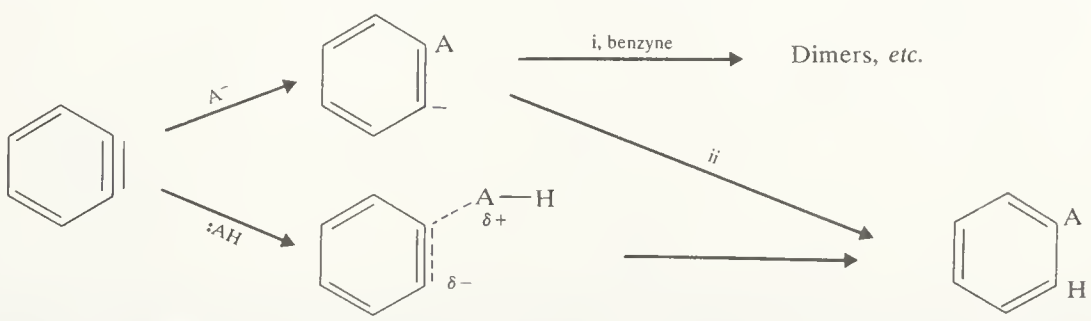


(**125**)

No certain route to 1,3-dehydrobenzene is yet available; the involvement of (**98c**), the bicyclo[3,1,0]hexatriene form, in the dehydrobromination of (**125**) is possible, but so are alternative mechanisms.[117] However, the 1,8-dehydronaphthalene (**102**) can readily be prepared by an extension of the aminotriazole route to benzyne.[118]

2.8.3.3 Reactions

Arynes are highly reactive towards nucleophilic attack (equation 65).[89] The aryl anion produced in the first step can take several possible paths: (i) add to further molecules of the aryne to give polymeric products; (ii) abstract a proton from any acidic enough species present, such as the solvent or the conjugate acid of the anion, to give the adduct (**126**); (iii) be quenched or trapped at the end of the reaction by an added reagent such as benzophenone or carbon dioxide. The conjugate acid of the nucleophile, if it is itself a nucleophile (*e.g.* ROH, RSH, RNH_2), can also add directly to the aryne *via* transition state (**127**), which then undergoes inter- or intra-molecular proton shift to give (**126**).[119]



(**127**) (**126**) (65)

e.g. $A^- = H^-$, $R\bar{N}H$, RO^-, RCO_2^-, Ar^-, R^-, enolates, halides, $^-PR_2$, $(RO)_2PO^-$, RS^-

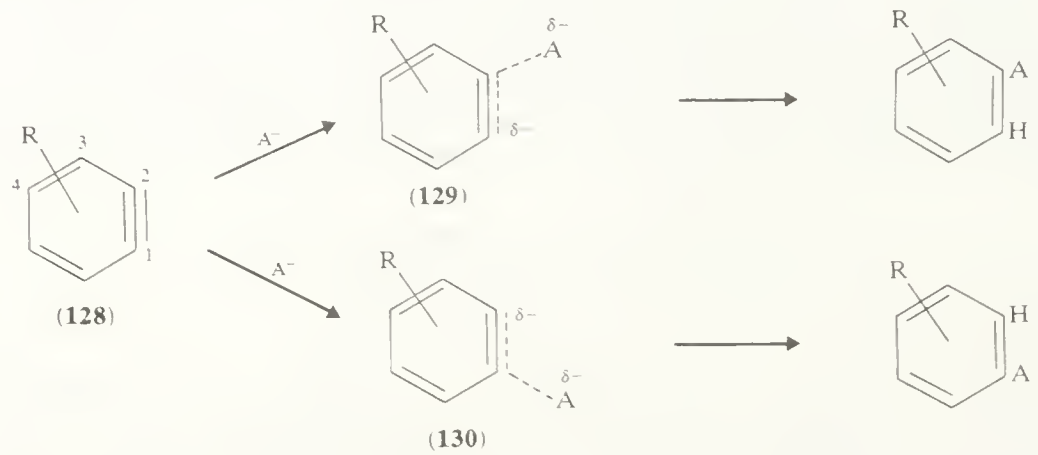
Since the easily polarized dehydro bond in benzyne gives it 'soft' acid character, its reactivity towards nucleophiles depends much on their polarizability.[89] The order of nucleophilicity shown below for various species does not, therefore, parallel exactly the order of their basicity.

(1) $BuLi > PhSLi > PhLi > Et_2NLi >$ Li piperidide $> PhNMeLi > PhC{\equiv}CLi > (C_6H_{11})_2NLi \gg ROLi$, ArOLi, for 9,10-phenanthryne in ether.
(2) $PhS^- \approx Ph_3C^- > PhC{\equiv}C^- \approx$ enolates $> PhO^- > RO^-$, I^-, CN^-, for benzyne in liquid ammonia.
(3) $I^- > Br^- > Cl^- >$ EtOH, for benzyne in alcohol.

This difference between nucleophilicity and basicity is very important in the synthesis of adducts using arynes generated from alkyl halides. The reaction is straightforward if the

anion to be added is both a strong enough base to generate the aryne and also has a conjugate acid with acidic enough hydrogens to make step (ii) easy. The adduct can then be obtained in high yield by carrying out the reaction in an excess of the conjugate acid, *e.g.* the amination of aryl halides. Difficulty arises, however, if the anion is too weak a base to generate the aryne. This can be solved for strongly nucleophilic anions by adding a catalytic amount of a strong base (*e.g.* NH_2^-) which is a weaker nucleophile; this serves to generate the aryne but is not consumed rapidly in a product-forming step. This technique has been used for the arynic phenylation of, for example, aromatic and aliphatic amines, thiols, and benzylic, enolate, and other stabilized carbanions using sodamide as the metallating agent. For anions which are both weak bases and weak nucleophiles (*e.g.* ROH, RCO_2H, RCO_2^-), it is usual to utilize a non-basic route to the aryne.

In reactions with monosubstituted arynes (**128**) the nucleophile can add to either end of the dehydro bond (equation 66). The ratio of isomers obtained depends primarily on the electronic effects of the substituent R and to a lesser degree on steric factors and the nucleophilicity of the reagent. The reacting dehydro bond is orthogonal to the π-system of the aryne ring and so is influenced mainly by the inductive effect of the substituent and less so by its mesomeric effect. Not surprisingly, therefore, the substituent exerts a much stronger orienting effect when in the 3-position than in the 4-position. The rate-determining transition states for nucleophilic addition can be visualized as (**129**) and (**130**); note that each has partial aryl anion character, and the preferred path will be *via* the one which is either more stabilized or less destabilized by the substituent, *i.e. via* (**129**) for $+I$ substituents and (**130**) for $-I$ substituents. This effect is somewhat modified by the substituents M effect, particularly when the nucleophile has a lone pair which can interact with the π-system of the aryne.

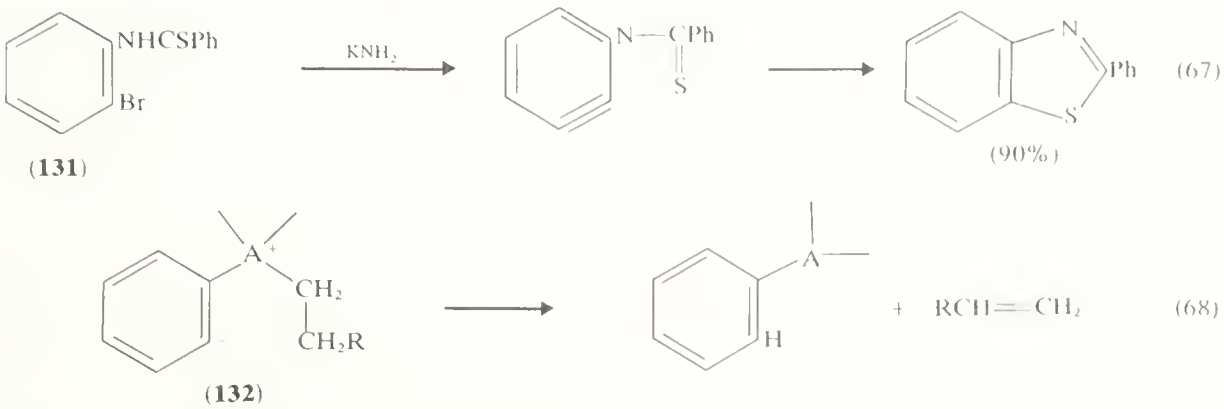


(66)

The isomer ratio also depends on the nucleophilicity of the attacking reagent. For example, Bunnet has shown that, for addition to 4-chlorobenzyne, the weak nucleophile methanol shows high selectivity ($k_p/k_m = 4.73$) compared with the reactive methoxide ion ($k_p/k_m = 1.91$).[119] This is due to the difference in the degree of bonding in the transition states. The bond to the ring will be more fully developed in the transition state for weak nucleophiles and consequently there will be more negative charge transferred to the ring carbon and so greater discrimination between the alternative reaction paths. The more reactive the nucleophile, the less will be the substituent orienting effect; for example, NH_2^-, a more powerful nucleophile than methoxide, is non-selective and gives $k_m/k_p = 1$.

Steric interactions also influence the isomer ratio; for example, in 3-substituted arynes the proportion of the *meta* isomer increases with increasing bulk of either substituent or nucleophile. The *peri* hydrogens also impede the approach of bulky nucleophiles to 1,2-naphthalyne and 9,10-phenanthyne.

Intramolecular addition of C, N, O, and S nucleophiles to the aryne bond has proved to be an important synthetic route[89] to a wide range of cyclic compounds with ring sizes from four to seventeen, *e.g.* the reaction of (**131**) in equation (67). Note that even O nucleophiles add in preference to the amide catalyst in intramolecular reactions.



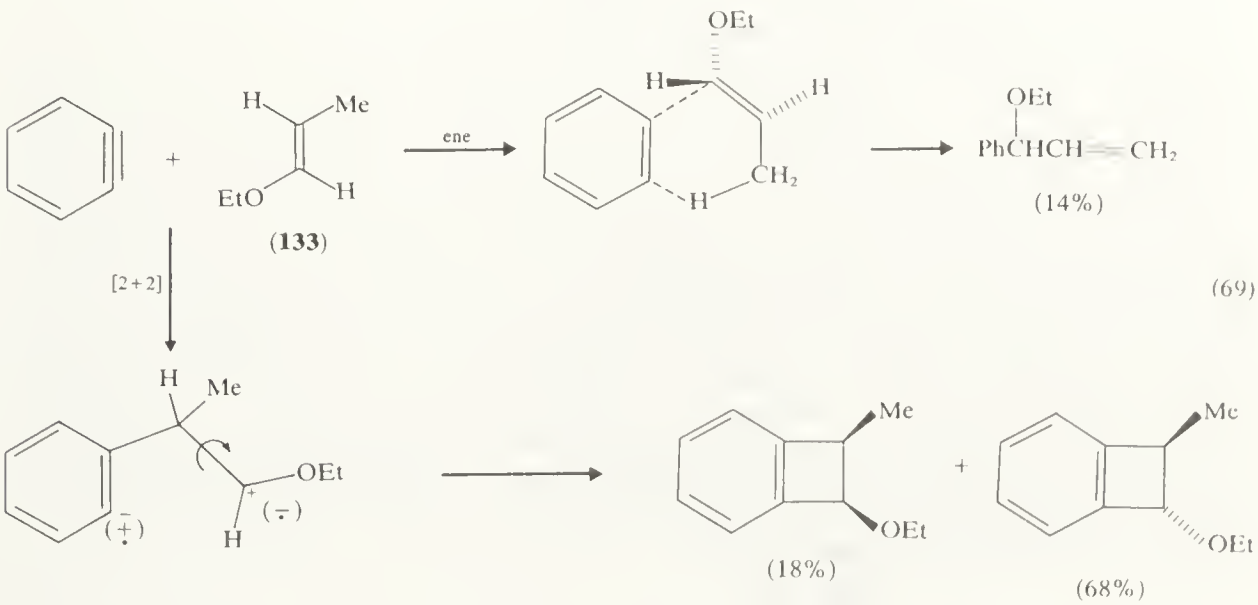
(131)

(132)

Neutral nucleophiles with no hydrogen attached to the nucleophilic atom react with arynes to give betaines (**132**), but cannot react further by proton transfer to give adducts and instead convert to products *via* various elimination or rearrangement reactions, or by interception with a trapping reagent. Space limitations prevent a discussion of the many reaction paths except to note the elimination to give alkenes (equation 68) is a major reaction if β hydrogens are present; or the betaine can convert to an ylide which may then undergo the Stevens rearrangement or a formal α-elimination.[89]

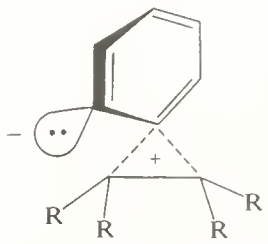
Arynes also react by electrophilic addition; for example, with Br_2, I_2, and ICl, and with organic derivatives of mercury, silicon, tin, boron, and phosphorus.[89]

As might be expected for such highly reactive species, arynes also combine readily with simple alkenes and a variety of other unsaturated systems. In general, however, the reactions are slower than the reactions with strong nucleophiles and so for optimum yields the generation of the aryne by non-basic methods is preferred.



Benzyne reacts exothermically with alkenes, *e.g.* (**133**), both by [2+2] cycloaddition and also by the 'ene' reaction if the alkene has an allylic hydrogen (equation 69). The cycloaddition is non-stereospecific in that each of the pure *cis*- or *trans*-alkenes gives both *cis* and *trans* products, but is somewhat stereoselective since the major product in each case retains the stereochemistry of the alkene.[120,121] This indicates a stepwise reaction occurring *via* an intermediate, which could be either a dipolar or a diradical species, with a lifetime at least long enough to allow some bond rotation before formation of the second bond to the ring. There has been much conjecture about the diradical or dipolar nature of the intermediate and several groups have concluded that, for simple unsubstituted alkenes at least, the lack of rearrangements in the intermediate and absence of solvent effects point to diradical character.[122] The stepwise nature of the reaction is

consistent with benzyne having a symmetrical singlet ground state, so precluding a concerted $[_{\pi}2_s + _{\pi}2_s]$ approach.[120] Recent calculations have found that the potential energy surface for the benzyne–ethylene reaction is complex with three distinct valleys, one of which is a *cul-de-sac* and is interpreted as representing an intermediate like (**134**) which converts to the benzocyclobutene product by a complex rotation and relaxation.[123]



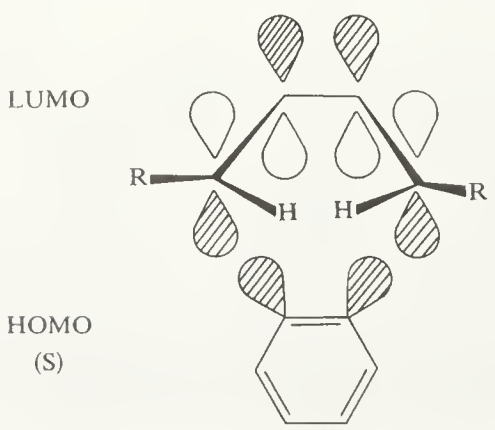
(**134**)

The 'ene' reaction is often competitive with the [2+2] cycloaddition, its relative rate depending much on the substitution and stereochemistry of the alkene, *e.g.* the *cis*-isomer of (**133**) gave only 1% of the 'ene' product. There is much evidence that the reaction is concerted and that it is facilitated if the alkene can easily attain a conformation with a minimum torsional angle between C-3—H bond and the C-2 *p*-orbital about the C-2—C-3 bond.[124]

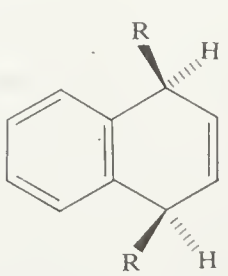
Alkynes also undergo [2+2] cycloaddition, giving an unstable benzocyclobutadiene which either dimerizes or reacts with another molecule of benzyne and thence converts to products by rearrangements.[89] 'Ene' reactions to give allenes also occur, but in low yield.

Arynes dimerize to biphenylenes if they are present in high enough concentration in an unreactive solvent. The best yields (>80%) are obtained from the oxidation of (**121**) and provide a valuable synthetic route to this system.

Arynes are very reactive dienophiles giving Diels–Alder adducts, *e.g.* (**97**), often in very high yield with a wide range of dienes.[89] These reactions have often been used in mechanistic studies as a diagnostic test for the presence of arynes, particularly using tetracyclone, furan, or 1,3-diphenylisobenzofuran, all of which give high yields. The [4+2] cycloaddition is stereospecific, *i.e.* it gives only the *cis* adduct (**136**) and so must be concerted (equation 70). This is consistent with a symmetrical singlet ground state for benzyne and an 'allowed' concerted reaction which is suprafacial on both benzyne and diene components (**135**). That this reaction is in fact concerted is supported by several observations that its rate depends on the ease with which the diene can attain the *cis* planar conformation required for maximum orbital overlap in (**135**); compounds in which the *cis* planar conformation is sterically destabilized give very little [4+2] adduct, the benzyne either dimerizing or reacting by the alternative [2+2] mode.[120,125] Similarly, in cyclic dienes the yield of the [4+2] adduct is related to the torsional angle between the two double bonds (**137**), *e.g.* in cycloheptatriene where the angle is large (40°) only [2+2] and 'ene' products are obtained, while cycloheptadiene ($\theta = 20$–$25°$) gives the [4+2] (70%) and [2+2] (28%) adducts.[124,126]

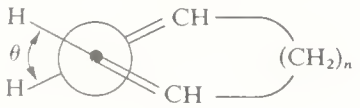


(**135**)



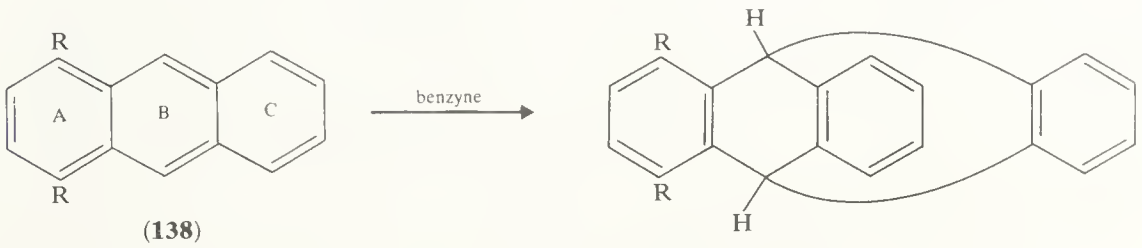
(**136**)

(70)

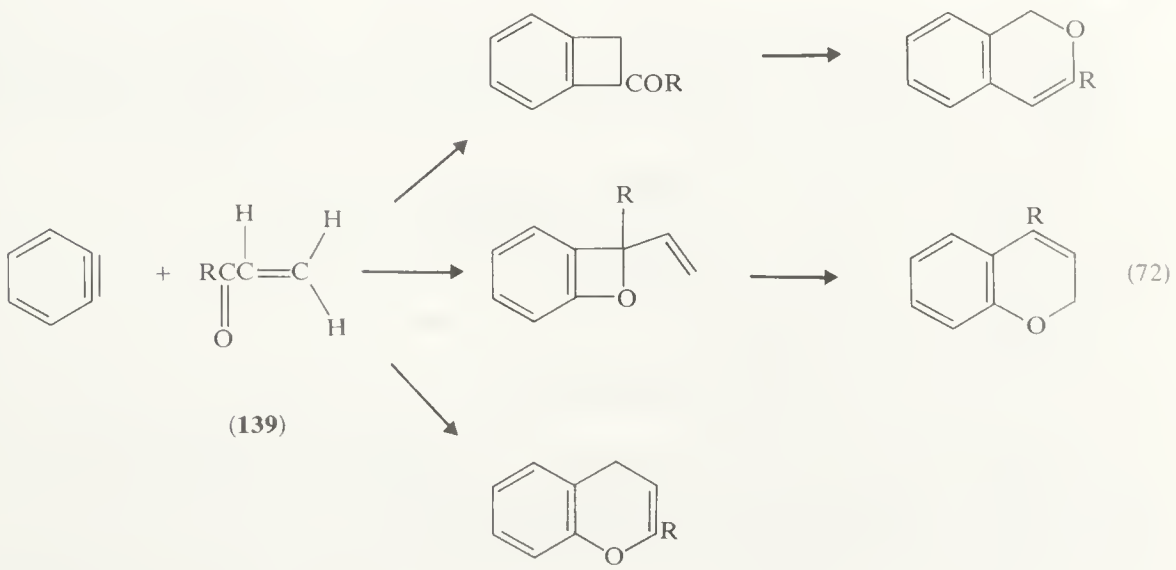


(**137**)

As expected for an electrophilic species like benzyne, the reactivity of the diene is increased by electron-donating groups and reduced by electron-withdrawing groups. An interesting example is provided by the relative reactivity of the two rings in anthracene (**138**), shown in equation (71). For unsubstituted anthracene (**138**; R = H) the relative reactivity of the A ring is low (B/A = 30), but when R = OMe it is raised to give B/A = 2.4. This competition between A and B ring addition has been used to show that the benzynes produced from a wide variety of precursors have identical reactivity and therefore are true, independent intermediates.[127] The reactivity of dienes towards benzyne generally parallels that towards other reactive dienophiles like maleic anhydride, but benzyne is less selective owing to its higher reactivity. Other differences are attributable to different steric interactions in the transition state arising from the perpendicular approach of benzyne (**135**) as distinct from the parallel approach of alkene-type dienophiles.[127]



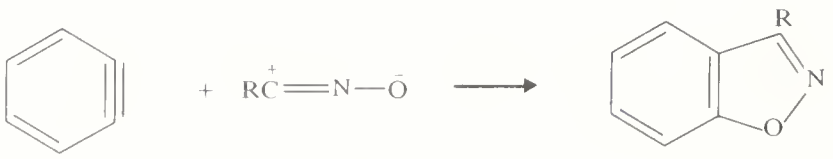
(**138**) (71)



(**139**) (72)

α,β-Unsaturated carbonyl compounds (**139**) can react by [2+2] cycloaddition to either the carbonyl or the alkene bond or by [4+2] cycloaddition, depending on the reactivity of the carbonyl group (equation 72).[128]

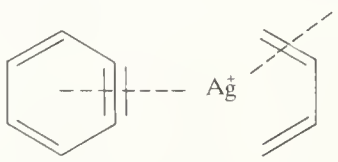
As would be expected, benzyne also reacts with a wide range of 1,3-dipoles, *e.g.* (**140**), to provide an important synthetic route to five-membered heterocyclic compounds with an annelated benzene ring (equation 73).[89]



(140) (73)

Benzyne is reactive enough to give both [2+2] and [4+4] cycloadditions and 'ene' reactions with aromatic compounds; the yields of the cycloaddition products are low for benzyne itself but the more electrophilic tetrahalobenzynes give [4+2] adducts in high yield.[129]

The presence of low concentrations of Ag^+ ions has a major effect on the partitioning between the various modes of reaction between benzyne and unsaturated molecules, *e.g.* in the absence of silver ions, benzyne reacts with cycloheptatriene to give the 'ene' product and the [2+2] adduct, while in the presence of silver ions only the [4+2] adduct is obtained.[130] The silver-modified reactions are thought to involve a benzyne–silver–alkene complex such as (**141**). Cycloadditions of the 1,3-dehydro species (**102**) have also been studied; unlike benzyne, it undergoes concerted stereospecific addition to alkenes, as would be expected from the predicted A symmetry of its HOMO.[118,131] Thus in reactions with conjugated dienes, *e.g.* cyclopentadiene, 1,2-addition is preferred (47%) over 1,4-addition (9%) but, unpredictably, a 1,3-adduct is also formed in substantial amount (44%). Both it and the 1,4-adduct are probably formed in a stepwise radical process.[132,133]



(**141**)

References

1. Comprehensive treatment will be found in: (a) D. C. Nonhebel and J. C. Walton, 'Free Radical Chemistry', Cambridge University Press, 1974; (b) J. M. Hay, 'Reactive Free Radicals', Academic, New York, 1974; (c) J. K. Kochi, 'Free Radicals', Wiley, New York, 1973; (d) G. Sosnovsky, 'Free Radical Reactions in Preparative Organic Chemistry', Macmillan, New York, 1964; (e) 'Free Radicals in Biology', ed. W. A. Pryor, Academic, New York, 1976.
2. J. C. Evans and P. J. Emes, *MTP Internat. Rev. Sci., Org. Chem. Ser. One*, 1973, **10,** 293.
3. H. Lankamp, W. Th. Nauta, and C. MaClean, *Tetrahedron Letters*, 1968, 249.
4. D. H. Hey and W. A. Waters, *Chem. Rev.*, 1937, **21,** 202.
5. M. S. Kharasch, H. Engelmann, and F. R. Mayo, *J. Org. Chem.*, 1937, **2,** 288.
6. P. J. Flory, *J. Amer. Chem. Soc.*, 1937, **59,** 241.
7. J. K. Kochi, *Adv. Free Radical Chem.*, 1975, **5,** 189; H. Fischer, in 'Free Radicals', ed. J. K. Kochi, Wiley, New York, 1973, vol. II, chapter 19.
8. R. Kaptein, *Adv. Free Radical Chem.*, 1975, **5,** 319.
9. (a) A. L. J. Beckwith, *MTP Internat. Rev. Sci., Org. Chem. Ser. One*, 1973, **10,** 1; (b) C. Rüchardt, *Angew. Chem. Internat. Edn.*, 1970, **9,** 830.
10. (a) D. Griller and K. U. Ingold, *Accounts Chem. Res.*, 1976, **9,** 13; (b) A. R. Forrester, J. M. Hay, and R. H. Thomson, 'Organic Chemistry of Stable Free Radicals', Academic, New York, 1968.
11. D. M. Golden and S. W. Benson, *Chem. Rev.*, 1969, **69,** 125.
12. L. Kaplan, in 'Free Radicals', ed. J. K. Kochi, Wiley, New York, 1973, vol. II, chapter 18.
13. (a) J. C. Martin, in 'Free Radicals', ed. J. K. Kochi, Wiley, New York, 1973, vol. II, chapter 20; (b) ref. 1(a), p. 128.
14. E. S. Huyser, 'Free Radical Chain Reactions', Wiley, New York, 1970.
15. T. Koenig, in 'Free Radicals', ed. J. K. Kochi, Wiley, New York, 1973, vol. I, chapter 3.
16. R. J. Drewer, in 'The Chemistry of the Hydrazo, Azo, and Azoxy Groups', ed. S. Patai, Wiley, New York, 1975, part 2, chapter 20.
17. (a) C. S. Rondestvedt, *Org. Reactions.*, 1976, **24,** 225; (b) R. O. C. Norman and W. A. Waters, *J. Chem. Soc.*, 1958, 167; J. I. G. Cadogan, *Pure. Appl. Chem.*, 1967, **15,** 153.
18. J. I. G. Cadogan, *Accounts Chem. Res.*, 1971, **4,** 186.

19. (a) J. I. G. Cadogan, *J. Chem. Soc.*, 1962, 4257; (b) J. I. G. Cadogan, D. A. Roy and D. M. Smith., *J. Chem. Soc. (C)*, 1966, 1249; (c) L. Friedman and J. F. Chlebowski, *J. Org. Chem.*, 1968, **33,** 1633, (d) I. P. Gragerov, A. F. Levit, L. A. Kiprianova and A. L. Buchachenko, *Org. Magn. Resonance*, 1973, **5,** 445; (e) P. Hassanaly, G. Vernin, H. J. M. Dou, and J. Metzger, *Bull. Soc. chim. France*, 1974, 560; (f) S. H. Korzeniowski and G. W. Gokel, *Tetrahedron Letters*, 1977, 3519.
20. (a) L. Fisera, J. Kovac, E. Komanova, and J. Lesko, *Tetrahedron*, 1974, **30,** 4123; (b) J. I. G. Cadogan, R. G. M. Landells, and J. T. Sharp, *J.C.S. Perkin I*, 1977, 1841.
21. (a) R. H. Hesse, *Adv. Free Radical Chem.*, 1969, **3,** 83; (b) D. H. R. Barton, *Pure Appl. Chem.*, 1968, **16,** 1.
22. (a) W. V. Sherman, *Adv. Free Radical Chem.*, 1969, **3,** 1; (b) A. J. Swallow, *MTP Internat. Rev. Sci., Org. Chem. Ser. One*, 1973, **10,** 263.
23. G. A. Russell, in 'Free Radicals', ed. J. K. Kochi, Wiley, New York, 1973, vol. I, chapter 7.
24. A. Nechvatal, *Adv. Free Radical Chem.*, 1972, **4,** 175.
25. M. L. Poutsma, in 'Free Radicals', ed. J. K. Kochi, Wiley, New York, 1973, vol. II, chapter 14.
26. P. I. Abell, in 'Free Radicals', ed. J. K. Kochi, Wiley, New York, 1973, vol. II, chapter 13.
27. (a) C. Walling and E. S. Huyser, *Org. Reactions.*, 1963, **13,** 91; (b) F. W. Stacey and J. F. Harris, *ibid.*, 1963, **13,** 150.
28. H. W. Sidebottom, J. M. Tedder, and J. C. Walton, *Internat. J. Chem. Kinetics*, 1972, **4,** 249.
29. J. M. Tedder and J. C. Walton, *Trans. Faraday Soc.*, 1966, **62,** 1859.
30. J. M. Tedder and J. C. Walton, *Accounts Chem. Res.*, 1976, **9,** 183.
31. P. S. Skell and K. J. Shea, in 'Free Radicals', ed. J. K. Kochi, Wiley, New York, 1973, vol. II, chapter 26.
32. (a) M. Julia, *Accounts Chem. Res.*, 1971, **4,** 386; (b) J. W. Wilt, in 'Free Radicals', ed. J. K. Kochi, Wiley, New York, 1973, vol. I, chapter 8.
33. (a) M. J. Perkins, in 'Free Radicals', ed. J. K. Kochi, Wiley, New York, 1973, vol. II, chapter 16; (b) R. Bolton and G. H. Williams, *Adv. Free Radical Chem.*, 1975, **5,** 1.
34. K. C. Bass and P. Nababsing, *Adv. Free Radical Chem.*, 1972, **4,** 1.
35. R. A. Abramovitch, *Adv. Free Radical Chem.*, 1967, **2,** 87.
36. K. U. Ingold, in 'Free Radicals', ed. J. K. Kochi, Wiley, New York, 1973, vol. I, chapter 2.
37. T. Koenig and H. Fischer, in 'Free Radicals', ed. J. K. Kochi, Wiley, New York, 1973, vol. I, chapter 4.
38. P. P. Gaspar and G. S. Hammond, in 'Carbenes', ed. R. A. Moss and M. Jones, Wiley, New York, 1975,
39. J. F. Harrison, in 'Carbene Chemistry', ed. W. Kirmse, Academic, New York, 2nd edn., 1971, p. 159; *Accounts Chem. Res.*, 1974, **7,** 378.
40. N. Bodor, M. J. S. Dewar, and J. S. Wasson, *J. Amer. Chem. Soc.*, 1972, **94,** 9095.
41. J. Hine, 'Divalent Carbon', Ronald Press, New York, 1964.
42. G. L. Closs, *Topics Stereochem.*, 1968, **3,** 193.
43. R. A. Moss and U. H. Dolling, *J. Amer. Chem. Soc.*, 1971, **93,** 954.
44. W. H. Pirkle and G. F. Koser, *Tetrahedron Letters*, 1968, 3959.
45. K. E. Krajca and W. M. Jones, *Tetrahedron Letters*, 1975, 3807.
46. P. S. Skell, S. J. Valenty, and P. W. Humer, *J. Amer. Chem. Soc.*, 1973, **95,** 5041.
47. W. Kirmse, in 'Carbene Chemistry', ed. W. Kirmse, Academic, New York, 2nd edn., 1971.
48. R. A. Moss, in 'Carbenes', ed. R. A. Moss and M. Jones. Wiley, New York, 1973, vol. I, p. 153.
49. W. J. Baron, M. R. DeCamp, M. E. Hendrick, M. Jones, R. H. Levin, and M. B. Sohn, in 'Carbenes', ed. R. A. Moss and M. Jones, Wiley, New York, 1973, vol. I, p. 1.
50. H. Dürr, *Fortsch. Chem. Forsch.*, 1975, **55,** 87.
51. R. H. Levin and M. Jones, *Tetrahedron*, 1971, **27,** 2031.
52. J. Casanova and B. Waegell, *Bull. Soc. chim. France*, 1975, 922.
53. R. H. Shapiro, *Org. Reactions*, 1976, **23,** 405.
54. T. Aratani, Y. Yoneyoshi, and T. Nagase, *Tetrahedron Letters*, 1975, 1707.
55. R. W. Hoffmann, *Angew. Chem. Internat. Edn.*, 1971, **10,** 529.
56. G. W. Griffin and N. R. Bertoniere, in 'Carbenes', ed. R. A. Moss and M. Jones, Wiley, New York, 1973, vol. I, p. 305.
57. S. S. Hixson, *J. Amer. Chem. Soc.*, 1973, **95,** 6144.
58. E. V. Dehmlow, *Angew. Chem. Internat. Edn.*, 1974, **13,** 170.
59. R. A. Jones, *Aldrichim. Acta*, 1976, **9,** 35.
60. S. L. Regen, *J. Org. Chem.*, 1977, **42,** 875.
61. G. Köbrich, *Angew. Chem. Internat. Edn.*, 1972, **11,** 473.
62. R. A. Moss, M. A. Joyce, and F. G. Pilkiewicz, *Tetrahedron Letters*, 1975, 2425.
63. D. Seyferth, *Accounts Chem. Res.*, 1972, **5,** 65; and in 'Carbenes', ed. R. A. Moss and M. Jones. Wiley, New York, 1975, vol. II, p. 101.
64. H. Simmons, T. L. Cairns, S. A. Vladuchick, and C. M. Hoiness, *Org. Reactions*, 1973, **20,** 1.
65. S. Miyano and H. Hashimoto, *Bull. Chem. Soc. Japan.*, 1973, **46,** 892.
66. G. L. Closs and B. E. Rabinow, *J. Amer. Chem. Soc.*, 1976, **98,** 8190.
67. G. L. Closs, in 'Carbenes', ed. R. A. Moss and M. Jones, Wiley, New York, 1975, vol. II, 159.
68. H. D. Roth, *Accounts Chem. Res.*, 1977, **10,** 85.
69. A. P. Marchand, in 'The Chemistry of Double-bonded Functional Groups', Supplement A, ed. S. Patai, Wiley, New York, 1977, part 1, chapter 7.
70. R. Hoffmann, D. M. Hayes, and P. S. Skell, *J. Phys. Chem.*, 1972, **76,** 664.

71. R. A. Moss and C. B. Mallon, *J. Amer. Chem. Soc.*, 1975, **97,** 344.
72. H. Dürr, *Fortschr. Chem. Forsch.*, 1973, **40,** 103.
73. R. A. Moss, in 'Selective Organic Transformations', ed. B. S. Thyagarajan, Wiley, New York, 1970, vol. I, p. 35.
74. R. Hoffmann, C. C. Levin, and R. A. Moss, *J. Amer. Chem. Soc.*, 1973, **95,** 629.
75. H. Fujimoto and R. Hoffmann, *J. Phys. Chem.*, 1974, **78,** 1167.
76. C. W. Jefford, J. Mareda, J.-C. E. Gehret, T. Kabenegele, W. D. Graham, and U. Burger, *J. Amer. Chem. Soc.*, 1976, **98,** 2585.
77. R. C. Dobson, D. M. Hayes, and R. Hoffmann, *J. Amer. Chem. Soc.*, 1971, **93,** 6188.
78. D. Bethell and K. McDonald, *J.C.S. Chem. Comm.*, 1974, 467.
79. W. Ando, *Accounts Chem. Res.*, 1977, **10,** 179.
80. J. A. Altmann, I. G. Csizmadia, and K. Yates, *J. Amer. Chem. Soc.*, 1975, **97,** 5217.
81. E. P. Kyba and C. W. Hudson, *J. Amer. Chem. Soc.*, 1976, **98,** 5696.
82. Y. Yamamoto, S. I. Murahashi, and I. Moritani, *Tetrahedron*, 1975, **31,** 2663.
83. M. Jones, *Accounts Chem. Res.*, 1974, **7,** 415.
84. J. Fenwick, G. Frater, K. Ogi, and O. P. Strausz, *J. Amer. Chem. Soc.*, 1973, **95,** 124.
85. C. Wentrup, *Fortschr. Chem. Forsch.*, 1976, **62,** 173.
86. T. T. Coburn and W. M. Jones, *J. Amer. Chem. Soc.*, 1974, **96,** 5218.
87. W. E. Billups and L. E. Recd, *Tetrahedron Letters*, 1977, 2239.
88. C. Wentrup, E. Wentrup-Byrne, and P. Müller, *J.C.S. Chem. Comm.*, 1977, 210.
89. R. W. Hoffmann, 'Dehydrobenzene and Cycloalkynes', Academic, New York, 1967.
90. R. Hoffmann, A. Imamura, and W. J. Hehre, *J. Amer. Chem. Soc.*, 1968, **90,** 1499.
91. M. J. S. Dewar and W.-K. Li, *J. Amer. Chem. Soc.*, 1974, **96,** 5569.
92. O. L. Chapman, C.-C. Chang, J. Kolc, N. R. Rosenquist, and H. Tomioka, *J. Amer. Chem. Soc.*, 1975, **97,** 6586.
93. J. I. G. Cadogan, J. K. A. Hall, and J. T. Sharp, *J. Chem. Soc.* (*C*), 1967, 1860.
94. L. Friedman and J. F. Chlebowski, *J. Amer. Chem. Soc.*, 1969, **91,** 4864.
95. P. Caubere, *Accounts Chem. Res.*, 1974, **7,** 301.
96. R. A. Olofson and C. M. Dougherty, *J. Amer. Chem. Soc.*, 1973, **95,** 582.
97. O. M. Nefedov and A. I. Dyachenko, *Angew. Chem. Internat. Edn.*, 1972, **11,** 507.
98. M. Stiles and R. G. Miller, *J. Amer. Chem. Soc.*, 1960, **82,** 3802.
99. L. Friedman and F. M. Logullo, *J. Org. Chem.*, 1969, **34,** 3089.
100. R. Gompper, G. Seybold, and B. Schmolke, *Angew. Chem. Internat. Edn.*, 1968, **7,** 389.
101. C. Rüchardt and C. C. Tan, *Angew. Chem. Internat. Edn.*, 1970, **9,** 522.
102. J. I. G. Cadogan, *Accounts Chem. Res.*, 1971, **4,** 186.
103. J. I. G. Cadogan, C. D. Murray, and J. T. Sharp, *J.C.S. Perkin II*, 1976, 583.
104. B. Baigrie, J. I. G. Cadogan, J. R. Mitchell, A. K. Robertson, and J. T. Sharp, *J.C.S. Perkin I*, 1972, 2563.
105. R. W. Hoffmann, W. Sieber, and G. Guhn, *Chem. Ber.*, 1965, **98,** 3470.
106. R. T. Luibrand and R. W. Hoffmann, *J. Org. Chem.*, 1974, **39,** 3887.
107. O. L. Chapman, C. L. McIntosh, J. Pacansky, G. V. Calder, and G. Orr, *J. Amer. Chem. Soc.*, 1973, **95,** 4061, 6134.
108. C. D. Campbell and C. W. Rees, *J. Chem. Soc.* (*C*), 1969, 742, 748, 752.
109. J. I. G. Cadogan and J. B. Thomson, *Chem. Comm.*, 1969, 770.
110. M. Keating, M. E. Peek, C. W. Rees, and R. C. Storr, *J.C.S. Perkin I*, 1972, 1315.
111. E. K. Fields and S. Meyerson, *Accounts Chem. Res.*, 1969, **2,** 273.
112. R. F. C. Brown and R. K. Solly, *Chem. and Ind.* (*London*), 1965, 1462.
113. R. S. Berry, J. Clardy, and M. E. Schafer, *Tetrahedron Letters*, 1965, 1003, 1011.
114. R. A. Rossi, R. H. de Rossi, and H. E. Bertorello, *J. Org. Chem.*, 1971, **36,** 2905.
115. R. G. Bergman, *Accounts Chem Res.*, 1973, **6,** 25.
116. R. Breslow, J. Napierski, and T. C. Clarke, *J. Amer. Chem. Soc.*, 1975, **97,** 6275.
117. A. H. Amaro and K. Grohmann, *J. Amer. Chem. Soc.*, 1975, **97,** 5946.
118. C. W. Rees and R. C. Storr, *J. Chem. Soc.* (*C*), 1969, 760.
119. J. F. Bunnett and J. K. Kim, *J. Amer. Chem. Soc.*, 1973, **95,** 2254.
120. M. Jones and R. H. Levin, *J. Amer. Chem. Soc.*, 1969, **91,** 6411.
121. H. H. Wasserman, A. J. Solodar, and L. S. Keller, *Tetrahedron Letters*, 1968, 5597; 1974, 4355.
122. P. G. Gassman and H. P. Benecke, *Tetrahedron Letters*, 1969, 1089.
123. D. M. Hayes and R. Hoffmann, *J. Phys. Chem.*, 1972, **76,** 656.
124. P. Crews and J. Beard, *J. Org. Chem.*, 1973, **38,** 522.
125. R. W. Atkin and C. W. Rees, *Chem. Comm.*, 1969, 152.
126. L. Lombardo and D. Wege, *Tetrahedron*, 1974, **30,** 3945.
127. B. H. Klanderman and T. R. Criswell, *J. Amer. Chem. Soc.*, 1969, **91,** 510; *J. Org. Chem.*, 1969, **34,** 3426.
128. A. T. Bowne and R. H. Levin, *Tetrahedron Letters*, 1974, 2043.
129. H. Heaney, *Forschr. Chem. Forsch.*, 1971, **16,** 35.
130. P. Crews and J. Beard, *J. Org. Chem.*, 1973, **38,** 529.
131. R. W. Hoffmann, G. Guhn, M. Preiss, and B. Dittrich, *J. Chem. Soc.*, (*C*), 1969, 769.
132. J. Meinwald and G. W. Gruber, *J. Amer. Chem. Soc.*, 1971, **93,** 3802.
133. J. Meinwald, L. V. Dunkerton, and G. W. Gruber, *J. Amer. Chem. Soc.*, 1975, **97,** 681.

PART 3

HALO COMPOUNDS

3

Halo Compounds

R. D. CHAMBERS and S. R. JAMES
University of Durham

3.1 INTRODUCTION 493
3.2 METHODS OF HALOGENATION 494
3.2.1 Homolytic substitution of hydrogen 494
3.2.2 Homolytic substitution of groups other than hydrogen 497
3.2.3 Homolytic addition to unsaturated systems 500
3.2.4 Electrophilic halogenation 504
3.2.5 Nucleophilic halogenations 513
3.2.6 Synthesis of highly halogenated compounds 520
3.3 HALOALKANES 524
3.3.1 Bonding properties 524
3.3.2 Industrial aspects 525
3.3.3 Nucleophilic displacement of halogen 527
3.3.4 Reduction 535
3.3.5 Displacement by metals 537
3.3.6 Eliminations 538
3.4 HALOALKENES 544
3.4.1 Synthesis 544
3.4.2 Nucleophilic attack 545
3.4.3 Radical additions 549
3.4.4 Electrophilic additions 552
3.4.5 Cycloadditions 554
3.5 HALOALKYNES 557
3.6 HALOARENES 560
3.6.1 Displacement of halogen 560
3.6.2 Rearrangements 566

3.1 INTRODUCTION

This chapter covers a very wide area of chemistry and, in the space available, cannot be comprehensive in itself. However, it is hoped that there are sufficient key and up-to-date references to take the reader to the greater detail that may be required and a number of important publications should be acknowledged at the outset.[1–12]

Discussion and interest in halogen-containing organic compounds falls into two parts. The first concerns the halogen atom as a functional group in organic chemistry and the various ramifications of this. The second concerns the effect of halogen atoms on other functional groups and reactive sites in a molecule including, of course, the effect on

biochemistry,[13] although this subject cannot be treated here. The ultimate in this approach lies in the development of the chemistry of perhalocarbons. In principle, a whole synthetic organic chemistry is possible based on halocarbon, rather than on hydrocarbon, skeletons, together with the various functional groups and reactive sites and, as we will see later, this area has progressed to a considerable degree and with fascinating consequences.

3.2 METHODS OF HALOGENATION

Methods available for the introduction of halogen into an organic molecule are legion and impossible to classify accurately. Nevertheless, we will attempt to discuss them, on a broadly mechanistic basis, hoping that clarity will compensate for some of the extrapolations or assumptions made about mechanism. We can only hope to cover principles here. Examples are given in the Tables 2, 4, 5 and 6, but reference should be made to other works[1–9] for greater detail.

3.2.1 Homolytic substitution of hydrogen

3.2.1.1 Direct halogenation[1(i),14–18]

The halogenation process can be separated into the steps shown in equations (1)–(4) and the enthalpy change for each step in the reaction of methane with halogen is given. These data illustrate some of the problems involved in direct halogenation and explain, in part, the differences that are observed in the behaviour of each halogen with hydrocarbons.

	ΔH (kJ mol^{-1})				
	X = F	Cl	Br	I	
$X_2 \rightarrow 2X\cdot$	155	243	192	151	(1)
$X\cdot + CH_4 \rightarrow HX + CH_3\cdot$	−134	4	69	138	(2)
$CH_3\cdot + X_2 \rightarrow CH_3X + X\cdot$	−285	−109	−100	−84	(3)
$X_2 + CH_4 \rightarrow CH_3X + HX$	−418	−105	−31	54	(4)

The stoichiometry of the chain reaction (4) is the algebraic sum of the chain-propagating steps (2) and (3) and, therefore, the overall enthalpy change for the halogenation of methane is the sum of ΔH for steps (2) and (3). Obviously, the differences in enthalpy change observed for these halogenations are very significant and some of the consequences are discussed below.

(*i*) *Selectivity of halogenation.* We can consider a number of factors which will influence selectivity:

(*a*) The nature of the transition state during hydrogen abstraction. These may be represented by the following spectrum of possibilities:

C—H---X·	[C---H---X]·	·C---H—X
Like initial state	'Concerted'	Like final state

In strongly exothermic reactions the transition state will resemble the initial state (Hammond postulate), *i.e.* where there has been little C—H bond stretching, and so there will be little dependence on the nature of the C—H bond. Only in the case of fluorine is the step in which a halogen atom abstracts a hydrogen atom from a hydrocarbon exothermic and, understandably, these are the least selective halogenations.

(*b*) The structure of the radical resulting from hydrogen abstraction. This is most important for those reactions where the transition state resembles the products, *i.e.* in the more endothermic halogenations, and accounts, at least in part, for the well known order of preference for halogenation, *viz.* $R_3CH > R_2CH_2 > RCH_3$.

(*c*) Polar effects. It is probable that, because the attacking halogen atoms are electrophilic, a factor contributing to the greater reactivity of tertiary positions is that the alkyl groups, being electron donating, may increase the electron density at these positions, *i.e.* $(\overset{\delta+}{R}\rightarrow)\overset{\delta-}{C}H$. A simple example of a polar influence may be seen by comparing the reactions of methyl radicals and chlorine atoms with propionic acid.[16] Clearly, attack by the more electrophilic chlorine atoms at the position α to the carboxylate group is inhibited:

$$\overset{\delta\delta+}{C}H_3—\overset{\delta+}{C}H_2—CO_2H$$

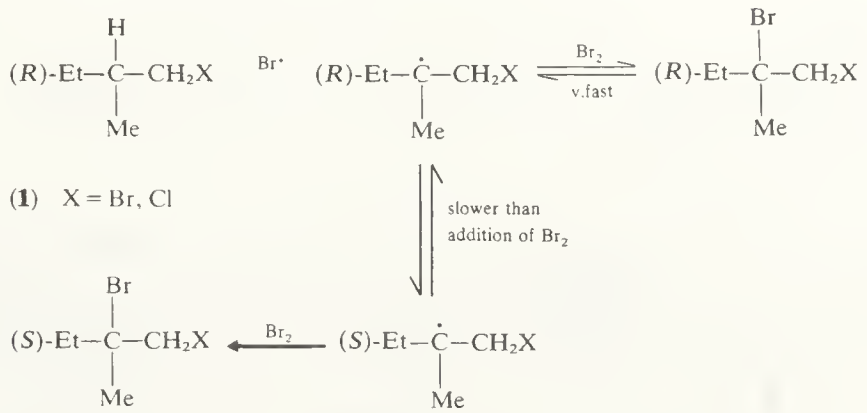
Relative selectivities	1	7.8	$CH_3\cdot$	Radicals
	1	0.03	$Cl\cdot$	

Similarly, the presence of halogen atoms attached to a hydrocarbon chain inhibits further halogenation at adjacent positions:[1(i)]

e.g. $CH_3—CH_2—CH_2—CH_2—Cl$ with Cl_2 at 35 °C has
1.0 4.2 2.2 0.7 monochlorination product distribution,
and $CH_3—CH_2—CH_2—CH_2—CF_3$ with Cl_2 at 75 °C has
1.0 4.3 1.2 0.04 monochlorination product distribution.

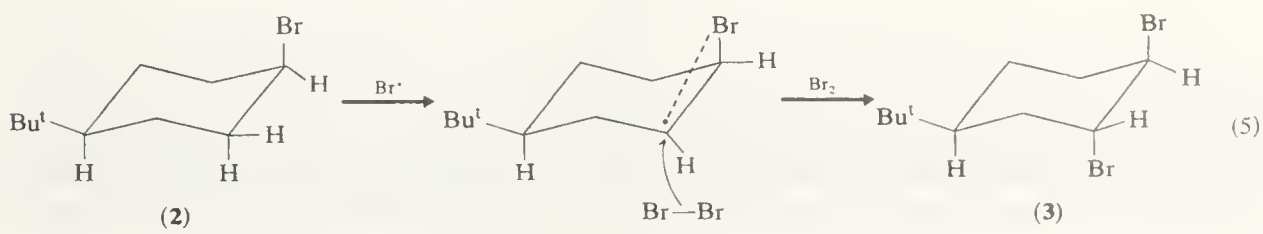
These results clearly indicate that the production of highly halogenated compounds will require steadily more vigorous conditions.

(*d*) Bridging of adjacent atoms.[17,18] In principle, the inversion of a radical should be rapid but in some cases stereoselectivity is observed, *e.g.* the bromination of (**1**) in Scheme 1 leads to optically active products.



SCHEME 1

The simplest explanation of this result would be that the intermediate radical has a very short lifetime and reacts with bromine at a faster rate than its rate of inversion. However, evidence has been presented to suggest that the stereoselectivity may result from bromine or chlorine bridging with the adjacent radical centre. Evidence for bridging is particularly persuasive in the cyclohexane system (**2**) where the diaxial product (**3**) is obtained, (equation 5).



(5)

TABLE 1

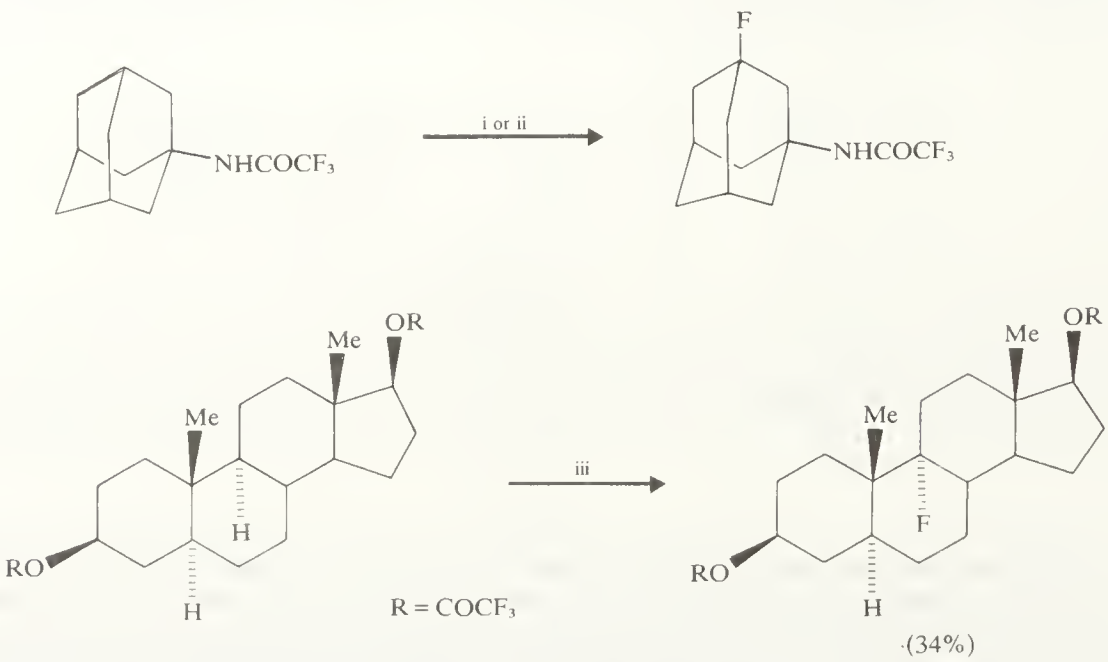
Chlorination of 2,3-Dimethylbutane plus CS_2 (25 °C)[a]

Molar conc. of CS_2	K_t/K_p *(statistically corrected)*
2	15
4	33
11	161
12	225

[a] Ref. 1, p. 568.

(*e*) Solvent. Although solvent effects in homolytic reactions are much less important than those in heterolytic processes, nevertheless solvents can significantly affect selectivity in halogenation. Some solvents are able to act as weak acceptors and appear to complex with halogen atoms, thus making the hydrogen-abstraction step less exothermic and the overall process more selective. For example, carbon disulphide complexes effectively with chlorine atoms and this can lead to increased selectivity, as in the chlorination of 2,3-dimethylbutane. From the data given in Table 1 it can be seen that the reaction becomes more selective as the concentration of carbon disulphide increases.[1(i)]

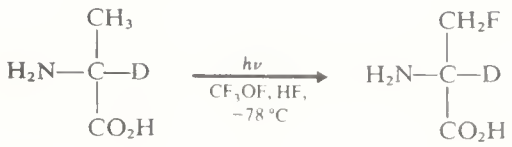
(*ii*) *Selectivity in direct fluorination.*[18a] Bearing in mind the exothermic nature of fluorination reactions, it is understandable that examples of selective formation of C—F bonds from fluorine are limited. Surprisingly, however, reaction between adamantanes or steroids, and either fluorine or CF_3OF,[19,20] is very selective (see Scheme 2).



i, CF_3OF and radical inhibitor (yield 65%); ii, F_2, no inhibitor (yield = 83%); iii, F_2, N_2, $CFCl_3$, $CHCl_3$, −22 °C.

SCHEME 2

Radical inhibitors suppress some of the reaction but can increase the selectivity, which strongly suggests that both homolytic and heterolytic processes occur in these systems. Photofluorination (equation 6) of (*R*)-[2-^{2}H]alanine has led to the synthesis of 3-fluoro-(*R*)-[2-^{2}H]alanine (**4**) which is a component of a novel antimicrobial combination that, it is claimed, is effective *in vitro* and *in vivo* against every bacterial strain tested.[21]

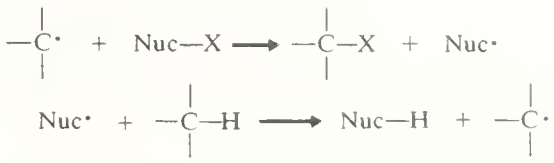


(6)

(4)

3.2.1.2 Halogen derivatives as reagents

Compounds containing weak bonds to halogen may be used as halogenating species. If the reagent takes part in the chain-propagating steps, *i.e.*



then the abstraction of hydrogen by Nuc· in a number of cases will be less exothermic than abstraction by X·, depending on the nature of Nuc·. Weak bonds to O, S, N, P, or other halogens are exploited in this way in a number of reagents, although not all are selective for this reason. *N*-Bromosuccinimide, for example, acts selectively by providing trace amounts of bromine, which are reformed from the hydrogen bromide produced in the bromination step (equation 7). This mechanism is now generally accepted, although in the past it has been a source of considerable controversy.[15] Some of the modifying influences obtained by varying Nuc in Nuc—X actually change the mechanism from homolytic to electrophilic and, no doubt, there are some borderline systems.[22]

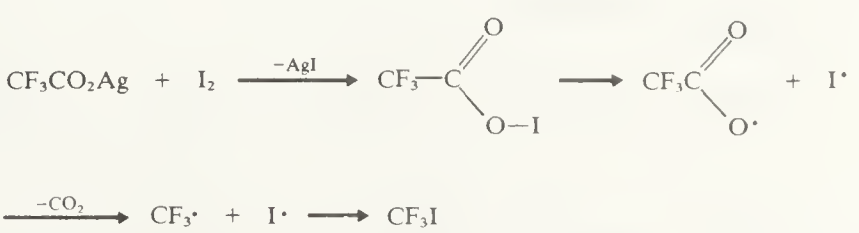
(7)[5]

3.2.2 Homolytic substitution of groups other than hydrogen

The Hunsdiecker synthesis of alkyl halides is effected[2,7,10] by decarboxylation of the silver salts of carboxylic acids in the presence of halogens:

$$CF_3CO_2Ag + I_2 \xrightarrow{\Delta} CF_3I + AgI + CO_2$$

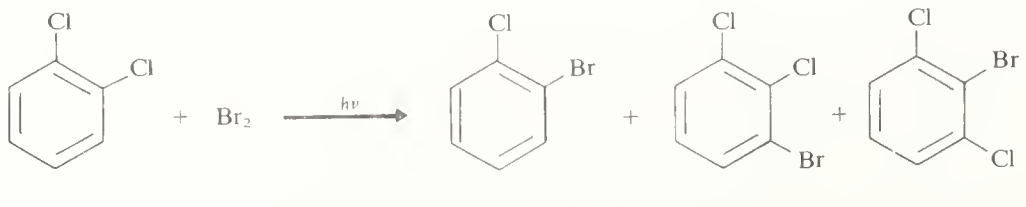
The mechanism of this process is most probably radical in nature:



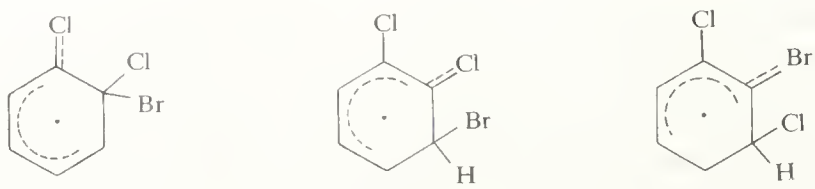
The reaction suffers from the scrupulously anhydrous conditions required, but a useful modification[5,23] involves the addition of halogen to a solution of acid and mercuric oxide in halogenated solvent (equation 8).

(8)

Homolytic displacement of chlorine occurs[24,25] in the photobromination of dichlorobenzenes (equation 9). The products of the reaction have been rationalized as a so-called *ipso* attack by a bromine atom on the aromatic ring to give the intermediate radical (**5**), which can then rearrange to either of the radical intermediates (**6**) or (**7**). Further illustrations of homolytic substitution reactions involving halogens, halogen derivatives, and metal halides are given in Table 2.



(9)



(**5**) (**6**) (**7**)

TABLE 2
Homolytic Substitution Reactions

(a) *Of hydrogen*

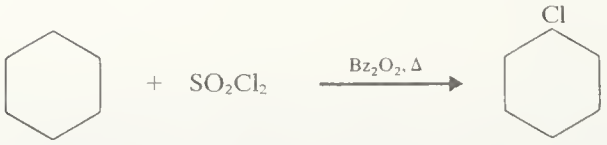
		$CH_3—CH_2—CH_2—CH_2—Bu^n$				
1.	n-Octane + Cl_2 (light, 20 °C)	14.3	30.4	28.4	26.7	% monohalogeno product[a]
	n-Octane + Bu^tOCl (light, 20 °C)	6.3	38.2	28.7	26.2	
	n-Octane + *N*-Chlorosuccinimide (Bz_2O_2, 98 °C)	15.0	30.9	28.5	25.4	

2. $CF_3CH_2CH_3 \xrightarrow{Cl_2,\ h\nu} CF_3CH_2CH_2Cl\ (23\%) + CF_3CH_2CHCl_2\ (47\%) + CF_3CH_2CCl_3\ (29\%)$[b]

3. $PhCH_2CH_3 \xrightarrow{Cl_2,\ PCl_5} PhCHClCH_3 \xrightarrow[90\ °C]{Cl_2,\ I_2} PhCCl_2CH_3 + PhCHClCH_2Cl$

$PhCH_2CH_3 \xrightarrow[70–100\ °C]{Cl_2,\ h\nu} PhCCl_2CCl_3$[c]

4. $PhCH_3 \xrightarrow{Br_2,\ h\nu} PhCH_2Br\ (60\%) \xrightarrow[135\ °C]{Br_2,\ h\nu} PhCHBr_2 \xrightarrow[160\ °C]{Br_2,\ h\nu} PhCBr_3$[d]

5.  + SO_2Cl_2 $\xrightarrow{Bz_2O_2,\ \Delta}$ (89%) + Dichlorocyclohexane (11%)[e]

6. $i\text{-}C_4H_{10} + CCl_4 \xrightarrow[130–140\ °C]{Bu^t_2O_2} (CH_3)_3CCl$[f]

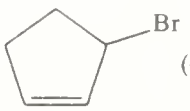
TABLE 2 (*continued*)

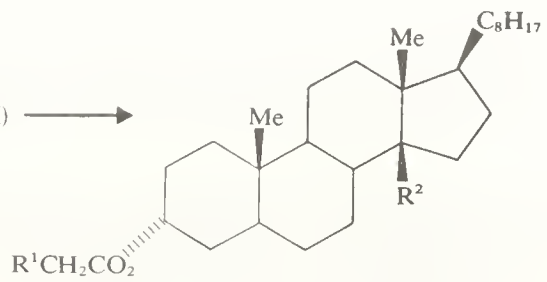
(a) *Of hydrogen (cont.)*

7. $n\text{-}C_4H_{10} + (CH_3)_3COI \xrightarrow{h\nu} CH_3CH_2CHICH_3\ (95\%) + CH_3CH_2CH_2CH_2I\ (5\%)$[g]

8. $R{-}H + Bu^tOCl + BrCCl_3\ (\text{excess}) \xrightarrow{h\nu} R{-}Br$[h]

9. $H{-}C{\equiv}C{-}CO_2H + KOCl \longrightarrow Cl{-}C{\equiv}C{-}CO_2H$[i]

10.  + *N*-Bromosuccinimide $\xrightarrow[CCl_4,\ \text{reflux}]{Bz_2O_2}$  (63%)[j]

11. (**I**) $\xrightarrow[\text{pentane}]{Cl_2,\ 0\,^\circ C}$ (**II**) $\longrightarrow$  [k]

(**III**)

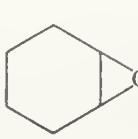
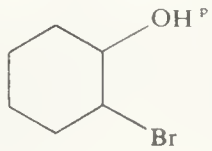
(**I**), $R^1 = p\text{-}C_6H_4I$, $R^2 = H$; (**II**), $R^1 = p\text{-}C_6H_4ICl_2$, $R^2 = H$; (**III**), $R^1 = p\text{-}C_6H_4I$, $R^2 = Cl$

12. $CH_3CN \xrightarrow[350\,^\circ C]{Cl_2} CCl_3CN\ (80\%)$[l]

13. $PhCOCH_3 \xrightarrow[CH_3CO_2H]{Cl_2,\ h\nu} PhCOCH_2Cl\ (78\%)$[m]

14. $CH_3CH_2CO_2H \xrightarrow{Cl_2,\ h\nu} CH_3CHClCO_2H\ (30\%) + CH_2ClCH_2CO_2H\ (70\%)$[n]

15. $Me(CH_2)_2CO_2H \xrightarrow[\text{chloranil, 2.5 h}\ 120\,^\circ C,\ \text{in the dark}]{ClSO_3H,\ O_2,\ Cl_2} MeCH_2CHClCO_2H\ (82\%) + MeCHClCH_2CO_2H\ (1.6\%)$[o]

16. $R^1COCHR^2R^3 + Br_2 +$  $\xrightarrow{h\nu} R^1COCBrR^2R^3 +$  [p]

$R^1 = Me$, $R^2 = Ph$, $R^3 = \text{alkyl}$

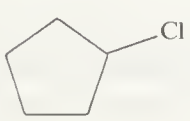
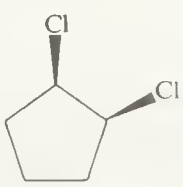
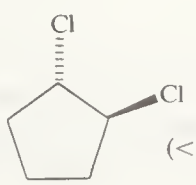
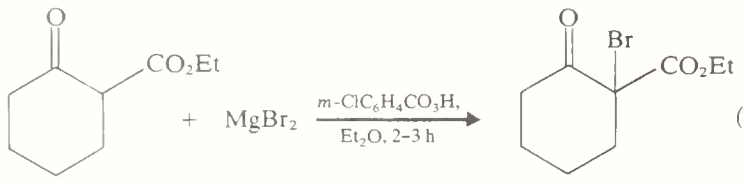
17.  + $MoCl_5 \xrightarrow[25\,^\circ C]{CH_2Cl_2}$  (88%) +  (<1%)[q]

TABLE 2 (*continued*)

(a) *Of hydrogen (cont.)*

18. 

(100%)[r]

19. $(CH_3)_2CO + CuCl_2 \xrightarrow[24\ h]{LiCl,\ reflux} ClCH_2COCH_3$ (60%)[s]

(b) *Of functional groups*

20. $MeO_2C(CH_2)_4CO_2Ag \xrightarrow[reflux]{Br_2,\ CCl_4} MeO_2C(CH_2)_3CH_2Br$ (65–68%)[t]

21. $Me(CH_2)_5CH(OCOMe)(CH_2)_{10}CO_2H \xrightarrow[CCl_4,\ reflux]{I_2,\ h\nu,\ Pb(OCOMe)_4} Me(CH_2)_5CH(OCOMe)(CH_2)_9CH_2I$[u]

[a] Ref. 1 (i), p. 549. [b] Ref. 2, p. 597. [c] Ref. 2, p. 741. [d] Ref. 3, p. 334. [e] Ref. 1 (i), p. 79. [f] J. P. West and L. Schmerling, *J. Amer. Chem. Soc.*, 1950, **72,** 3525. [g] D. D. Tanner and G. C. Gidley, *ibid.*, 1968, **90,** 808. [h] Ref. 5, p. 267. [i] Ref. 2, p. 782. [j] Ref. 3, p. 225. [k] R. Breslow, R. J. Corcoran, B. B. Snider, R. O. Doll, P. L. Khanna, and R. Kaleya, *J. Amer. Chem. Soc.*, 1977, **99,** 905. [l] Ref. 2, p. 634. [m] Ref. 2, p. 619. [n] Ref. 2, p. 626. [o] Y. Ogata, T. Harada, K. Matsuyama, and T. Ikejiti, *J. Org. Chem.*, 1975, **40,** 2960. [p] V. Calo, L. Lopez, and G. Pesce, *J.C.S. Perkin I*, 1977, 501. [q] J. San Filippo, Jr., A. F. Sowinski, and L. J. Romano, *J. Org. Chem.*, 1975, **40,** 3463. [r] N. Inukai, H. Iwamoto, T. Tamura, I. Yanagisawa, Y. Ishii, and M. Marakami, *Chem. Pharm. Bull. (Japan)*, 1976, **24,** 820. [s] J. K. Kochi, *J. Amer. Chem. Soc.*, 1955, **77,** 5274. [t] C. F. H. Allen and C. V. Wilson, *Org. Synth. Coll. Vol.* 3, 1955, 578. [u] D. H. R. Barton, H. P. Faro, E. P. Serebryakov, and N. F. Woolsey, *J. Chem. Soc.*, 1965, 2438.

3.2.3 Homolytic addition to unsaturated systems[17,18]

3.2.3.1 Hydrogen halides

Homolytic additions of hydrogen halides to olefins only proceed readily with hydrogen bromide and this is of some historical importance because it was one of the first cases where it was established that a reaction may proceed *via* either an ionic or a radical mechanism. The important steps in the radical mechanism are the addition and transfer steps:

$$X\cdot + CH_2{=}CH_2 \rightarrow X{-}CH_2CH_2\cdot \qquad \text{Addition step}$$
$$X{-}CH_2CH_2\cdot + HX \rightarrow XCH_2CH_3 + X\cdot \qquad \text{Transfer step}$$

It is evident from the data given in Table 3 that only in the case of hydrogen bromide are both the addition and transfer steps exothermic. Consequently, radical chain processes are only observed in special circumstances for hydrogen chloride and iodide additions.

TABLE 3

The Enthalpy Change for the Addition of Hydrogen Halides to Ethylene

HX	ΔH (kJ mol^{-1}) *Addition*	*Transfer*
HBr	−20.9	−46.0
HCl	−108.9	20.9
HI	29.3	−113.0

The regiospecificity of these homolytic processes is important because the addition is in opposition to Markownikov's rule. Therefore, by varying the reaction conditions, constitutionally isomeric products result (see Scheme 3).

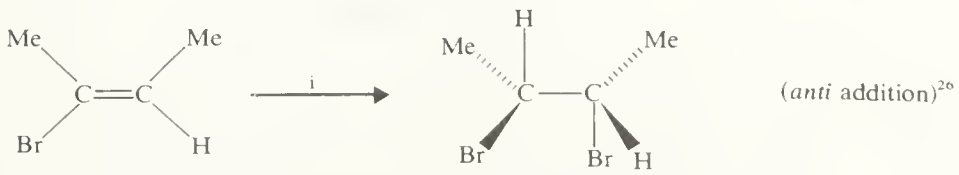
$$CH_3CH{=}CH_2 + HBr \xrightarrow{i} CH_3CHBrCH_3$$

$$CH_3CH{=}CH_2 + HBr \xrightarrow{ii} CH_3CH_2CH_2Br$$

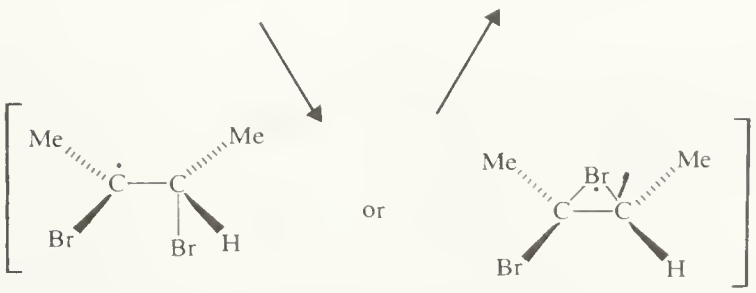
i, dark, $FeCl_3$, slow; ii, peroxides, fast.

SCHEME 3

Stereospecificity may also be controlled to some extent since at low temperatures and with high concentrations of hydrogen bromide, stereospecific *anti* addition may be observed in some cases. However, at higher temperatures and with lower concentrations of hydrogen bromide, the stereospecificity decreases (see Scheme 4).



1. *cis*-isomer — *meso*-product (90%)



(**8**) (**9**)

2. *trans*-isomer $\xrightarrow{i}$ (±)-product (~100%)

3. *trans*- or *cis*-2-bromobut-2-ene $\xrightarrow{ii}$ *meso*- (25%) + (±)-products (75%)

i, excess HBr, −78 °C; ii, excess HBr, 25 °C.

SCHEME 4

These observations can be interpreted in one of two ways: at low temperatures, either an almost concerted *anti* addition of hydrogen bromide occurs with minimal rotation or inversion of the intermediate radical (**8**), or a bridged radical (**9**)[27] is involved. At higher temperatures the inversion or rotation of (**8**) would occur more readily and consequently

an intermediate such as (**9**) would be less likely. Either way, the reaction, though still stereoselective, is no longer stereospecific.

3.2.3.2 Halogens

The free radical addition of halogens to unsaturated systems is very similar to the addition of hydrogen halides in so far as the chain-propagation steps are similar. Therefore, the topic will not be discussed here but the reader is referred to a more comprehensive review.[28]

Examples of the homolytic addition of halogens and hydrogen halides to olefins are given in Table 4 (a few examples involving halogen derivatives, such as $PhICl_2$, and metal chlorides, such as $CuCl_2$ and $MoCl_5$, are also included, although in these cases a radical mechanism is by no means certain).

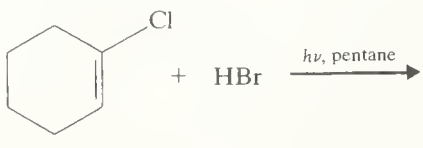
TABLE 4
Homolytic Addition Reactions

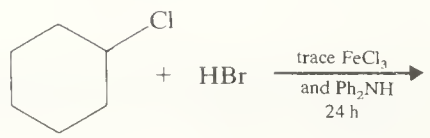
(a) *By hydrogen halides*

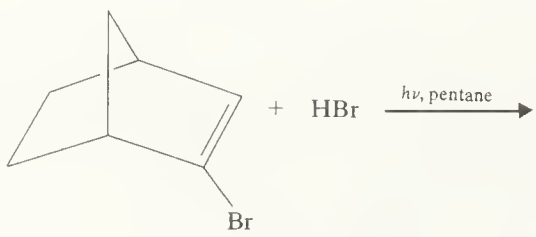
1. $CH_2{=}CHCH_2Br + HBr \xrightarrow[\text{peroxides}]{\text{lighter}} BrCH_2CH_2CH_2Br$[a]

2. $CF_2{=}CHCH_3 + HBr \xrightarrow{h\nu} CHF_2CHBrCH_3$ (93%)[b]

3. $CF_3CH{=}CH_2 + HBr \xrightarrow{h\nu} CF_3CH_2CH_2Br$ (90–97%)[c]

4.  (80% *anti* addition)[d]

cf.  (79%)[d]

5.  (60–70% *syn* addition)

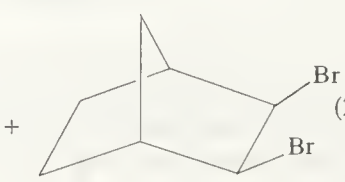
+  (20–30% *anti* addition)[e]

TABLE 4 (*continued*)

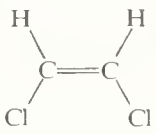
(b) *By halogens*

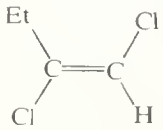
6. $Ph_2C{=}CH_2 \xrightarrow[-78\,^\circ C]{F_2,\ CFCl_3} Ph_2CFCH_2F\ (14\%) + PhC{=}CHF\ (78\%) + Ph_2CHFCHF_2\ (8\%)$[f]

7. $CF_3CF{=}CFCF_3 \xrightarrow[-75\,^\circ C]{F_2,\ CFCl_3} CF_3CF_2CF_2CF_3$[g]

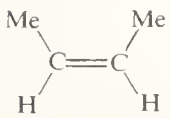
8. $CCl_2{=}CClCCl_3 \xrightarrow[<50\,^\circ C]{Cl_2,\ h\nu}$ n-C_3Cl_8[h]

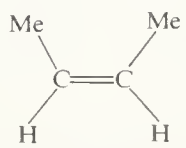
9. $CCl_2{=}CClCCl{=}CCl_2 \xrightarrow[h\nu]{\text{liq. } Cl_2}$ n-C_4Cl_{10}[i]

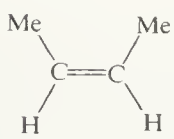
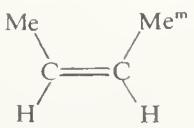
10. $HC{\equiv}CH \xrightarrow[\text{activated C}]{Cl_2}$  (90% + $CHCl_2CHCl_2$ (10%)[j]

11. $EtC{\equiv}CH \xrightarrow[\text{(radical)}]{Cl_2,\ h\nu}$  (90%)[k]

cf. $EtC{\equiv}CH \xrightarrow[\text{in dark, } -9\,^\circ C\ \text{(ionic)}]{Cl_2,\ O_2}$ (very slow reaction)[k]

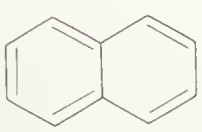
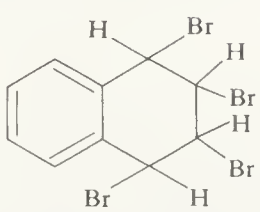
12.  $\xrightarrow[-9\,^\circ C\ \text{(radical)}]{Cl_2,\ N_2}$ *meso*-MeCHClCHClMe (28%) + (±)-MeCHClCHClMe (56%)[l]

cf.  $\xrightarrow[-9\,^\circ C\ \text{(ionic)}]{Cl_2,\ O_2}$ (±)-MeCHClCHClMe (98%)[l]

13.  $\xrightarrow[C_3H_8,\ -42\,^\circ C]{I_2,\ h\nu}$ MeCHICHIMe $\xrightarrow[-I_2]{25\,^\circ C}$ 

14. $(PhCO)_2CH_2$ (97 % enol) $\xrightarrow{I_2,\ MeCO_3H}$ $(PhCO)_2CHI$[n]

$(PhCO)_2CHMe$ (100% keto) $\xrightarrow{I_2,\ MeCO_3H}$ no reaction[n]

15.  $\xrightarrow[CCl_4,\ 0\,^\circ C]{Br_2,\ h\nu}$  (30%)[o]

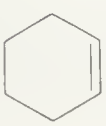
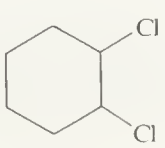
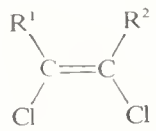
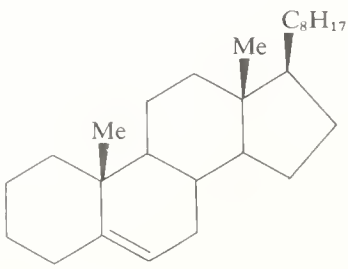
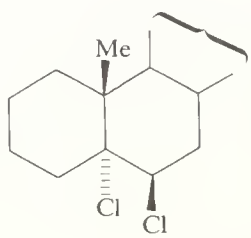
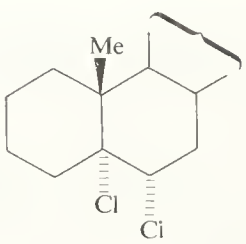
16.  + $SO_2Cl_2 \xrightarrow[\text{reflux}]{CCl_4,\ Bz_2O_2}$  (90% *cis* addition)[p]

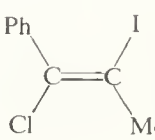
TABLE 4 (*continued*)

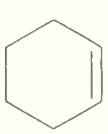
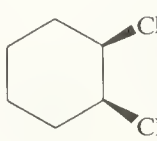
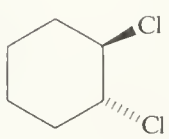
(b) *By halogens (cont.)*

17. $R^1—C{\equiv}C—R^2 + PhICl_2 \longrightarrow$  (85–97%)[q]

18.  + $PhICl_2$ $\xrightarrow{h\nu,\ CCl_4}$  (50%)

+  (43%)[r]

19. $PhC{\equiv}CMe + CuCl_2 \xrightarrow{I_2,\ MeCN}$  (93%)[s]

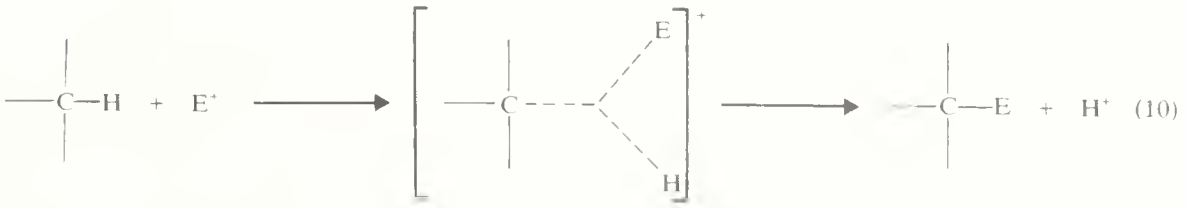
20.  + $MoCl_5$ $\xrightarrow{CH_2Cl_2,\ -78\ °C}$  (68%) +  (<2%)[t]

[a] F. R. Mayo, in 'Vistas in Free Radical Chemistry', ed. W. A. Waters, Pergamon. New York, 1959, p. 139. [b] Ref. 3, p. 115. [c] Ref. 3, p. 116. [d] H. L. Goering and L. L. Sims, *J. Amer. Chem. Soc.*, 1955, **77,** 3465. [e] N. A. Le Bel, *ibid.*, 1960, **82,** 623. [f] R. F. Merritt and F. A. Johnson, *J. Org. Chem.*, 1967, **32,** 416. [g] J. M. Tedder, *Adv. Fluorine Chem.*, 1961, **2,** 104; W. T. Miller, Jr., J. O. Stoffer, G. Fuller, and A. C. Currie, *J. Amer. Chem. Soc.*, 1964, **86,** 51. [h] Ref. 2, p. 534. [i] Ref. 2, p. 534, [j] Ref. 2, p. 551. [k] M. L. Poutsma and J. L. Kartch, *Tetrahedron*, 1966, **22,** 2167. [l] M. L. Poutsma, *J. Amer. Chem. Soc.*, 1965, **87,** 4285. [m] P. S. Skell and R. R. Pavlis, *ibid.*, 1964, **86,** 2956. [n] I. Urasaki and Y. Ogata, *J.C.S. Perkin I*, 1975, 1285. [o] Ref. 3, p. 100. [p] M. S. Kharasch and H. C. Brown, *J. Amer. Chem. Soc.*, 1939, **61,** 3432. [q] A. Debon, S. Masson, and A. Thuillier, *Bull. Soc. chim. France*, 1975, **11–12,** Pt. 2, 2493. [r] A. Zarecki, J. Wicha, and M. Kocor, *Tetrahedron*, 1976, **32,** 559. [s] S. Vemura, H. Okazaki, A. Onoe, and M. Okano, *J.C.S. Perkin I*, 1977, 676. [t] J. San Filippo, Jr., A. F. Sowinski, and L. J. Romano, *J. Amer. Chem. Soc.*, 1975, **97,** 1599.

3.2.4 Electrophilic halogenation

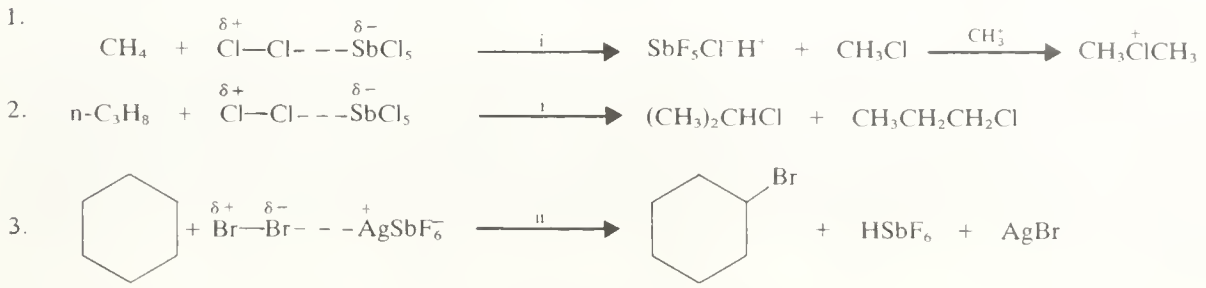
3.2.4.1 Substitution at saturated C—H

Largely through the work of Olah and his co-workers,[29,30] electrophilic substitution at saturated C—H is now a relatively familiar process. Direct electrophilic attack at the σ-bond may take place apparently *via* a three-centre transition-state or intermediate (**10**), as shown in equation (10).



(10)

The difficulty with these halogenations lies in describing the nature of the positive halogen species.[22] For example, although successful chlorination of methane and higher alkanes with chlorine in the dark, and in the presence of Friedel–Crafts type catalysts has been achieved, the process may not be wholly ionic. It is still possible that positive halogens, X^+, exist in triplet ground states and, if so, these reactions could be defined as those of radical cations. Nevertheless, for our purposes there is a clear distinction between processes which involve halogen atoms and those which involve charged species.



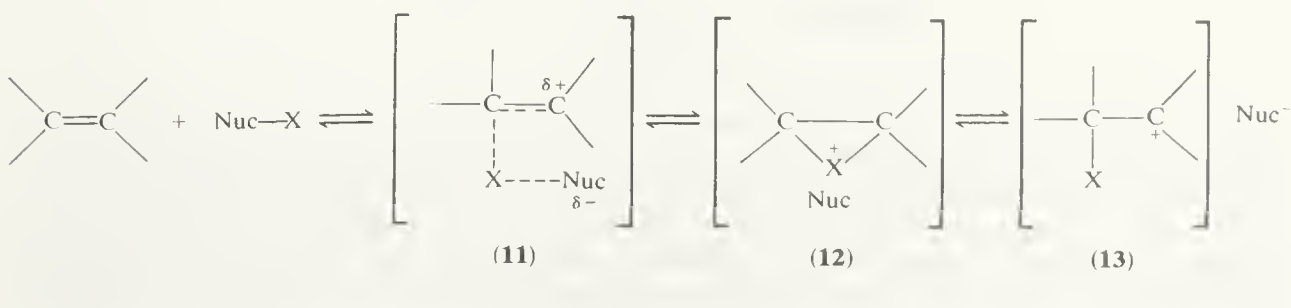
i, SO_2ClF, −78 °C; ii, CH_2Cl_2, 25 °C.

SCHEME 5

In addition to the examples given in Scheme 5 and in Table 5 (p. 510), the fluorinations described earlier, which were carried out in the presence of radical inhibitors,[19,20] would almost certainly fall into this category and could have been included here.

3.2.4.2 Reactions with unsaturated systems[22,31,32]

(*i*) *Alkenes.* It is well known that halogens may act as electrophilic species and this electrophilicity can be enhanced by using various covalent derivatives. Effective examples of these are compounds with halogen bonded to nitrogen, oxygen, sulphur, or phosphorus, as well as the interhalogens. We can represent an overall mechanism for addition, to include these halogen derivatives, where Nuc is the nucleophilic part of the species in Nuc—X in equation (11). Regioselectivity is complicated by the involvement of the bridged species (**12**). In general, the regioselectivity for reactions of electrophilic halogen is lower than for additions of hydrogen halides. For example, Markownikov addition occurs exclusively for the addition of HCl to propene (equation 12). Compare this with the regiospecificity shown by the reagents in equations (13)–(15).



(**11**) (**12**) (**13**)

$$CH_3CH{=}CH_2 \xrightarrow{HCl} (CH_3)_2CHCl \quad (12)$$

$$CH_3CH{=}CH_2 + ClOH \longrightarrow 91\%\ \text{Markownikov product} \quad (13)$$

$$CH_3CH{=}CH_2 + BrOH \longrightarrow 79\%\ \text{Markownikov product} \quad (14)$$

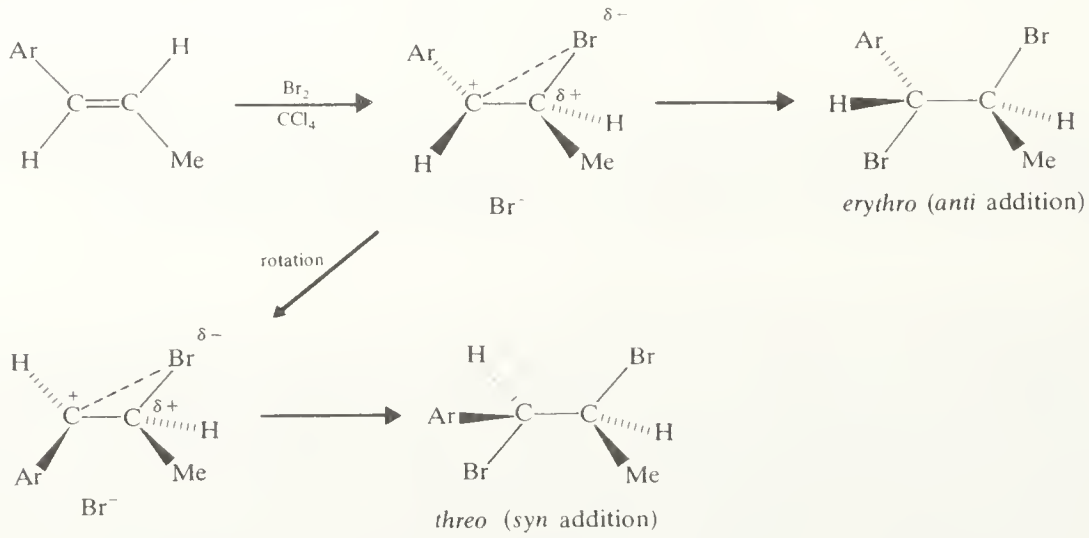
$$CH_3CH{=}CH_2 + BrCl \longrightarrow 54\%\ \text{Markownikov product} \quad (15)$$

The clear indication is that the halogens most likely to form a bridged species (**12**) lead to the lowest regiospecificity, since attack by Nuc^- on (**12**) may occur at either carbon atom. A particularly interesting case is the addition of ClOH to 3-bromopropene (equation 16), where the bromine substituent becomes involved in the bridging process, as evidenced by bromine migration.[22,33] The stereoselectivity of this process depends on (i)

$$BrCH_2CH{=}CH_2 + ClOH \longrightarrow \underset{\substack{\diagup\ \diagdown \\ Br\ \ OH}}{CH_2{-}CH{-}CH_2Cl} \longrightarrow HOCH_2CHBrCH_2Cl + BrCH_2CH(OH)CH_2Cl \quad (16)$$

$$BrCH_2CH{=}CH_2 \longrightarrow BrCH_2CHClCH_2OH$$

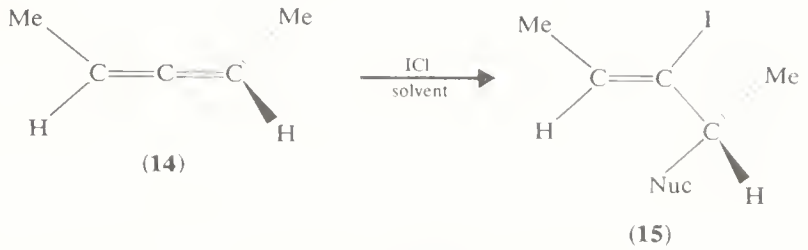
the halogen involved in the addition, (ii) substituents attached to the double bond, and (iii) solvent. Also, the magnitude of the rate constants for product formation will be very important, *e.g.* if products are formed very rapidly from (**11**), then the selectivity may not vary much with the halogen, but if product formation is slow, then bridging will occur as in (**12**). The effectiveness of halogens at bridging is in the order $F \ll Cl < Br < I$. Preferred *anti* addition is usually observed, *e.g.* in the bromination of 1-arylpropenes[22] as shown in Scheme 6.



Ar	Composition of dibromides	
	threo	*erythro*
C_6H_5	0.12	0.88
o-$MeOC_6H_4$	0.37	0.63

SCHEME 6

It is general that as the substituents at the double bond become more capable of stabilizing the developing positive charge, without the assistance of bridging, then the lower is the stereoselectivity of addition. More ionizing solvents lead to lower stereoselectivity and, in some cases, the solvent may compete for the intermediate cationic species. In pyridine the optically active product (**15a**) was obtained from the allene (**14**) in 85% yield, whereas in methanol the corresponding methyl ethers (**15b**) were produced (see Scheme 7).

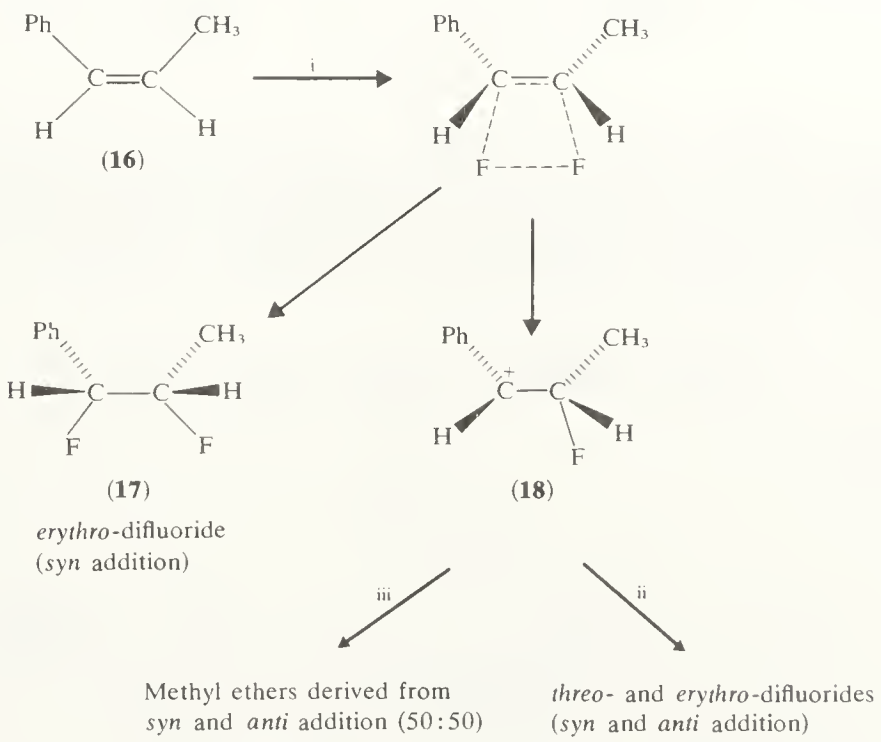


(14) (15)

(a) solvent = pyridine, Nuc = Cl
(b) solvent = MeOH, Nuc = OMe

SCHEME 7

(*ii*) syn *Additions.*[22] In the general mechanistic scheme for addition of electrophilic halogen to olefins, outlined in equation (11), the first stage intermediate (**11**) is likely to collapse most rapidly for electrophilic fluorinations. However, because fluorine is the halogen least effective at bridging to an adjacent carbenium ion, so collapse by capture of fluoride ion is the most likely outcome. This type of explanation has been advanced (see Scheme 8) to account for the preference for *syn* addition of fluorine to 1-phenylprop-1-ene (**16**) to give (**17**). A carbenium ion is apparently formed at some stage because an intermediate (**18**) may be trapped by using methanol as the solvent to give a 50:50 mixture of *threo*- and *erythro*-2-fluoro-3-methoxy-3-phenylpropane.



(16) (17) (18)

erythro-difluoride (*syn* addition)

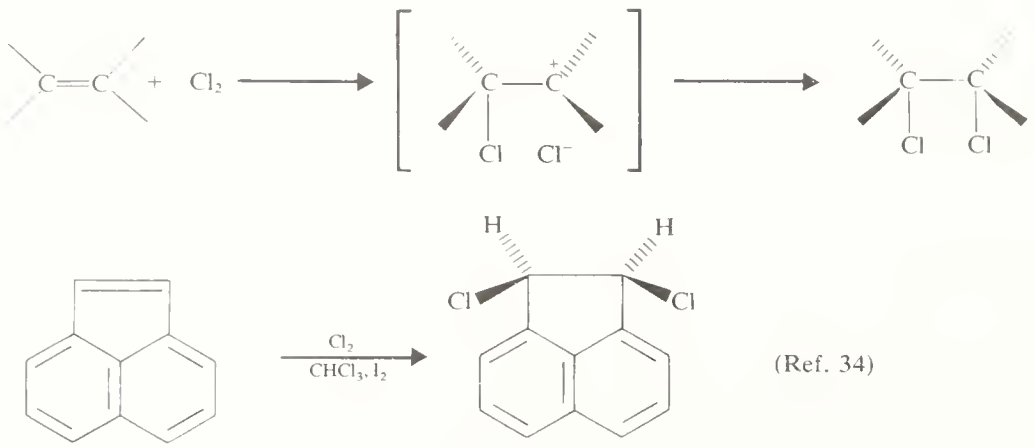
Methyl ethers derived from *syn* and *anti* addition (50:50)

threo- and *erythro*-difluorides (*syn* and *anti* addition)

i, F_2, $CFCl_3$, −78 °C; ii, F^-; iii, MeOH.

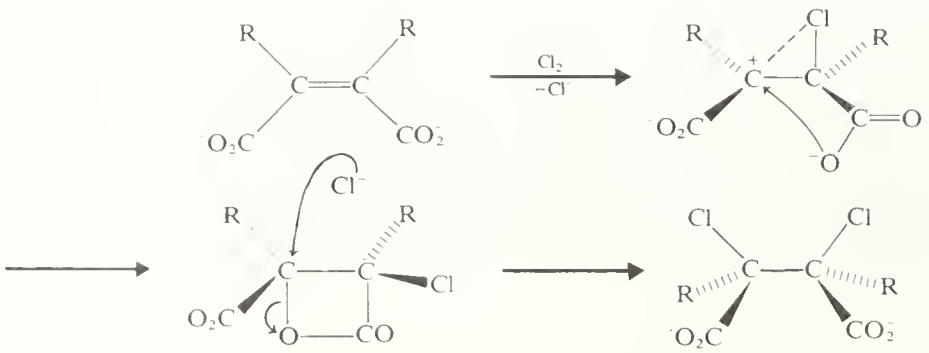
SCHEME 8

Preferred *syn* addition of chlorine appears to be characteristic of reactions where the double bond is in conjugation with an aromatic system (see Scheme 9). There is evidence to suggest than an intermediate carbenium ion is generated, but a process involving a four-membered ring transition-state cannot be ruled out. The stereochemistry of addition may also be influenced by competition between halogen and either neighbouring groups (Scheme 10) or solvent in the bridging step.[35]



(Ref. 34)

SCHEME 9



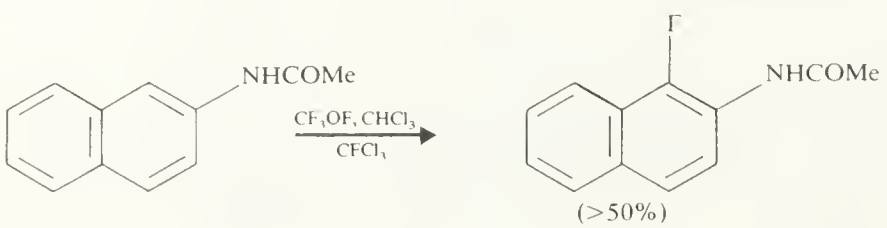
SCHEME 10

(*iii*) *Aromatic substitution.* Direct fluorination of aromatic compounds can be achieved under carefully controlled conditions and the isomeric proportions (Scheme 11) indicate the electrophilic nature of these reactions.[36] Fluoroxy compounds, *e.g.* CF_3OF, have also been shown to be excellent reagents for the substitution of fluorine for hydrogen in electron-rich aromatic systems (equation 17).[18a]

$$F_2 + XC_6H_5 \xrightarrow[-35\,^\circ C]{MeCN} XC_6H_4F$$

	ortho	+ *meta*	+ *para*
$X = CH_3$	50	10	40
$X = F$	40	10	50
$X = NO_2$	13	79	8

SCHEME 11



(17)

Tin, silicon, boron, mercury, magnesium, and thallium organometallic systems have been particularly effective in aromatic brominations and iodinations[37] (see Scheme 12).

1. $p\text{-}R^1_3SnC_6H_4R^2 \xrightarrow[CCl_4]{I_2} IC_6H_4R^2 + R^1_3SnI$

2. $PhSiMe_3 \xrightarrow[H_2O]{Br_2} PhBr + Me_3SiOH + HBr$

SCHEME 12

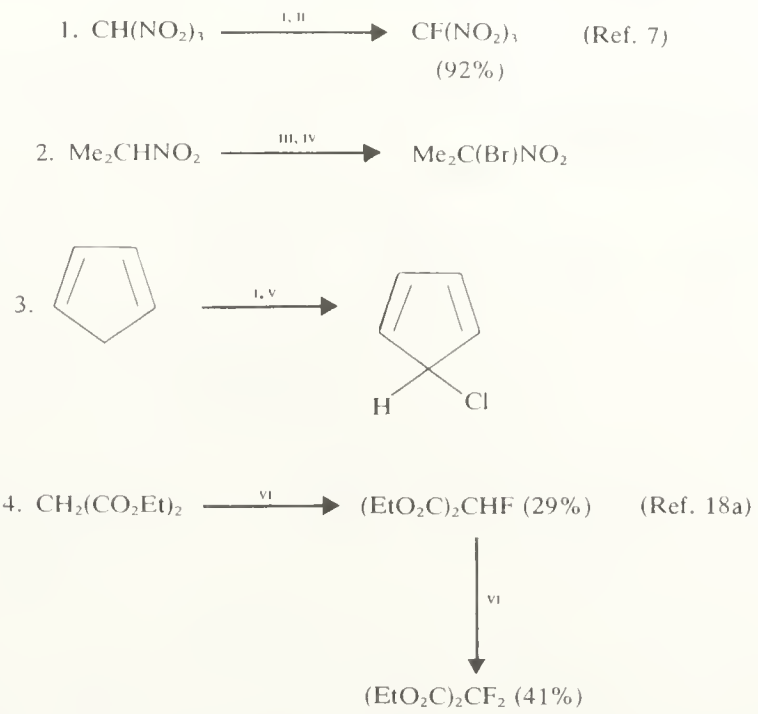
The literature on the substitution of aromatic compounds by electrophilic halogenating agents is vast and in general no attempt has been made to cover the area, except with regard to unusual aspects such as electrophilic fluorination, *etc.*, which has been briefly covered here and in other sections. Some general examples are given in the tables but the reader is referred to other works on the subject[37,38] for more detail.

3.2.4.3 Reactions with carbanions

Just as the electrophilic nature of halogen may be modified by covalent bonding to other atoms, so the electrophilic halogenation of carbon at C—Y may be enhanced by a

(18)

variety of groups (Y in equation 18). Clearly this particular process is facilitated by groups or atoms that make the carbon atom more carbanionic in character, the extreme case being a reaction in which a carbanion is generated.[1] For some examples, see Scheme 13.



i, OH ; ii, F_2, N_2, H_2O, 0–5 °C; iii, base; iv, Br_2; v, ClONa; vi, NaOEt, ClO_3F.

SCHEME 13

The displacement of tin (and other metals) has already been mentioned under electrophilic aromatic substitution (see p. 508). Similar displacements also take place at saturated carbon and many of these are clearly electrophilic substitutions (equation 19).[1]

(19)

Relative rates: R = Me, 100; Et, 84; Pr^n, 12; Pr^i, 2.5.

Selected examples of electrophilic halogenation are listed in Table 5.

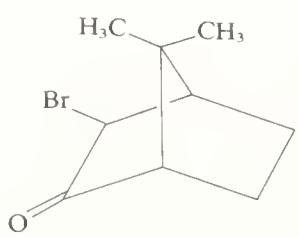
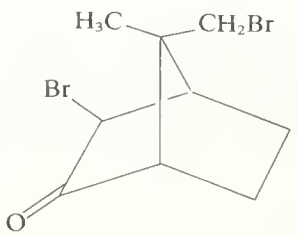
TABLE 5
Electrophilic Halogenation

(a) *Substitution at saturated carbon*

1. $Me_2CHCH_3 + Br_2 \xrightarrow[-20\,^\circ C]{SbF_5,\ SO_2} Me_2CHCH_2Br + Me_2CBrCH_2Br$[a]

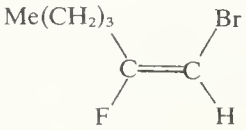
2. $CH_3CH_2CH_3 + Cl_2 \xrightarrow[dark]{PCl_5,\ 25\,^\circ C} (CH_3)_2CHCl\ (17.4\%) + CH_3CH_2CH_2Cl\ (12.6\%)$[b]

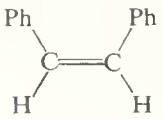
3. Dodecane + Br_2/Cl_2 $\xrightarrow{\text{catalyst}}$ Bromododecane + HCl[c]

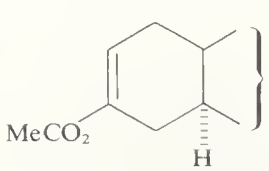
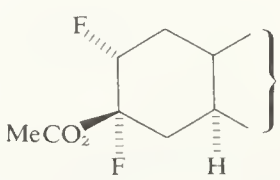
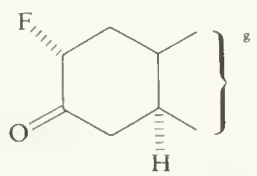
4.  $\xrightarrow{Br_2,\ ClSO_3H}$  [d]

(b) *Reaction with unsaturated systems*

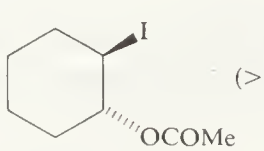
(i) *Aliphatic addition*

5. $Me(CH_2)_3C{\equiv}CH + BrF\ (HF,\ MeCONHBr) \xrightarrow{Et_2O,\ -78\,^\circ C}$  (95%) + *cis* product (5%)[e]

6.  + *N*-Bromosuccinimide $\xrightarrow[Et_2O]{HF,\ pyridine}$ (±)-*erythro*-PhCHFCHBrPh (43%) + (±)-*threo*-PhCHFCHBrPh (18%)[f]

7.  $\xrightarrow{CF_3OF,\ CFCl_3}$  $\xrightarrow{OH^-}$  [g]

8. $PhC{\equiv}CH \xrightarrow{EtOCl} PhC(OEt)_2CHCl_2 \xrightarrow{H_2O} PhCOCHCl_2$[h]

9.  + *N*-Iodosuccinimide $\xrightarrow[CHCl_3]{MeCO_2H}$  (>95%)[i]

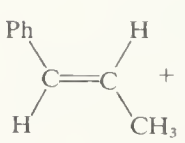
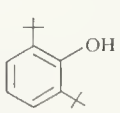
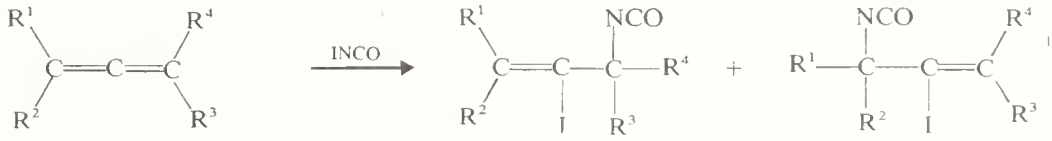
10.  + DBr $\xrightarrow[dark]{\text{trace}}$  (±)-*threo*-$CH_3CHDCHBrPh$ (87% *cis* addition)[j]

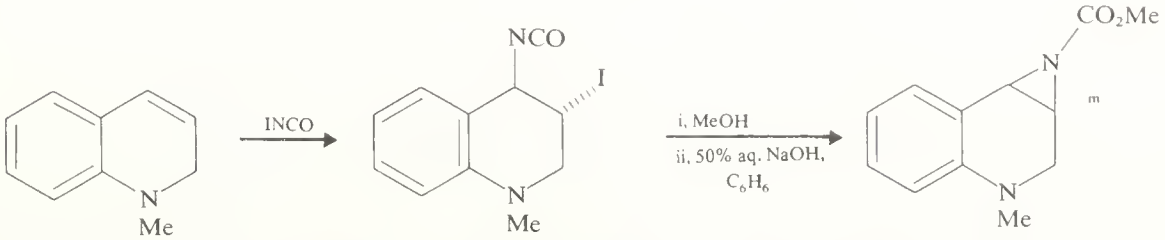
TABLE 5 (*continued*)

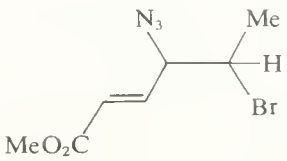
(b) *Reaction with unsaturated systems (cont.)*

(*i*) *Aliphatic addition (cont.)*

11. *cis*- or *trans*-MeCH=CHMe + DBr $\xrightarrow[\text{radical inhibitor}]{CH_3CO_2D}$ *threro*-MeCHBrCHDMe (60%) + *erythro*-MeCHBrCHDMe (40%)[k]

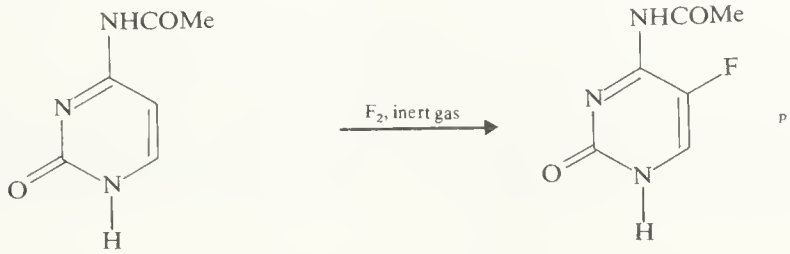
12. 

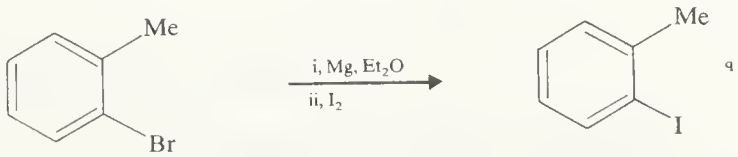
13. 

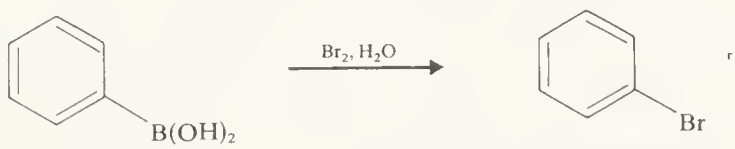
14. *trans,trans*-$MeO_2CCH{=}CH{-}CH{=}CHMe$ $\xrightarrow[CH_2Cl_2,\ 25\,^\circ C]{BrN_3}$ 

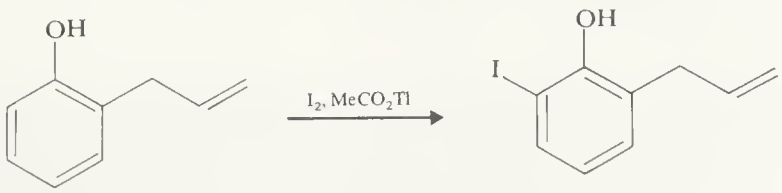
15. *trans*-MeCH=CHMe $\xrightarrow{IN_3}$ *erythro*-$MeCHN_3CHIMe$[o]

(*ii*) *Aromatic substitution*

16. 

17. 

18. 

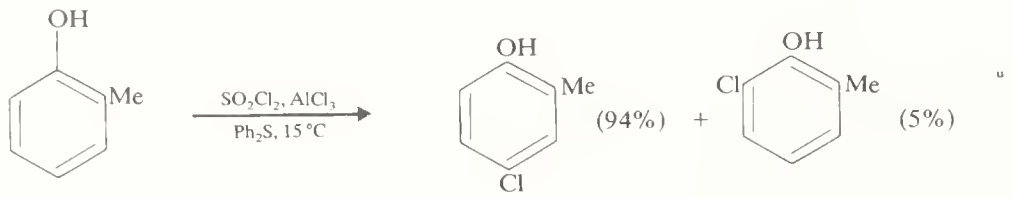
19. 

20. 

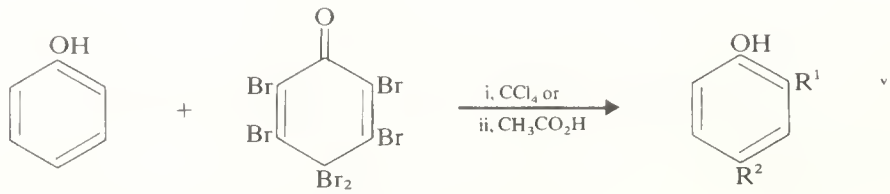
TABLE 5 (*continued*)

(b) *Reaction with unsaturated systems*

(*ii*) *Aromatic substitution*

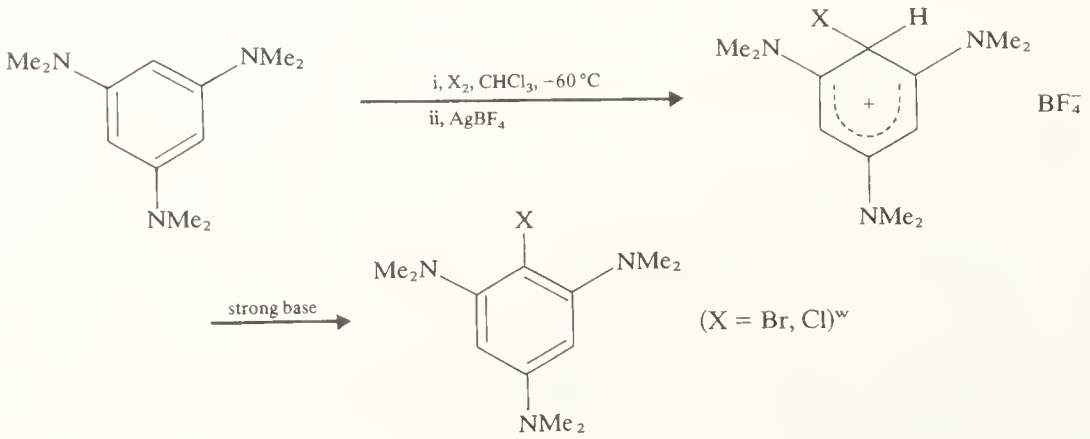
21. 

[u]

22. 

[v]

i, $R^1 = Br$, $R^2 = H$; $R^1 = H$, $R^2 = Br$ 87 : 13
ii, $R^1 = Br$, $R^2 = H$; $R^1 = H$, $R^2 = Br$ 11 : 89

23. 

(X = Br, Cl)[w]

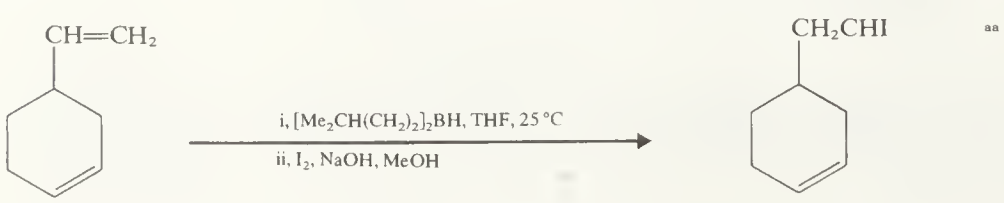
(c) *Reactions with carbanions*

24. $n\text{-}C_4H_9CH_2CO_2Et \xrightarrow[\text{ii, } I_2, \text{ THF, } -78\ ^\circ C]{\text{i, } C_6H_{11}NLiPr^i, \text{ THF, } -78\ ^\circ C} n\text{-}C_4H_9CHICO_2Et$ [x] (95%)

25. $cis\text{-}ClHC{=}CHCl \xrightarrow[0\ ^\circ C]{PhLi,\ Et_2O} ClC{\equiv}CLi \xrightarrow[-50\ ^\circ C]{Br_2} ClC{\equiv}CBr$ [y]

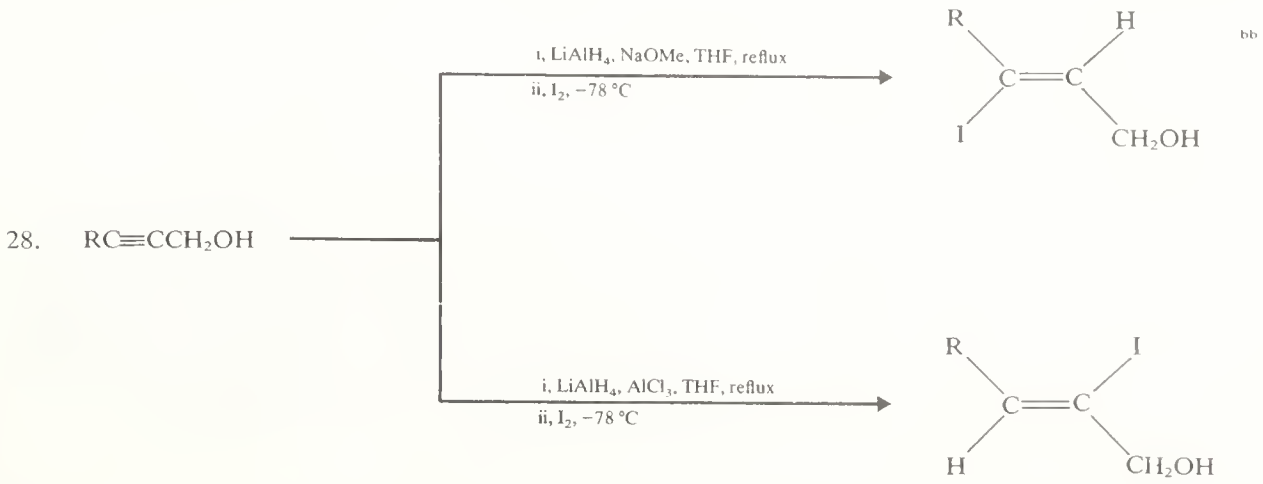
$HBrC{=}CBrH \xrightarrow[\text{ii, } I_2, -50\ ^\circ C]{\text{i, } LiNH_2, \text{ liq. } NH_3} BrC{\equiv}CI$ [y]

26. $R^1R^2C{=}CHCu \xrightarrow{HgBr_2} (R^1R^2C{=}CH)_2Hg \xrightarrow[py]{Br_2} R^1R^2C{=}CHBr$ [z]

27. 

[aa]

TABLE 5 (*continued*)

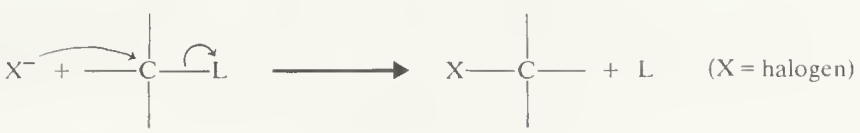


[a] Y. Halpern, *Israel J. Chem.*, 1975, **13,** 99 (*Chem. Abs.*, 1976, **85,** 32 350). [b] G. A. Olah, P. Schilling, R. Renner, and I. Kerekes, *J. Org. Chem.*, 1974, **39,** 3472. [c] Ref. 5, p. 523. [d] C. R. Eck, R. W. Mills, and T. Money, *J.C.S. Perkin I*, 1975, 251. [e] R. E. A. Dear, *J. Org. Chem.*, 1970, **35,** 1703. [f] M. Zupan and A. Pollak, *J.C.S. Perkin I*, 1976, 971. [g] D. H. R. Barton, *Pure Appl. Chem.*, 1970, **21,** 285. [h] Ref. 22, p. 116. [i] M. Adinolfi, M. Parrilli, G. Barone, G. Laonigro, and L. Mangoni, *Tetrahedron Letters*, 1976, 3661. [j] M. J. S. Dewar and R. C. Fahey, *J. Amer. Chem. Soc.*, 1963, **85,** 3645. [k] D. J. Pasto, G. R. Meyer, and S. Kang, *ibid.*, 1969, **91,** 2163. [l] T. Greibrokk, *Acta Chem. Scand.*, 1973, **27,** 3368. [m] *ibid.*, 1972, **26,** 3305. [n] A. Hassner and J. Keogh, *Tetrahedron Letters*, 1975, 1575 (used in prep. of azirine in low yield). [o] A. Hassner, G. J. Mathews, and F. W. Fowler, *J. Amer. Chem. Soc.*, 1969, **91,** 5046 (used in prep. of aziridine). [p] T. Kanai, M. Ichino, and T. Nakamura, *Japan Kokai*, **74**, 76 882 (*Chem. Abs.*, 1975, **82,** 16 863). [q] R. L. Datta and H. K. Mitter, *J. Amer. Chem. Soc.*, 1919, **41,** 287. [r] Ref. 37, p. 255. [s] R. C. Cambie, P. S. Rutledge, T. Smith-Palmer, and P. D. Woodgate, *J.C.S. Perkin I*, 1976, 1161. [t] Ref. 101, p. 42; R. D. Chambers, unpublished observation. [u] W. D. Watson, *Tetrahedron*, 1976, **30,** 2591. [v] V. Calo, L. Lopez, G. Pesce, F. Ciminale, and P. E. Todesco, *J.C.S. Perkin II*, 1974, 1189. [w] P. Menzel and F. Effenberger, *Angew. Chem. Internat. Edn.*, 1972, **11,** 922. [x] M. W. Rathke and A. Lindert, *Tetrahedron Letters*, 1971, 3995. [y] E. Kloster-Jenson, *Tetrahedron*, 1971, **27,** 33. [z] J. F. Normant, C. Chuit, G. Cahiez, and J. Villieras, *Synthesis*, 1974, 803. [aa] H. C. Brown, M. W. Rathke, and M. M. Rogic, *J. Amer. Chem. Soc.*, 1968, **90,** 5038. [bb] E. J. Corey, J. A. Katzenellenbogen, and G. H. Posner, *ibid.*, 1967, **89,** 4245.

3.2.5 Nucleophilic halogenations [1–3,7–10,18a]

3.2.5.1 By displacement of functional groups

A simple process (Scheme 14) for introducing halogen employs halide ion in a nucleophilic displacement process:



Clearly, when the process involves displacement from a saturated carbon atom, then a suitably efficient leaving group is required, whereas for displacements from olefins or aromatic compounds, the system must be activated by substituent groups. Solvent plays a crucial role since the solvation energies of halide ions in water are F^-, 506; Cl^-, 364; Br^-, 335; and I^-, 293 kJ mol^{-1} and, not surprisingly, iodide is the most effective nucleophile in aqueous systems. In aprotic solvents, however, fluoride ion can be a very powerful nucleophile, although we still have the considerable effect of the counter-ion to consider. It is clear that interaction with the counter-ion is very significant because the efficiency of the

$$Me(CH_2)_2CH(Me)OTosyl + NaBr \xrightarrow{i} Me(CH_2)_2CH(Me)Br \quad (Ref.\ 5)$$

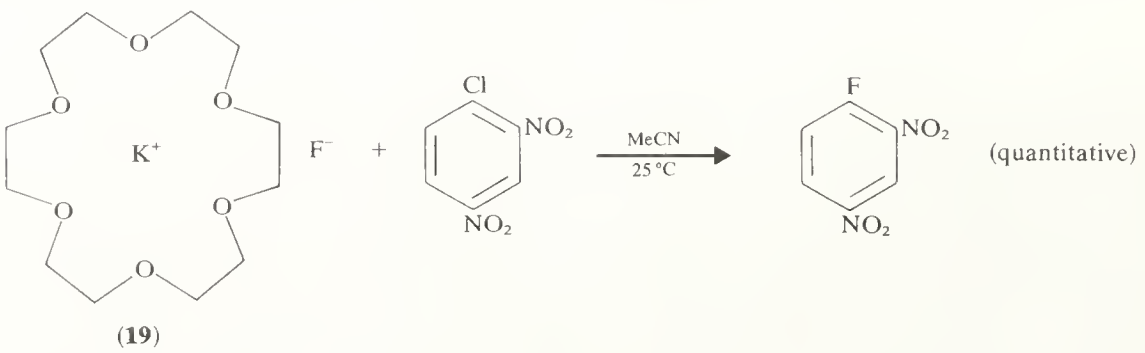
$$Me(CH_2)_2CH(OTs)CN \xrightarrow{ii} Me(CH_2)_2CHFCN\ (49\%) \quad (Ref.\ 18a)$$

$$C(NO_2)_4 \xrightarrow{iii} FC(NO_2)_3$$

i, $HO(CH_2)_2O(CH_2)_2OH$; ii, KF, $HO(CH_2)_2O(CH_2)_2OH$; iii, KF, DMF, 30 °C.

SCHEME 14

fluorides decreases, CsF > KF ≫ NaF, *i.e.* in the order of increasing lattice energy. Complexing the counter-ion with crown ethers such as 18-crown-6 (**19**) has very profound effects on reactivity (see Scheme 15) from two aspects: (i) reduced interaction between halide ion and counter ion enhances reactivity, and (ii) the complexes are sometimes soluble in the most unlikely solvents for alkali metal halides, *e.g.* the fluoride ion in the KF–18-crown-6 complex in benzene has been referred to as 'naked fluoride ion'.[39]



(**19**)

$$(\mathbf{19}) + KF + C_7H_{15}CH_2Br \xrightarrow[25\,^\circ C]{C_6H_6} C_7H_{15}CH_2F\ (92\%) + C_6H_{13}CH{=}CH_2\ (8\%)$$

SCHEME 15

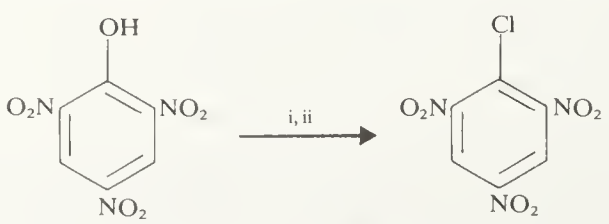
Phase-transfer catalysis is also a useful technique which may be applied to reactions with halide ions.[40,41] This technique depends on using aqueous solutions of, in this case, metal halides in contact with immiscible solvents and is exemplified by the reaction in equation (20). By adding tetra-alkylammonium salts the halides may be transferred at least partly into the non-aqueous phase, where the halide is less solvated and, therefore, more reactive.

$$C_7H_{15}CH_2OSO_2CH_3 + Cl^- \xrightarrow{i} C_7H_{15}CH_2Cl \qquad (20)$$

i, H_2O, hydrocarbon, tricaprylylammonium chloride.

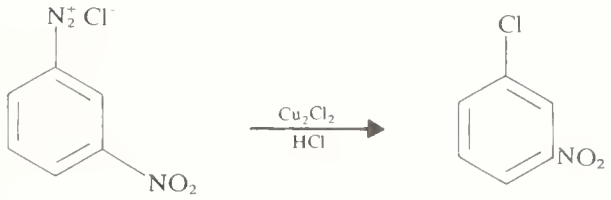
3.2.5.2 In aromatic systems

In the two well-known approaches, either the aromatic ring is activated by electron-withdrawing substituents as in equation (21) in order to promote an S_NAr process (substitution *via* addition–elimination, see later), or halide ion displaces the nitrogen of a diazonium salt[42] in the various processes like those attributed to Sandmeyer, Gattermann, and Balz–Schiemann,[7–10,43] as illustrated in equations (22)–(24).

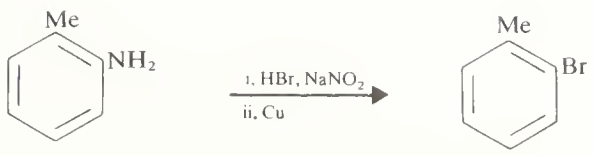


(21)

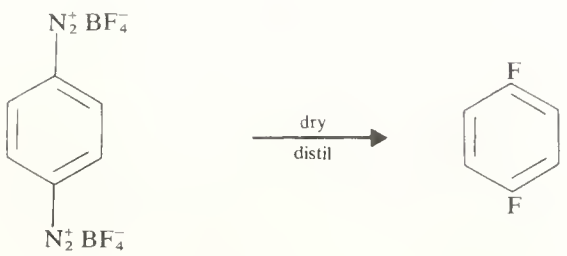
i, C_2H_5OH, pyridine; ii, $POCl_3$, C_6H_6



(68%) (Sandmeyer) (22)

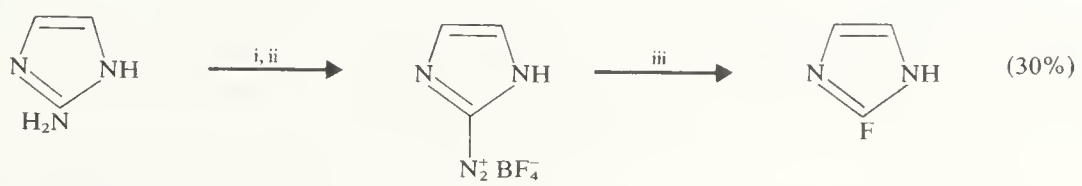


(Gattermann) (23)

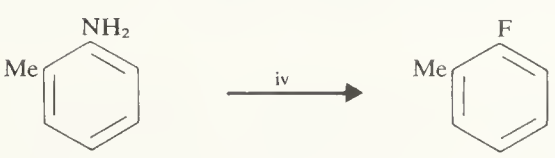


(30%) (Balz–Schiemann) (24)

Photolysis of diazonium tetrafluoroborates[44] and diazotization in the interesting pyridine–polyhalogen fluoride system has also been reported;[45] two examples are given in Scheme 16.



(not isolated)



i, 50% HBF_4; ii, $NaNO_2$; iii, $h\nu$; iv, NaF, pyridine $(HF)_n$, $NaNO_2$.

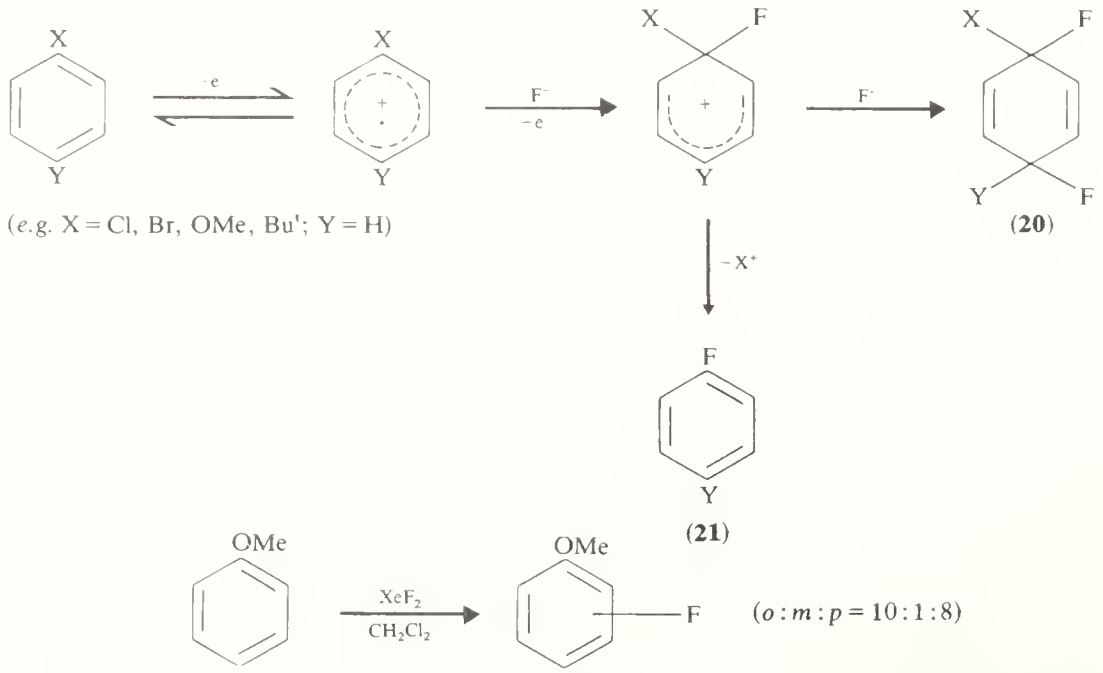
SCHEME 16

A relatively new technique of controlled fluorination[46] at a platinum anode may give (**20**) or (**21**), probably *via* a radical cation, and radical cations are also thought to be involved in reactions of xenon difluoride with aromatic systems[47] (see Scheme 17).

Other examples of nucleophilic halogenation are given in Table 6 (p.517).

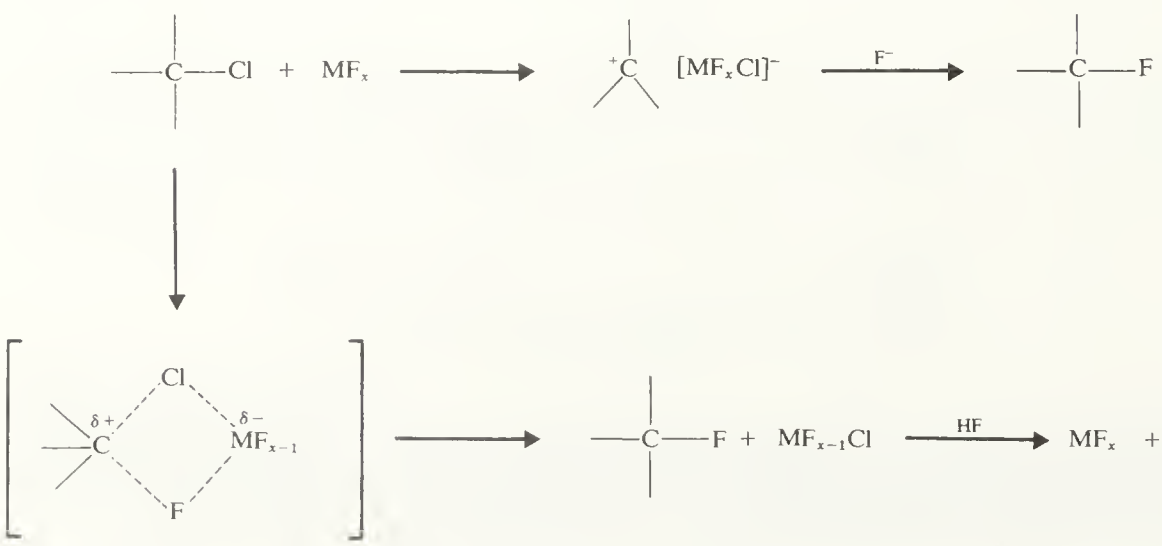
3.2.5.3 By halogen exchange

Essentially, there are two types of process available for halogen exchange involving either attack by Lewis acids or nucleophilic displacement by halide ion. The Lewis acid may either remove one halogen and transfer the other, or may be used in combination with a hydrogen halide, which then acts as the source of halide ion (equation 25). The Swarts reaction[1,2,3] illustrated in equation 25 is carried out on a considerable scale in industry and provides the basis of the fluorochemical business. As the number of fluorine



SCHEME 17

atoms attached to the chlorine-bearing carbon increases, it becomes progressively more difficult to effect further fluorination, as shown by the product distribution in equation (26). This is in agreement with the expectation that steric crowding encourages removal of chloride ion but that chlorine becomes a poorer donor as the electron-withdrawing power of the attached group is increased. Also consistent with this scheme is the observation (equation 27) that hexachloroethane is fluorinated in a symmetrical fashion, with no appreciable amounts of constitutionally unsymmetrical chlorofluoroethanes being formed.



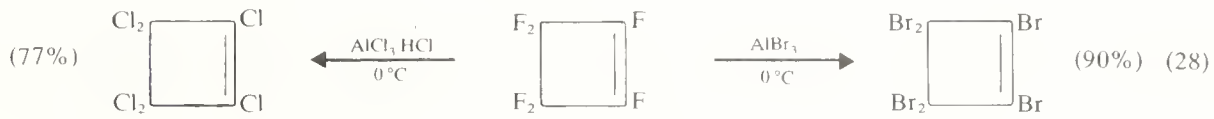
$$CCl_4 \xrightarrow{i} \underset{(9\%)}{CCl_3F} + \underset{(90\%)}{CCl_2F_2} + \underset{(0.5\%)}{CClF_3} \qquad (26)$$

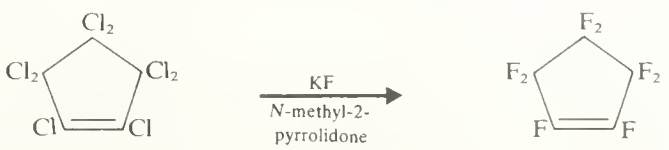
i, HF, $SbCl_3$, Cl_2, 110 °C, 30 atm.

$$CCl_3{-}CCl_3 \xrightarrow[SbF_5]{HF} CCl_3{-}CCl_2F \longrightarrow CCl_2F{-}CCl_2F \longrightarrow CCl_2F{-}CClF_2 \qquad (27)$$

$$\longrightarrow CClF_2{-}CClF_2$$

In contrast, exchange of fluorine for chlorine or bromine oftens occurs in reactions of fluorinated compounds with aluminium chloride or bromide[10] (equation 28). Exchange of chlorine for bromine will also occur, using boron tribromide[48] (equation 29). Halogen exchange may also be achieved by nucleophilic displacement[1(i),18(a)] by halide ion, either at a saturated carbon atom as in alkyl halides (equation 30) or from olefins or aromatic compounds, as in the synthesis of polyfluoro compounds (equation 31).





Examples of nucleophilic halogenation by halide exchange are given in Table 6.

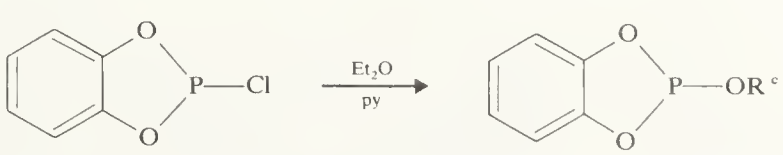
TABLE 6

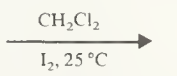
Nucleophilic Halogenations

(a) *By replacement of functional groups*

1. $CH_3(CH_2)_2CH_2OH + (C_2H_5)_2NCF_2CHClF \longrightarrow CH_3(CH_2)_2CH_2F$ (67%)[a]

2. $n\text{-}C_8H_{17}OH \xrightarrow[150\,°C]{Ph_2PF_3,\ CH_3CN} n\text{-}C_8H_{17}F$ (40%)[b]

3. ROH + 



4. 1-Adamantyl-OH $\xrightarrow[ii,\ NH_2NH_2]{i,\ COCl_2}$ $ROCONHNH_2 \xrightarrow{N.B.S.}$ RBr[d]

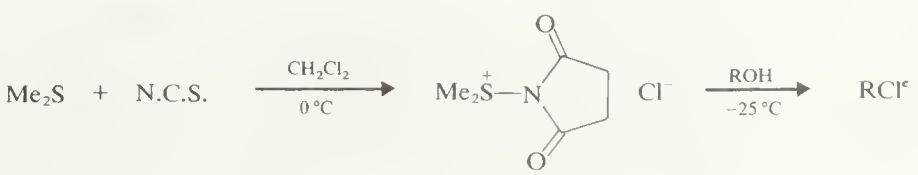
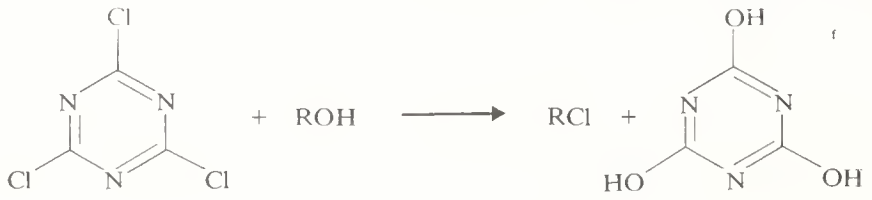
5. 

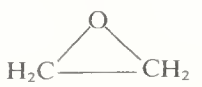
TABLE 6 (*continued*)

(a) *By replacement of functional groups cont.*)

6. 

[f]

7. $C_4H_9OC_4H_9 \xrightarrow[P_2O_5,\ \text{reflux}]{KI,\ H_3PO_4,} C_4H_9I$ (78%) [g]

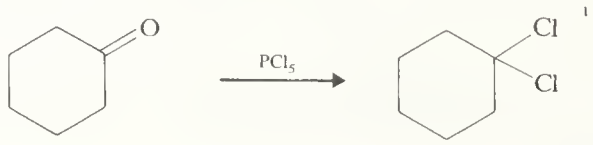
8. 

[h]

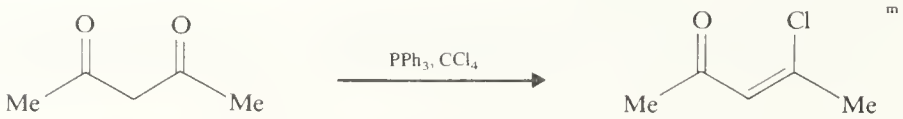
9. $PhCHO \xrightarrow[150\,^\circ C]{SF_4} PhCHF_2$ (81%) [i]

10. $HO_2CC{\equiv}CCO_2H \xrightarrow[170\,^\circ C]{SF_4} CF_3C{\equiv}CCF_3$ [j]

11. $Ph_2C{=}O \xrightarrow[CH_2Cl_2]{MoF_6,\ BF_3} Ph_2CHF_2$ (55%) [k].

12. 

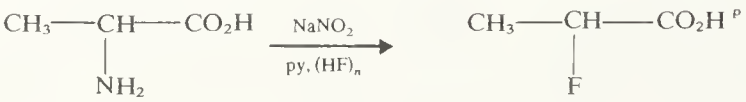
[l]

13. 

[m]

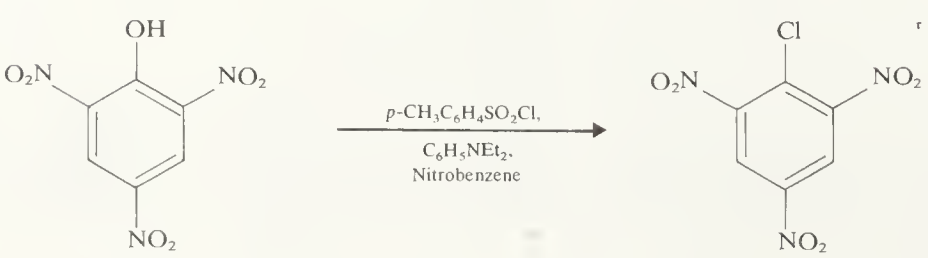
14. $PhCOBr + RhCl(PPh_3)_3 \longrightarrow PhBr$ (80%) [n]

15. $RCH_2NH_2 + CuX_2 + NO \xrightarrow{MeCN} RCHX_2$ [o]
R = $PhCH_2$, X = Cl (58%)

16. 

[p]

17. $C_6H_5OH \xrightarrow[Bu_3N,\ 50\,^\circ C]{COClF} C_6H_5OCOF \xrightarrow[800\,^\circ C]{Pt} C_6H_5F$ (70%) [q]

18. 

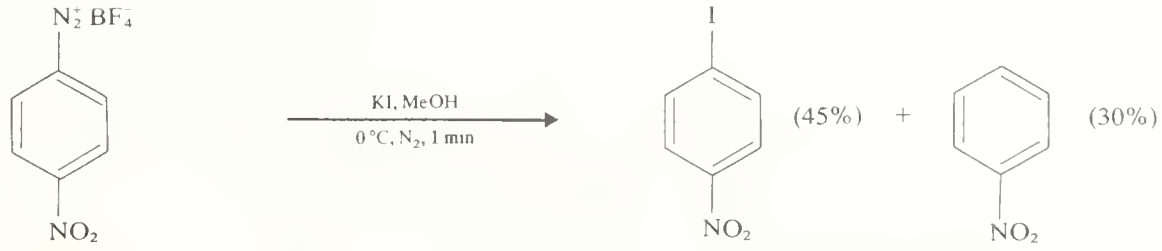
[r]

TABLE 6 (*continued*)

(a) *By replacement of functional groups*

19. 

(92–99%) [s]

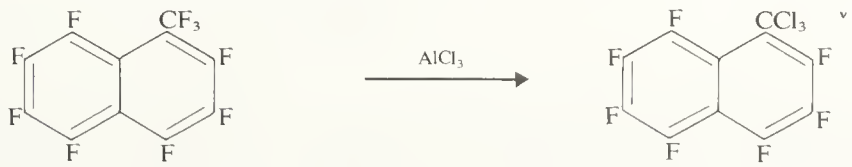
20. 

(45%) + (30%)

+ I_2 + CH_2O [t]

(b) *By halogen exchange*

21. $C_6H_5CCl_3 \xrightarrow[40\,^\circ C]{\text{anhydr. HF}} C_6H_5CF_3$ (70%) [u]

22. 

[v]

23. $R{-}Cl \xrightarrow{AlBr_3} R{-}Br$ [w]

24. $MeCHBrCH_2CH_2Br \xrightarrow[CH_2Cl_2]{MoCl_5} MeCHClCH_2CH_2Br$ (61%) [x]

25. $Ph_2CHBr + Bu_3SnCl \xrightarrow{50\,^\circ C} Ph_2CHCl$ (70%) [y]

26. $CHBrF_2 \xrightarrow[50\,^\circ C]{HgF_2} CHF_3$ [z]

27. $C_8H_{17}I \xrightarrow[100\,^\circ C]{AgF} C_8H_{17}F + C_6H_{13}CH{=}CH_2$ [aa]

28. $PhCD_2CH_2I \xrightarrow[25\,^\circ C,\ 7\ h]{HgF_2,\ \text{pentane}} PhCD_2CH_2F$ (12%) + $PhCH_2CD_2F$ (12%) [bb]

cf. $PhCH_2CH_2I \xrightarrow[C_6H_6,\ 96\ h,\ 90\,^\circ C]{\text{KF, 18-crown-6 ether}} PhCH{=}CH_2$ (99%) [bb]

29. $C_7H_{15}CH_2Br \xrightarrow[C_6H_6,\ 90\,^\circ C]{\text{KF, 18-crown-6 ether,}} C_7H_{15}CH_2F$ (92%) + $C_6H_{13}CH{=}CH_2$ (8%) [cc]

30. $HC{\equiv}C{-}CH_2Cl \xrightarrow{NaBr,\ DMF} HC{\equiv}C{-}CH_2Br$ [dd]

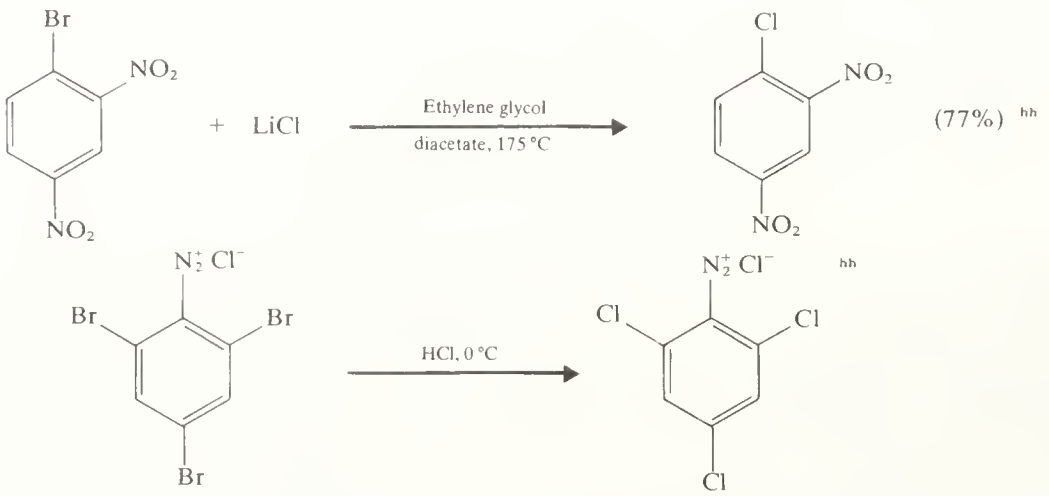
31. $Me_2CEtCl \xrightarrow[ZnCl_2,\ 100\ h]{NaI,\ CS_2,} Me_2CEtI$ (96%) [ee]

TABLE 6 (*continued*)

(b) *By halogen exchange (cont.)*

32. $n\text{-}C_8H_{17}Cl \xrightarrow[N\text{-methyl-2-pyrrolidinone}]{EtBr,\ NaBr} n\text{-}C_8H_{17}Br$ (93%) [ff]

33. $n\text{-}C_8H_{17}Cl \xrightarrow[\text{ammonium bromide}]{\text{Tricaprylylmethyl-}} n\text{-}C_8H_{17}Br$ [gg]

34. 

[a] Ref. 18a. [b] Ref. 18a. [c] E. J. Corey and J. E. Anderson, *J. Org. Chem.*, 1967, **32,** 4160. [d] D. L. J. Clive and C. V. Denyer, *Chem. Comm.*, 1971, 1112. [e] E. J. Corey, C. U. Kim, and M. Takeda, *Tetrahedron Letters*, 1972, 4339. [f] S. R. Sandler, *J. Org. Chem.*, 1970, **35,** 3967. [g] Ref. 3, p. 631. [h]. Ref. 7, p. 48. [i] Ref. 7, p. 49. [j] Ref. 7, p. 49. [k] Ref. 7, p. 52. [l] Ref. 2, p. 913. [m] L. Gruber, I. Tomoskozi, and L. Radics, *Synthesis*, 1975, 708. [n] J. Blum, E. Oppenheimer, and E. D. Bergmann, *J. Amer. Chem. Soc.*, 1967, **89,** 2338. [o] M. P. Doyle, B. Siegfried, and J. J. Hammond, *ibid.*, 1976, **98,** 1627. [p] G. A. Olah and J. Welch, *Synthesis*, 1974, 652. [q] K. O. Christie and A. E. Pavlath, *J. Org. Chem.*, 1966, **31,** 559. [r] Ref. 2, p. 896. [s] N. Saldabols, *Zhur. org. Khim.*, 1976, **12,** 1592 (*Chem. Abs.*, 1976, **85,** 160 030). [t] R. Kumar and P. R. Singh, *Tetrahedron Letters*, 1972, 613 (radical substitution of diazonium salt). [u] Ref. 7, p. 16. [v] Ref. 7, p. 102. [w] Ref. 5, p. 383. [x] J. San Filippo, Jr., A. F. Sowinski, and L. J. Romano, *J. Org. Chem.*, 1975, **40,** 3295. [y] E. C. Friedrich, P. F. Vartanian, and R. L. Holmstead, *J. Organometallic Chem.*, 1975, **102,** 41. [z] Ref. 7, p. 16. [aa] Ref. 7, p, 39. [bb] J. San Filippo, Jr. and L. J. Romano, *J. Org. Chem.*, 1975, **40,** 782. [cc] Ref. 39. [dd] Ref. 5, p. 383. [ee] J. A. Miller and M. J. Nunn, *J.C.S. Perkin I*, 1976, 416. [ff] W. E. Willy, D. R. McKean, and B. A. Garcia, *Bull. Chem. Soc. Japan*, 1976, **49,** 1989. [gg] C. M. Starks, *J. Amer. Chem. Soc.*, 1971, **93,** 195, and Ref. 40. [hh] J. Sauer and R. Huisgen, *Angew. Chem.*, 1960, **72,** 294.

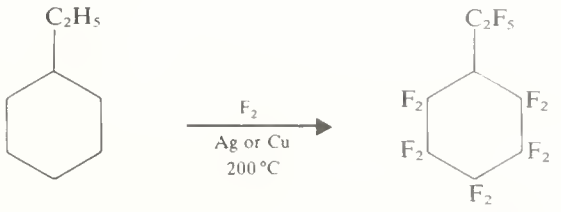
3.2.6 Synthesis of highly halogenated compounds

Many of the processes used for the synthesis of highly halogenated compounds are simply exhaustive halogenations using methods described under selective halogenation. However, in the following sections are some methods which are unique to the synthesis of highly halogenated derivatives.

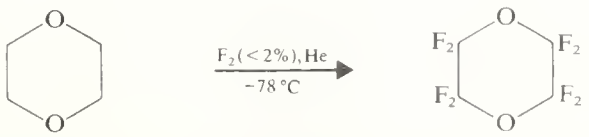
3.2.6.1 Polyfluoro compounds[2,7–11]

In principle, direct fluorination of an organic compound is an attractive possibility for the synthesis of highly fluorinated derivatives. As indicated earlier, such processes are highly exothermic and this creates the problem of how to carry out extensive fluorination without incurring C—C bond fission. Early work involved vapour-phase fluorination of hydrocarbons over metals (equation 32), the metal apparently being able to conduct

enough heat away from the system. This procedure is, however, of very limited application. More recent work has concentrated on high-dilution techniques and these have been used in the synthesis of a variety of fluorocarbon derivatives, *e.g.* equation (33), including polymers.[49]



(13%) (32)



(33)

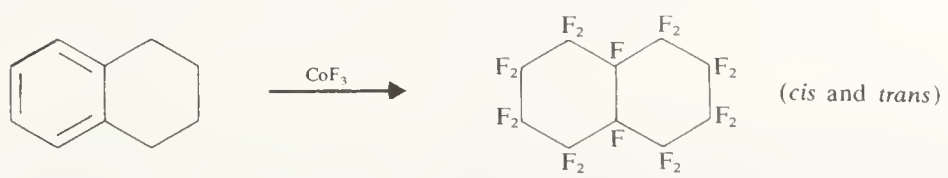
Graphite will absorb fluorine in the temperature range 300–500 °C, or react with fluorine atoms generated in a plasma, to form white solids with approximate composition $(CF)_n$.[50] They have excellent lubricating properties and high thermal stability, but the most interesting application is in lithium batteries as the cathode.

High-valency metal fluorides are easier to use than elemental fluorine for extensive fluorination. The process is illustrated in Scheme 18 by CoF_3, although many systems have now been investigated.[7–11,51]

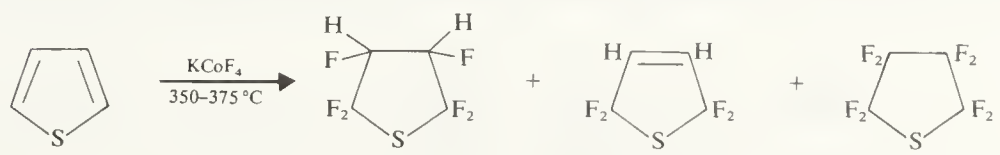
1. 

($\Delta H = -209$ to -230 kJ mol^{-1}, *cf.* -418 kJ mol^{-1} for direct fluorination)

2. $2CoF_2 + F_2 \longrightarrow 2CoF_3$ (ΔH (250 °C) = -234 kJ mol^{-1})

3. 

(*cis* and *trans*)

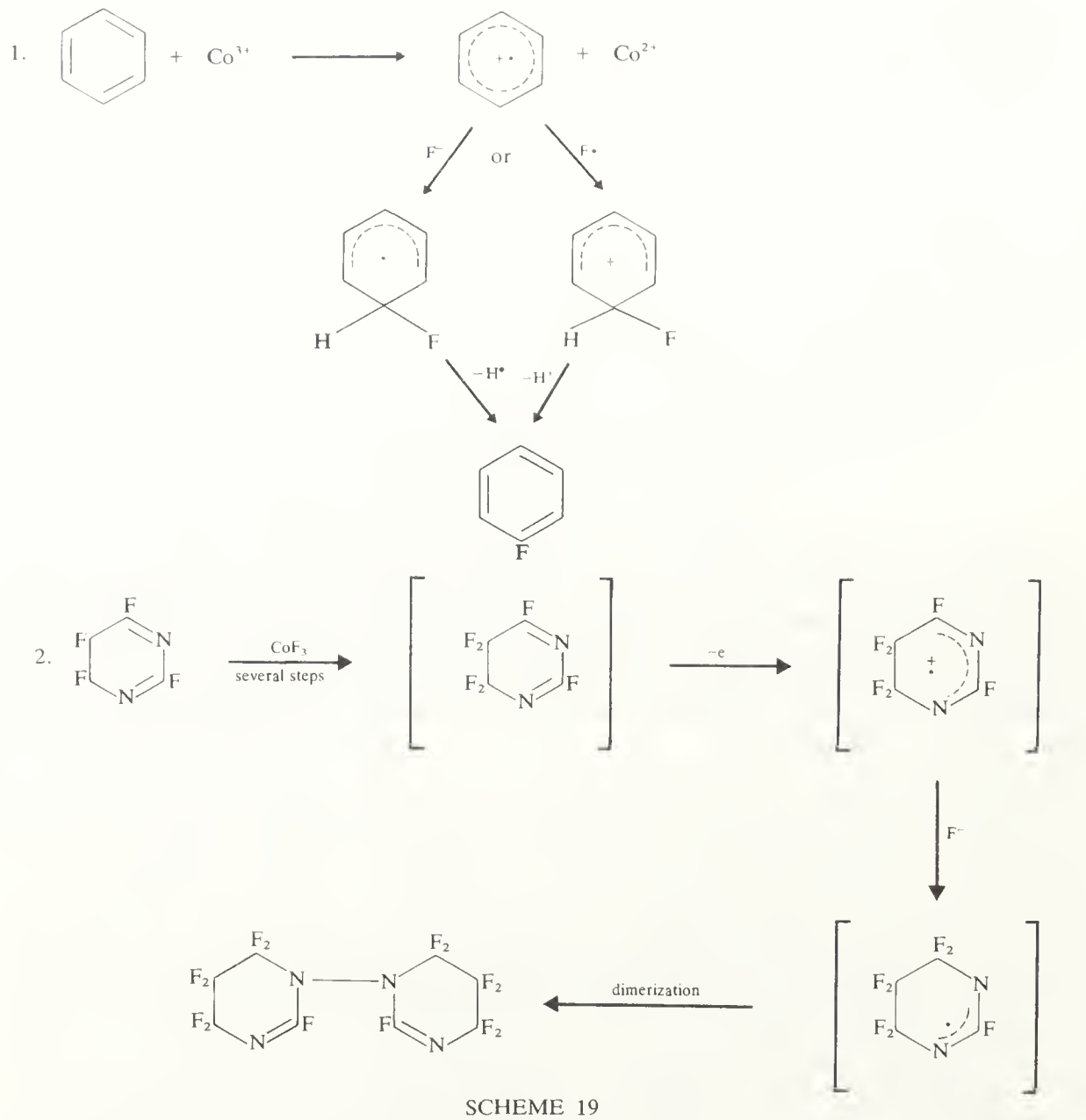
4. 

(25%) (21%) (14%)

SCHEME 18

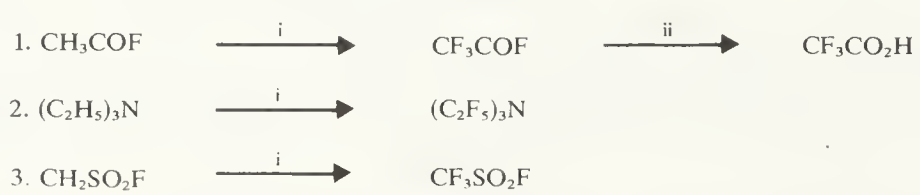
One-electron oxidations have been proposed as the first step for the reactions of CoF_3 and some experimental support for this comes from the product isolated from its reaction with tetrafluoropyrimidine[52] (see Scheme 19).

A procedure which has no direct equivalent in other halogenations is electrochemical fluorination.[7–11,53] Many organic compounds dissolve readily in anhydrous hydrogen fluoride to give conducting solutions and when direct electric current is passed through a solution of this type, or through a suspension of a compound in anhydrous hydrogen fluoride with electrolyte



SCHEME 19

added, then hydrogen is evolved at the cathode and organic material is fluorinated at the anode. This process is most advantageous for polar compounds such as amines or carboxylic acids (see Scheme 20).

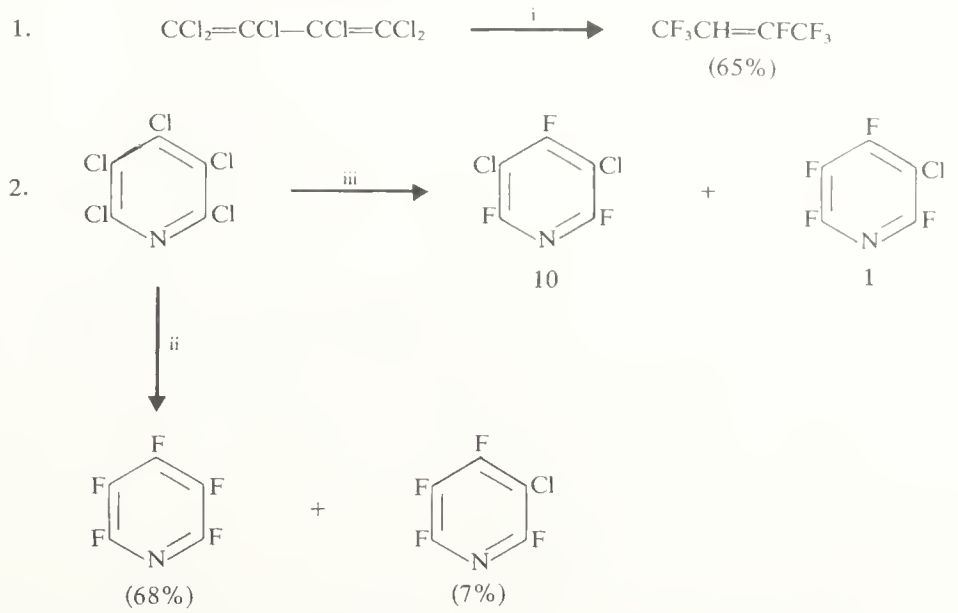


i, Electrochemical fluorination, HF; ii, H_2O.

SCHEME 20

In systems activated towards nucleophilic attack, potassium fluoride may be used to prepare highly fluorinated products from the corresponding polychloro compounds. It is well known that, although saturated polychlorocarbons are unreactive towards nucleophilic attack, polychloro-olefins and aromatics are quite reactive. Therefore the aromatic derivatives may be fluorinated by potassium fluoride, either in an aprotic solvent, or at

elevated temperatures, in the absence of a solvent. Using the latter process with aromatic polychlorinated nitrogen heterocycles, a whole range of polyfluorinated compounds may be obtained[7,12,54] (see Scheme 21).

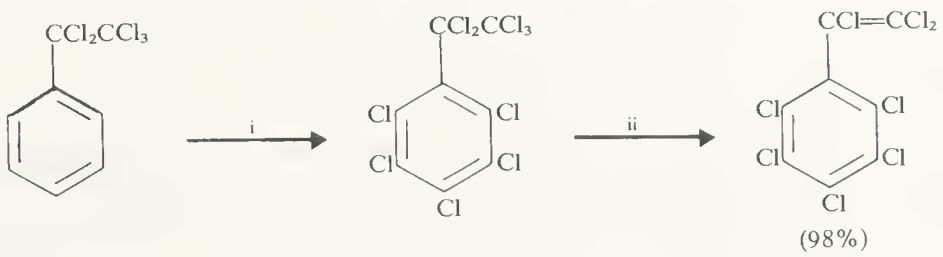


i, KF, *N*-methyl-2-pyrrolidone, >190 °C; ii, KF, 480 °C, autoclave; iii, KF, sulpholan, 190–210 °C.

SCHEME 21

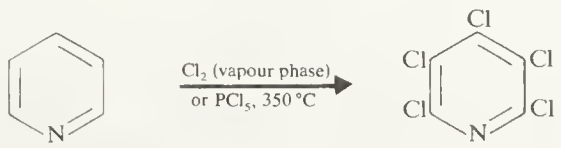
3.2.6.2 Other polyhalogenated compounds[12,55]

A truly remarkable chlorination procedure has been developed for the synthesis of polychlorobenzenoid aromatic compounds and certain heterocyclic systems. The reagent consists of a mixture of sulphuryl chloride, sulphur monochloride, and aluminium chloride, the relative proportions varying according to preference.[56] Fully chlorinated systems are produced with great ease, especially when the crowding in some of the molecules is considered (equation 34). A more conventional reaction is the exhaustive vapour-phase chlorination of pyridine[12] (equation 35).



(34)

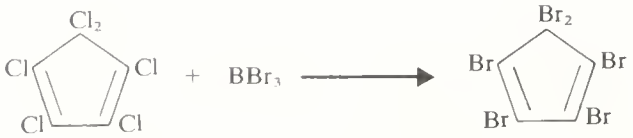
i, SO_2Cl_2, S_2Cl_2, $AlCl_3$; ii, KI, $MeCO_2H$.



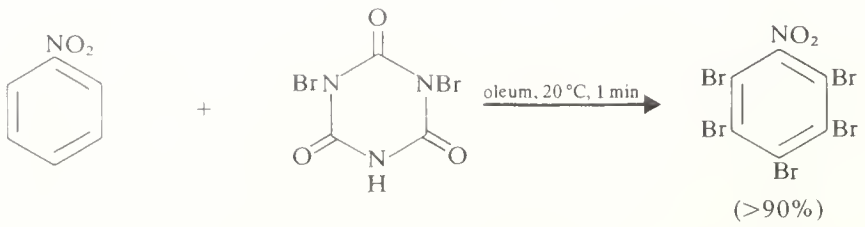
(35)

Polybromo compounds have been produced by the reaction of bromine monochloride under high pressure (equation 36),[57] and by treating a polychloro compound with boron tribromide[55] (equation 37). However, perhaps an even more promising procedure, illustrated in equations (38) and (39), employs dibromoisocyanuric acid in strong acids to effect the one-step perbromination of deactivated aromatic compounds.[58]

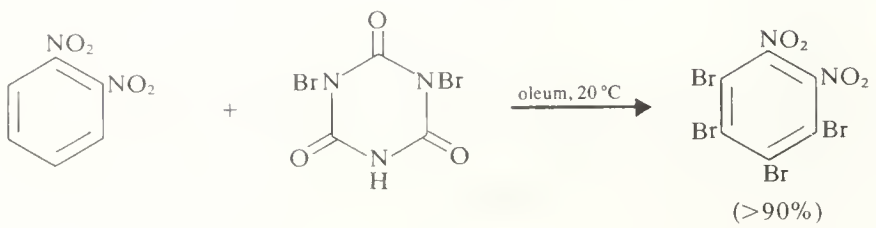
$$C_6H_6 + BrCl \xrightarrow[\text{high pressure}]{CH_2Cl_2,\ FeCl_3} C_6Br_6 \quad (98\%) \tag{36}$$



(37)



(38)



(39)

3.3 HALOALKANES

3.3.1 Bonding properties

Some average bond properties for halogen derivatives are given in Table 7, while carbon–halogen bond dissociation energies are in Table 8. It is evident from the data in Table 7 that steric effects will be very important for the halogens, except for fluorine, and from the data in Table 8 we see a sharp decline in bond dissociation energies from fluorine to iodine. Also, the influence of a steric effect is evident in comparing the dissociation energies of bonds to trifluoromethyl with those to trichloromethyl. There is, indeed, a closer relationship between the values for bonds to methyl and trifluoromethyl than to trichloromethyl, where it appears that crowding becomes important. In fact, it is this crowding which limits the stability of perchloroalkanes, where repulsive forces quickly lower the C—C bond dissociation energy with increasing length of the carbon chain. Consequently, polyperchloroethylene, $(CCl_2—CCl_2)_n$, has not been obtained, which is in sharp contrast to the very stable polytetrafluoroethylene, $(CF_2—CF_2)_n$.

TABLE 7

Average Bond Properties[a]

Bond	*Bond lengths* (pm)	*Covalent radii* (pm)	*van der Waals radii* (pm)
C—H	109.1	30	120
C—F	138.1	64	135
C—Cl	176.7	99	180
C—Br	193.7	114	195
C—I	213.5	133	215

[a] Ref. 1, p. 21.

TABLE 8

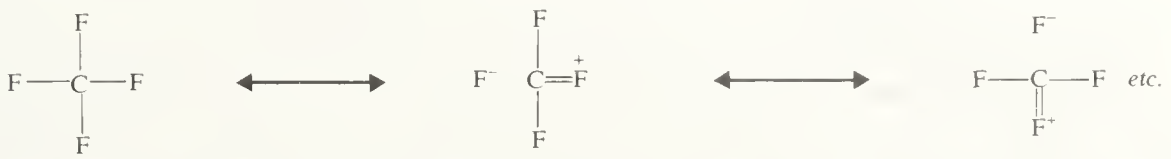
CY_3—X Bond Dissociation Energies (kJ mol^{-1})[a]

CY_3	X					
	H	F	Cl	Br	I	CH_3
CH_3	435	452	351	293	234	368
CF_3	444	(544)[b]	(360)[b]	297	226	(418)[b]
CCl_3	402	444	305	226	—	—

[a] Ref. 1, p. 687. [b] Values subject to larger uncertainties.

This highlights what is a unique relationship between highly fluorinated systems and the corresponding hydrocarbon compounds[7–10] because, in principle, a whole synthetic organic chemistry is possible, based on fluorocarbon rather than hydrocarbon skeletons, and a considerable literature already exists on the subject. The limitations of stereochemistry on the development of other polyhalocarbon systems only apply, of course, to the larger saturated systems and a vast array of perhalocarbons are known. However, the somewhat restricted development of the chemistry of these polyhalo systems arises from the relative dearth of structural probes. The main problem is that, whereas ^{19}F n.m.r. spectroscopy is available, only ^{13}C n.m.r. spectroscopy[59] is available for the other halocarbon systems and, so far, this has not made a major impact on the development of these systems.

Bond-shortening and -strengthening in fluoromethanes, with successive additions of fluorine, is well-known and the effect is a contributory factor to the stability of highly fluorinated alkanes. The basis of the effect has been the subject of much discussion, following Pauling's double-bond, no-bond description:[60]



However, regardless of the way in which the effect is rationalized it is, nevertheless, very significant, *e.g.* it is estimated[61] that disproportionation of fluoromethane to methane and tetrafluoromethane is exothermic by about 151 kJ mol^{-1} of tetrafluoromethane:

$$4CH_3F \rightleftharpoons CF_4 + 3CH_4 \quad \Delta H = -151 \text{ kJ mol}^{-1}$$

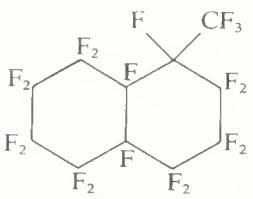
3.3.2 Industrial aspects

Many polyhaloalkanes are characterized by a high degree of chemical inertness and thermal stability and this is reflected in the examples of industrial applications given in Table 9. There is a high consumption of this group of compounds, especially as refrigerants, industrial solvents, and aerosol propellants. Much is being written and argued about the effect of chlorofluoroalkanes on the ozone layer[62] and this problem arises from the very inertness of these compounds (*e.g.* CF_2Cl_2) until they reach the stratosphere. Only at this stage can photolysis occur on interaction with the short-wavelength ultraviolet light and the chlorine atoms produced catalyse the decomposition of ozone. At the time of writing, however, it is impossible to say whether this will effect changes which are significant in comparison with the already large differences in the ozone layer, *e.g.* with latitude. Only careful monitoring will resolve this problem.

Polyfluoro compounds have the unique property of oil repellancy and, consequently, use as surfactants and in surface treatment of textiles, *etc.* is becoming an increasingly important aspect. The unusually low intermolecular forces in fluorocarbons result in very

TABLE 9

Some Industrial Applications of Haloalkanes and Related Compounds

Product	*Application*
CCl_4; $CHCl{=}CCl_2$; CH_3CCl_3; $CF_2ClCFCl_2$	Industrial solvents
CF_2Cl_2; $CF_2ClCFCl_2$	Refrigerants, aerosol propellants; blowing agent for foam plastics
CF_2ClBr; CF_2Br_2	Fire extinguishers
Various polybromo and polychloro compounds	Flame retardants
 $(C_4F_9)_3N$; telomers of chlorotrifluoroethylene, $X(CF_2CFCl)_nY$	Inert fluids
P.V.C., $(CH_2CHCl)_n$; P.V.F., $(CH_2CHF)_n$	Thermoplastics
P.V.C.; poly(vinylidine chloride), $(CH_2CCl_2)_n$	Fibres
P.T.F.E., $(CF_2CF_2)_n$; polychlorotrifluoro ethylene, $(CF_2CFCl)_n$; co-polymer of $CH_2{=}CF_2$ and $CF_3CF{=}CF_2$, 'Viton A' elastomer, $[CH_2CF_2CF_2CF(CF_3)]_n$	Materials of high thermal and chemical stability
$CF_3CHClBr$ ('Fluothan')	General anaesthetic
$CF_3(CF_2)_nBr$	Radio-opaque materials (X-ray inspection of organs)
Graphite fluorides, *e.g.* $(C_1F_1)_n$	High-temperature lubricants; cathodes for lithium batteries ($Li+C_1F_1 \rightarrow LiF+C$)
D.D.T., $(p\text{-}ClC_6H_4)_2CHCCl_3$	Insecticides
B.H.C., $C_6H_6Cl_6$	

similar boiling-points to the corresponding hydrocarbon, in spite of the substantial increase in molecular weight, and it is this same effect which produces the now familiar non-stick properties of polytetrafluoroethylene. There is a growing demand for the inert fluorocarbon fluids by, for example, the electronics industry, and some of these materials are even being suggested as potential artificial blood plasma.[63] This arises because they are biochemically inert while, like many other organic compounds, they are able to dissolve quite significant amounts of oxygen. Emulsions of perfluorocarbons have been used to replace completely the blood in dogs and monkeys, with the astonishing result that it is possible for the animal to survive and subsequently regenerate its own blood supply. This is with no apparent ill-effect, and the fluorocarbon is gradually exhaled through the lungs. However, use in humans is a long way from a clinical possibility but, much closer, is the use of such systems as media for temporary storage of organs during transplant procedures.

It is impossible here to deal with the large range of functional organic compounds containing halogen atoms which have industrial applications. Much activity is centred on the introduction of a single fluorine atom into biologically significant molecules or established drugs,[13,21,64] since the fluorine atom frequently increases the efficacy of the drug or creates some enzyme blocking agent. Many halogenated compounds, particularly chlorinated derivatives,[65] have found wide use as insectides, *e.g.* DDT, BHC, and plant protection agents. While some of these systems have led to severe environmental problems due to the long life of these materials and their accumulation in the fat of birds and animals, it would be a mistake to assume that all polychloro compounds will lead to similar problems.

Bromofluoro compounds like CF_3Br and CF_2BrCl are extremely important as fire-fighting agents.[66]

3.3.3 Nucleophilic displacement of halogen[1,67,68]

In comparing the processes which involve displacement of halogen from a saturated system there are several points to be borne in mind:

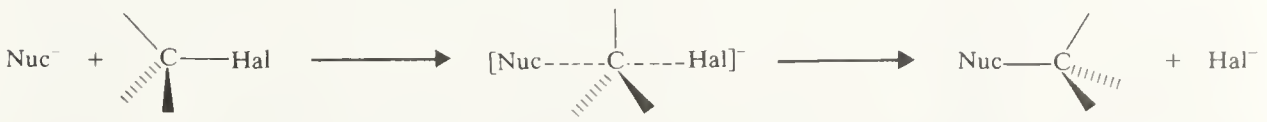
(i) Bond energies for the carbon–halogen bond decrease in the sequence F > Cl > Br > I and, therefore, if the rate-limiting step involves carbon–halogen bond-breaking, the fluoro compounds will often be least reactive.
(ii) Hydration energies of halide ions decrease in the series $F^- > Cl^- > Br^- > I^-$.
(iii) Hydrogen-bonding power of the halogens decreases in the order F > Cl, Br, I.
(iv) The van der Waals radii of halogens bound to carbon decrease in the order I > Br > Cl > F, so that bonding interactions occur at greater internuclear distances for iodo than for fluoro compounds.
(v) The availability of *d*-orbitals, allowing an increase in the covalency of halogen, decreases in the series I > Br > Cl > F.
(vi) Polarizability of the halogens decreases from iodine to fluorine.

Factors (i)–(iv) may be in conflict in deciding the reactivity of halo compounds, special circumstances sometimes leading to the importance of (ii) or (iii) over (i). It will be evident that factors (iv) and (vi) will be of importance with respect to the involvement of bridging halogens in carbenium ions and that factor (v) will influence the stability of carbanions.

A variety of mechanisms are available which involve either direct or indirect displacement of halogen and in the following sections are some of these mechanistic types with examples.

3.3.3.1 S_N2 Processes and related processes

Even this well-established mechanism is subject to healthy criticism.[69] However, the generally accepted model involves bond-breaking in the transition state (**22**) and a resulting inversion of configuration in chiral systems (see Scheme 22). Displacements from isopentyl halides, shown in Table 10, demonstrate clearly the lower reactivities of fluorides.



(**22**)

SCHEME 22

Rationalizing the effects of substituents at the reaction centre in S_N2 processes is a 'grey area' of understanding, but there is a clear deactivation by further introduction of halogen, *e.g.* reactivity decreases sharply in the series $CH_3Br \gg CH_2Br_2 > CBr_4$.

It has been calculated that perfluoroalkanes are thermodynamically unstable to hydrolysis, the reaction being exothermic by more than 305 kJ mol^{-1},[70] whereas the reality is that perfluorocarbons are essentially inert to hydrolysis below temperatures approaching 500 °C. Obviously, these systems are protected from hydrolysis by a kinetic barrier which

TABLE 10

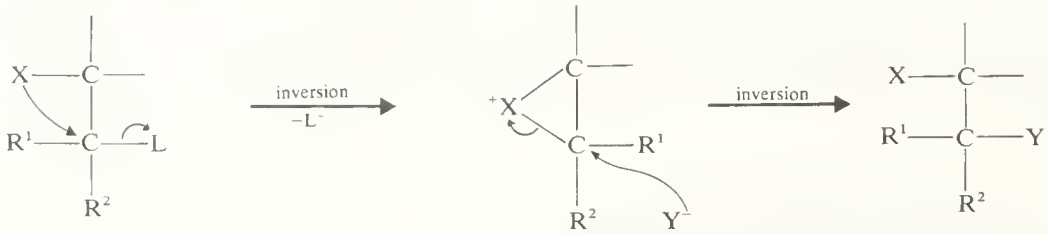
Relative Reactivities of Isopentyl Halides, $(CH_3)_2CH(CH_2)_2X$, with Piperidine and Sodium Methoxide at 18 °C

Reagent	X = F	Cl	Br	I
$C_5H_{11}N$	1	68.5	17 800	50 500
MeONa, MeOH	1	71	3550	4500

may be attributed to the difficulty of bringing up a nucleophile to the carbon skeleton which, in this case, is protected by a sheath of non-bonding electron-pairs associated with fluorine.

3.3.3.2 Neighbouring group participation[71-73]

The mechanistic subtleties and controversies surrounding this subject are inappropriate for discussion in this chapter. However, it is useful to note that in the displacement of a halogen the involvement of a neighbouring group or atom, X, at some position in a molecule (see Scheme 23) may occur so that, in effect, the overall process involves two S_N2-like substitutions with a resulting retention of configuration. This pattern of reaction, when it takes place, owes its preference over a direct displacement by Y^- to the lower entropy change in the intramolecular process. The participating group may be conventional nucleophilic sites such as OH, SH, NH, halogen, and CO_2H ligands. Cyclic intermediates of various ring sizes may be produced. Also, X may be the π-electrons of a double bond or aromatic system or, more controversially,[72,73] it is believed that σ-electrons may participate in a comparable way, as in cyclopropyl or norbornyl systems. Some examples are given in Scheme 24.



SCHEME 23

3.3.3.3 S_N1 Processes and relatively long-lived carbenium ions[74]

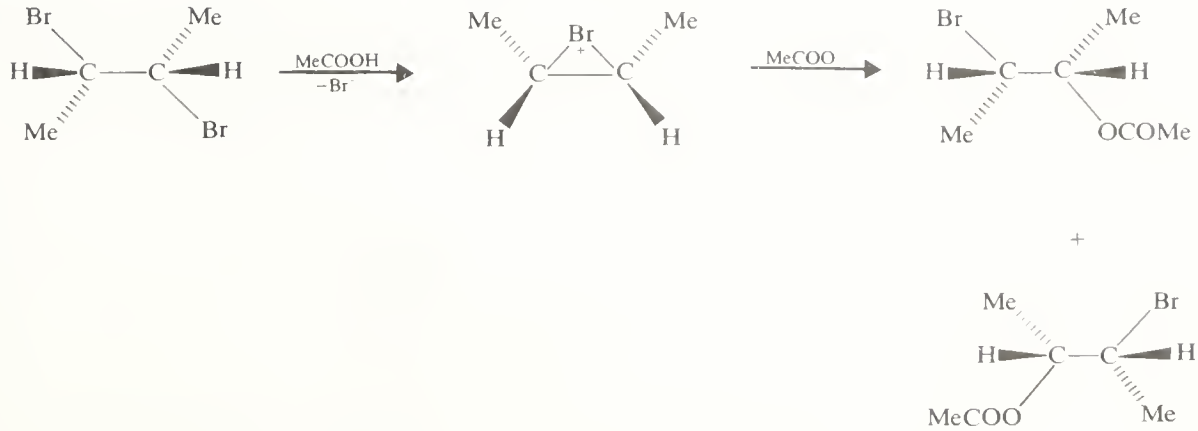
While an S_N1 process may be represented by a simple scheme, *i.e.* Scheme 25, involving the rate-determining (k_1) ionization of an organic halide, followed by production (k_2) of a racemic product from the intermediate carbenium ion (**23**), the reality is quite different. Completely racemic products are only rarely observed and a variety of effects have been postulated to account for the range of results. It is probable that partial inversion may arise from the preference for entry of the nucleophile on the side opposite to the leaving group L which, although ionized, may still be in association with the carbenium ion. Less often, partial retention is observed but in these cases it may be that there is association, *e.g.* hydrogen bonding, between L^- and the incoming nucleophile. Superimposed on all of this is the fact that internal return, *i.e.* the process labelled k_{-1}, is very significant in some cases.

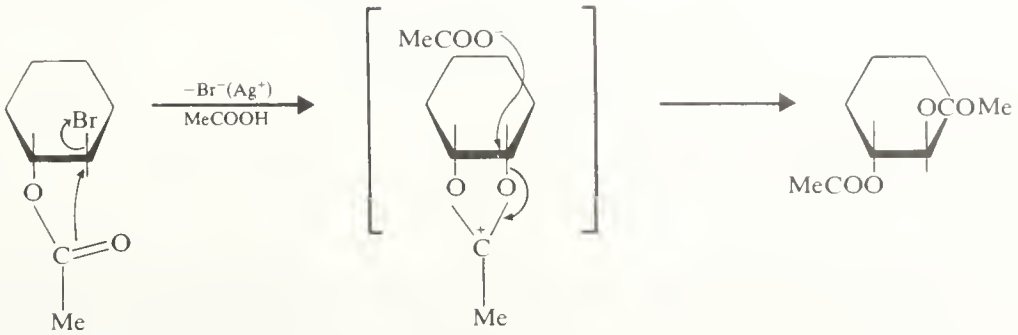
The spectacular success of the techniques developed by Olah and his co-workers for the ionization of halides and other derivatives, *e.g.* in antimony pentafluoride, or in solutions of sulphur dioxide at low temperatures, has now provided a multitude of observable carbenium ions for study, *e.g.* equation (40). Here, however, we will concentrate on carbenium ions which themselves contain halogen atoms.

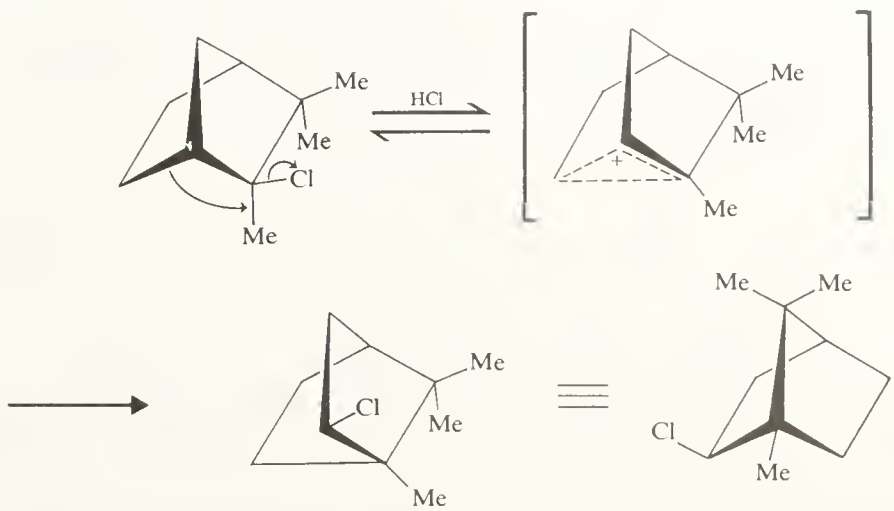
$$Me_2CHF \xrightarrow[37\,^\circ C]{SbF_5} Me_2\overset{+}{C}H\ SbF_6^- \qquad (40)^{74(ii)}$$

3.3.3.4 Halonium ions[75-77]

Participation by halogens, forming intermediate halonium ions, was originally suggested to account for the stereospecificity of certain reactions, *e.g.* the stereospecific *trans* addition of bromine to *cis*- and *trans*-but-2-ene. Also, rate-enhancements by participation by halogen have been claimed, *e.g.* the greater rate of acetolysis of (**24**) over (**25**) (X = Br

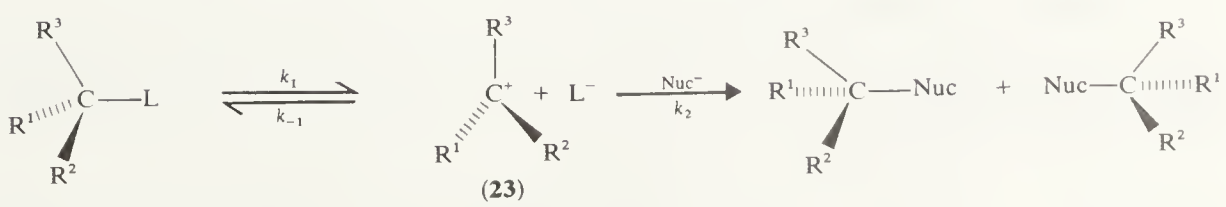
1. 

2. 

3. 

4. $Me_2CHCH_2I \xrightarrow[MeCOOH]{Ag^+} Me_3COCOMe$

SCHEME 24

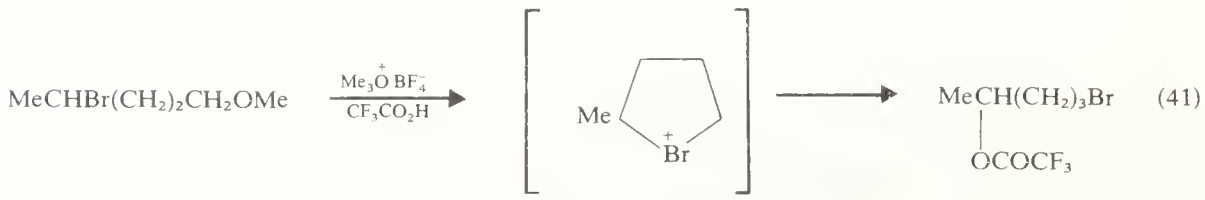


(**23**)

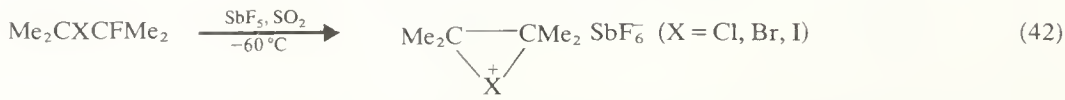
SCHEME 25

or I). Participation by chlorine in the same system was not, however, effective. In addition to the interaction of neighbouring halogen by the formation of three-membered rings in the halonium ion, there is evidence for the intermediacy of four-, five-, six-, and even seven-membered rings, *e.g.* the intermediate bromonium ion in equation (41).

(24) (25)

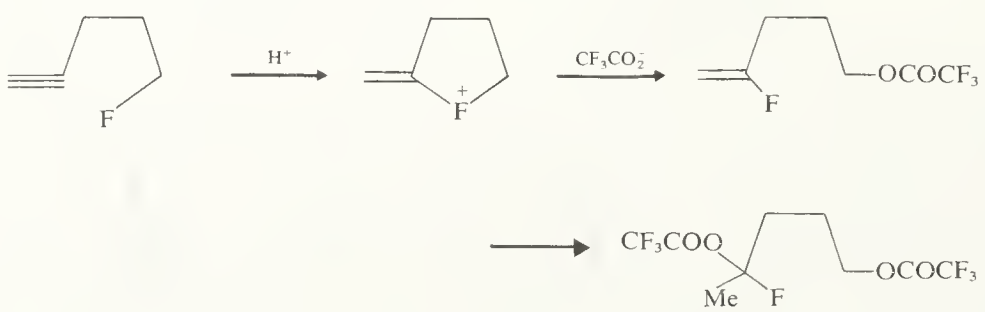


(41)



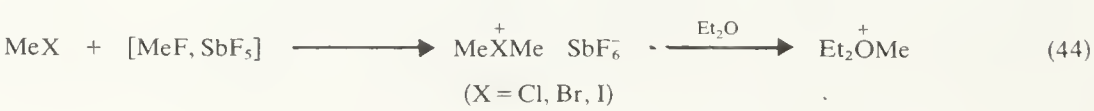
(42)

Direct observation of halonium ions by n.m.r. spectroscopy has provided clear descriptions of these species, *e.g.* equation (42). The n.m.r. spectroscopic data for the product of ionization of the difluoro compound (X = F) in equation (42) has been interpreted in terms of a rapidly equilibrating non-bridged ion, while other workers have argued that the data are not incompatible with a fluoronium ion.[77] Participation by fluorine, remote from the reaction centre, seems to be established in reaction (equation 43) between 5-fluoropent-1-yne with trifluoroacetic acid.[78]



(43)

Simple acyclic salts have been obtained by reaction of the methyl fluoride–antimony pentafluoride complex with alkyl halides (equation 44). The products are crystalline solids which are stable at room temperature and, understandably, they are very good alkylating agents.



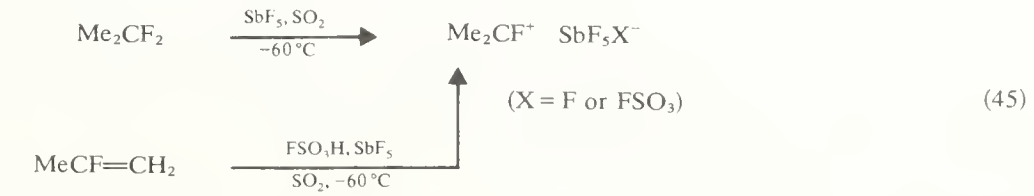
(44)

3.3.3.5 Halogen-containing carbenium ions[7,55,79]

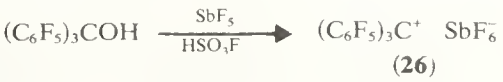
It is clear, from the foregoing discussion, that the distinction between the effect of halogen atoms situated at C-1 and C-2 with respect to a carbenium ion will often be complicated by bridging:

The situation with fluorine is more clear-cut than for the other halogens in that only a fluorine atom sited at C-1 is potentially stabilizing. This arises from the interaction of non-bonding *p*-electrons on fluorine with the vacant orbital on carbon (*i.e.* $\overset{+}{C}—\ddot{F} \leftrightarrow C=\overset{+}{F}$) which offsets, to a considerable degree, the destabilizing inductive electron withdrawal by fluorine. For fluorine attached at C-2, the accumulated evidence is that it is overall destabilizing.[7]

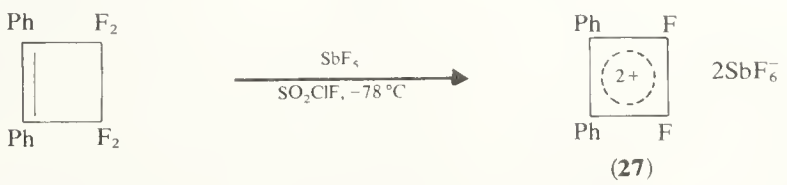
Relatively stable fluorocarbenium ions have been observed (equation 45) and the n.m.r. spectroscopic data indicate a substantial degree of interaction between the non-bonding electron pairs on fluorine and the vacant orbital on carbon. Conjugated systems give long-lived fluorinated carbenium ions more readily and, surprisingly, even highly fluorinated carbenium ions have been observed,[79–81] *e.g.* (**26**)–(**29**) in equations (46)–(49). The perfluoroallyl cation (**30**) has also been proposed as an intermediate in an unusual dimerization of hexafluoropropene[80] (equation 50).



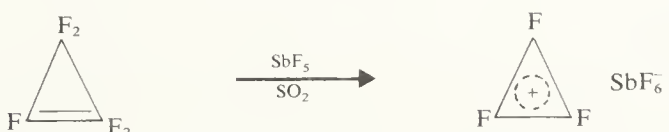
(45)



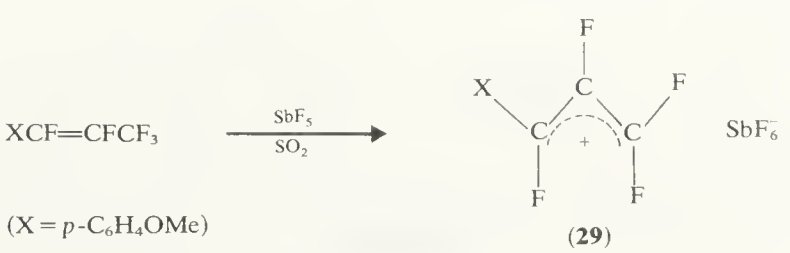
(**26**) (46)



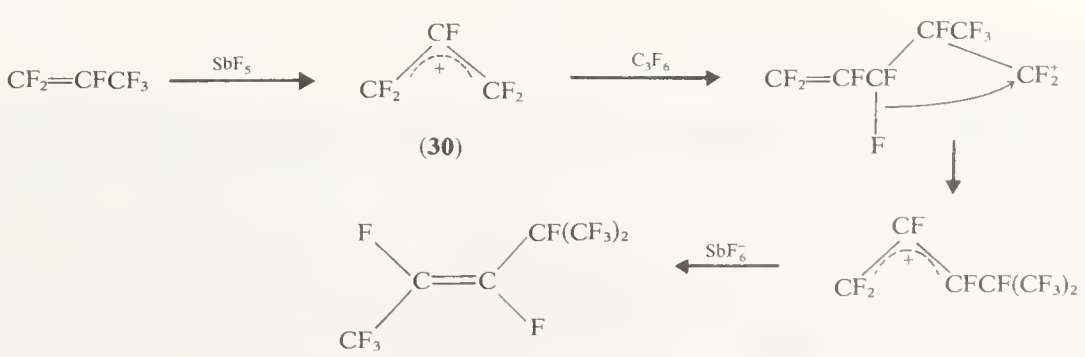
(**27**) (47)



(**28**) (48)

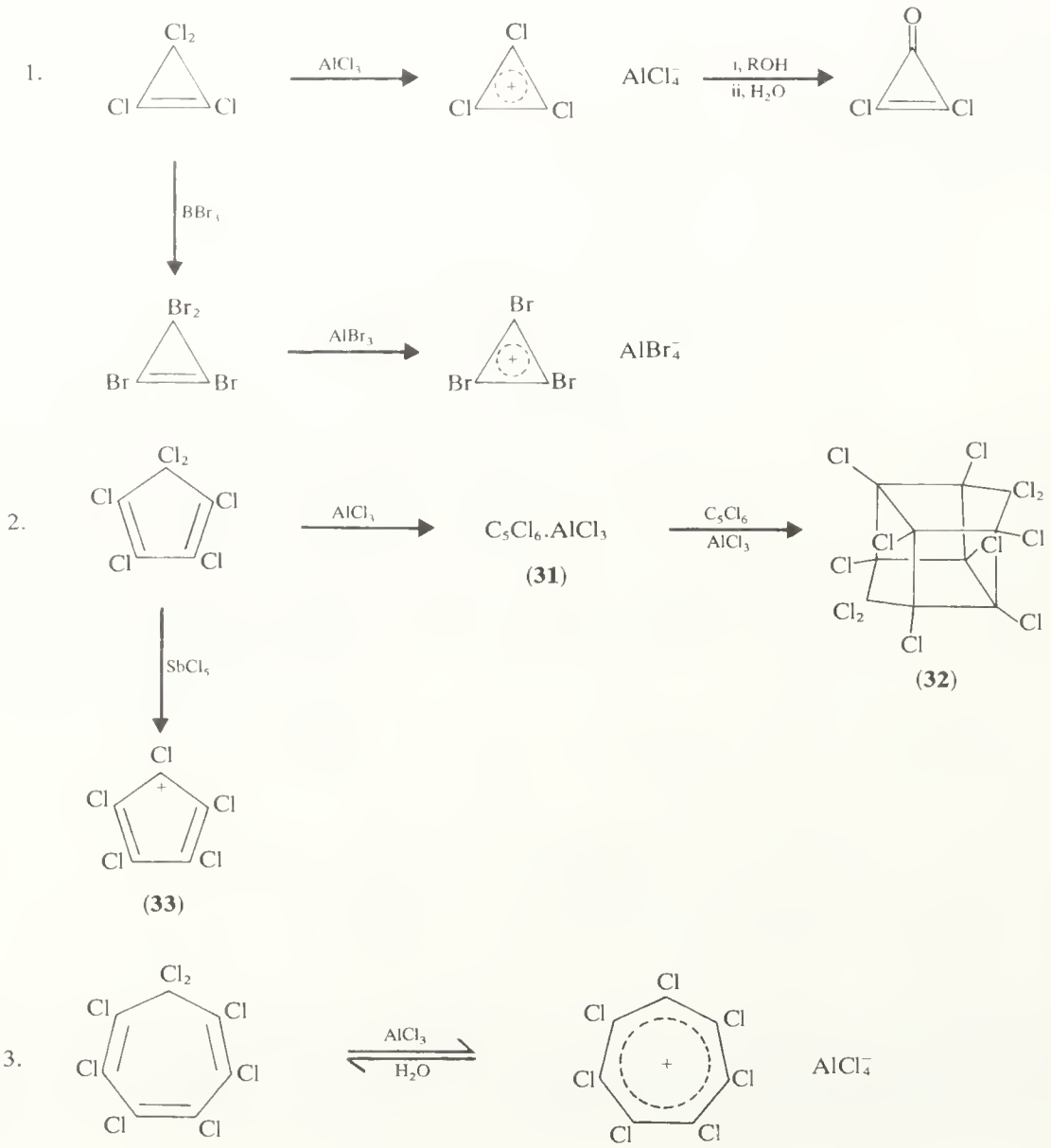


(**29**) (49)



(**30**) (50)

A range of perchlorinated carbenium ions is available (see Scheme 26) and some of these are strikingly stable, indicating the ability of chlorine to stabilize an attached positive centre on carbon.[82] Reaction of hexachlorocyclopentadiene with strong Lewis acids gives the so-called 'Prins dimer' (**32**) although, with aluminium trichloride, an intermediate red complex (**31**) may be isolated. This seems not to be the ionic anti-aromatic cation (**33**), although e.s.r. spectroscopic evidence indicates that this may be generated in solution in $SbCl_5$ and exists as a triplet ground-state.



SCHEME 26

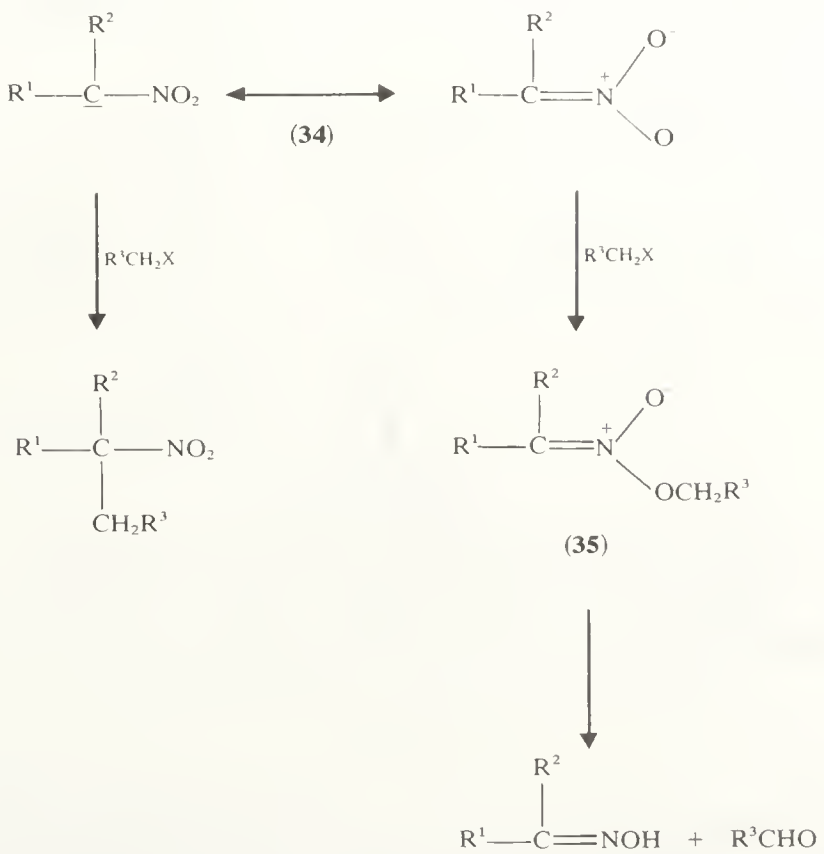
3.3.3.6 Substitution via *electron-transfer processes*[83]

In principle, an alternative mechanism for displacement of halogen from carbon involves electron transfer as the initial step, followed by halide loss and chain transfer:

$$\begin{aligned} Nuc^- + RX &\rightarrow Nuc\cdot + [RX]^{\cdot -} \quad (X = \text{halogen}) \\ [RX]^{\cdot -} &\rightarrow R\cdot + X^- \\ R\cdot + Nuc^- &\rightarrow [RNuc]^{\cdot -} \\ [RNuc]^{\cdot -} + RX &\rightarrow RNuc + RX^{\cdot -} \quad (\text{chain propagation}) \end{aligned}$$

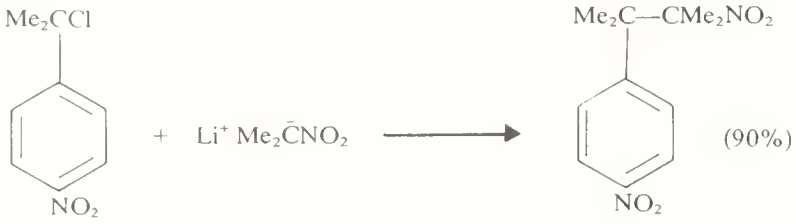
Examples of this type of process have now been established for displacement from both saturated carbon and from aryl groups (see later).

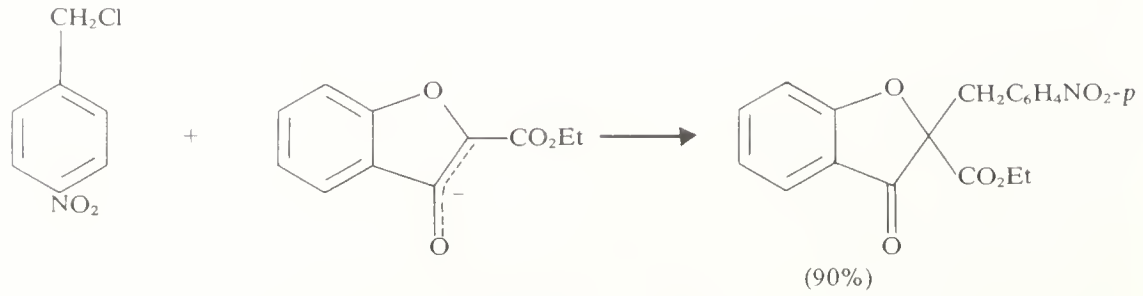
Treatment of the salt of an aliphatic nitro compound (**34**) with an alkyl halide may result in alkylation at carbon or at oxygen. In general, oxygen alkylation by an S_N2 process to produce a carbonyl compound and oxime, *via* the nitronic ester (**35**), is observed, with little if any concomitant carbon alkylation (see Scheme 27). However, Kornblum and co-workers have shown[83] that, in reactions of 2-nitropropane with *p*-nitrobenzyl halides, both *O*- and *C*-alkylation occurred, the relative proportion depending on the halogen being displaced. When the rate constants for the *O*- and *C*-alkylations were separated for the various halides, it was established that, on passing from Cl through Br to I, *O*-alkylation increased by a factor of 900, quite consistent with an S_N2 process, but *C*-alkylation increased by a factor of only 6. Such a small change is inconsistent with an S_N2 process and led to the suggestion of a radical-chain mechanism, as outlined at the beginning of this section. Further evidence for the process involves the identification of intermediate radicals by e.s.r. spectroscopy, the suppression of *C*-alkylation by addition of radical inhibitors, and the promotion of *C*-alkylation by photolysis. Additional examples of substitution *via* electron transfer are indicated in Scheme 28.



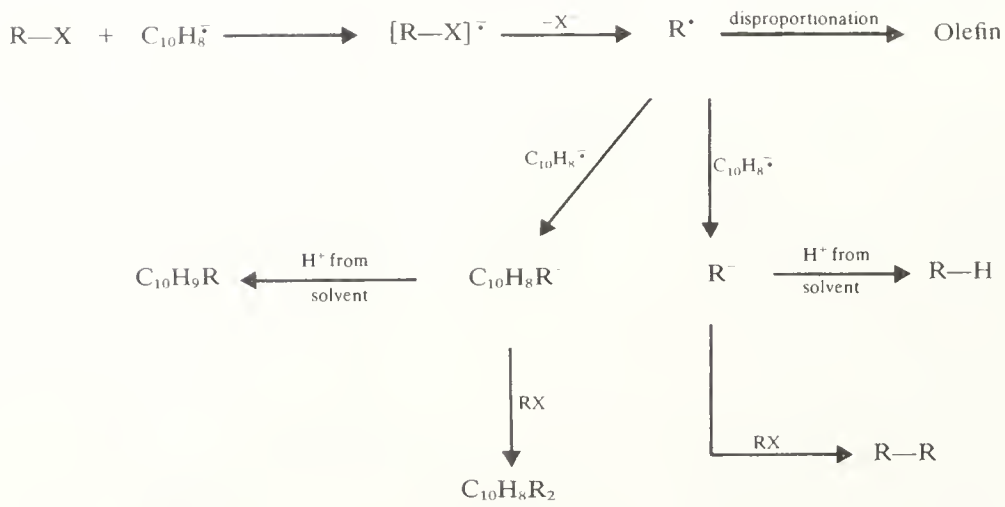
SCHEME 27

Electron-transfer processes involving reactions of alkali-metal derivatives of naphthalene with alkyl halides are well established.[84] Naphthalene is readily reduced by alkali metals in 1,2-dimethoxyethane to give an ionic species consisting of an alkali-metal cation with a naphthalene radical-anion and subsequent reaction with alkyl halides can produce a number of products, as shown in Scheme 29. It has been suggested[85] that a carbene radical-ion (**36**) is formed with geminal dihaloalkanes (equation 51). Reductions of halides using metals in isopropanol most probably involve electron transfer[86,87] (equations 52 and 53). Other examples of reduction are contained in the next section.

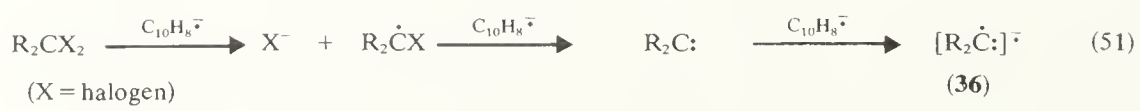
1. 

2. 

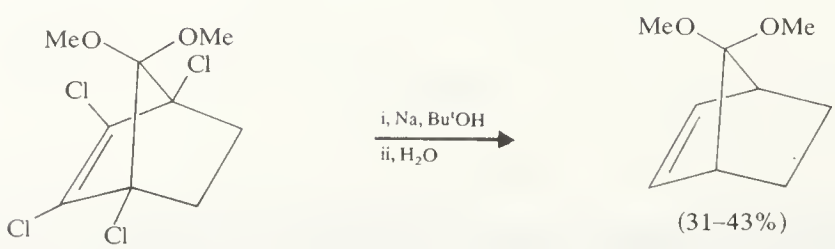
SCHEME 28



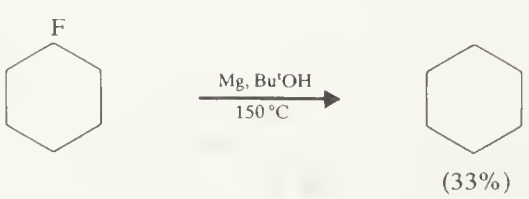
SCHEME 29



(51)



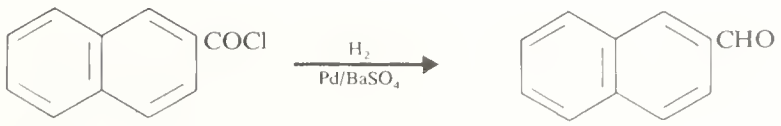
(52)



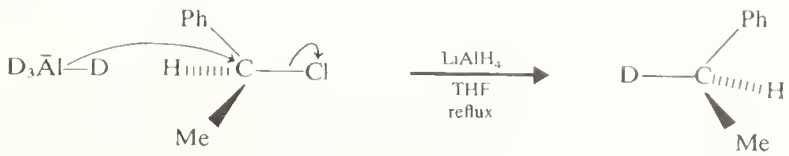
(53)

3.3.4 Reduction

Reduction of alkyl halides may be achieved in some cases by catalytic hydrogenation[88] but, in general, alkyl halides are much less readily reduced than aryl, allyl, or vinyl halides. Acid halides are very easily cleaved, as in the Rosenmund reduction (equation 54). Displacement of halogen by lithium aluminium hydride (deuteride) or sodium borohydride is believed to be an S_N2 process[88–90] (equations 55 and 56). However, for tertiary halides an elimination–hydroboration sequence has been established (see Scheme 30).

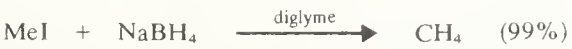


(54)

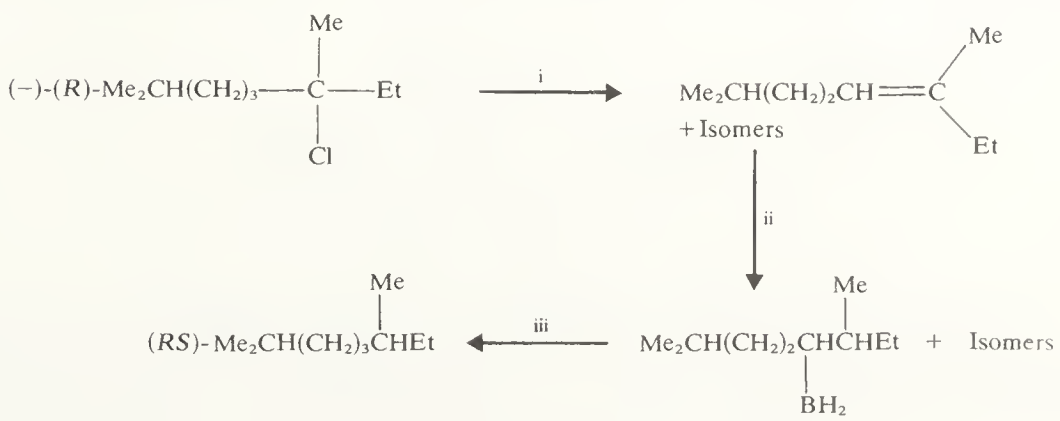


(optically pure) (79% optical purity)

(55)



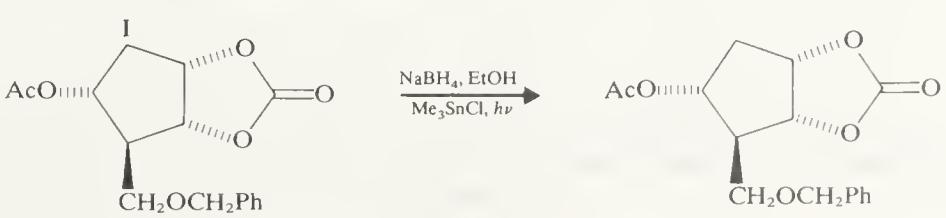
(56)



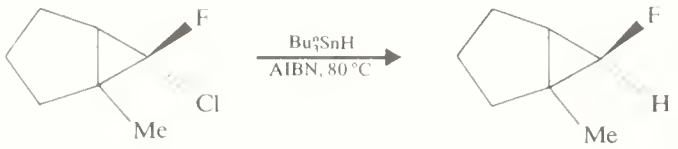
i, $NaBH_4$, DMSO, 100 °C; ii, BH_3; iii, Bu^nCOOH, reflux.

SCHEME 30

The use of these complex metal halides is, then, limited to systems that are susceptible to nucleophilic attack, and therefore a useful alternative involves a trialkyltin hydride.[88] This reagent takes part in an interesting free-radical process which involves radical attack on halogen (see Scheme 31). In a recent modification, the tin hydride is produced '*in situ*' from borohydride and a tin chloride[91] (equation 57). Some reductions which involve α-halocyclopropyl radicals as intermediates are stereospecific and this implies a slow rate of inversion of the intermediate radical,[92] as shown in equation (58).



(57)

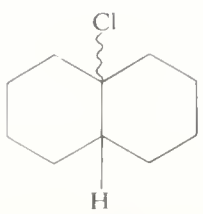


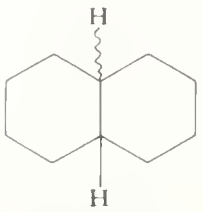
(70%) (58)

1. $Bu^n_3SnH \xrightarrow{i} Bu^n_3Sn\cdot$

$Bu^n_3Sn\cdot + RX \longrightarrow R\cdot + Bu^n_3SnX$

$R\cdot + Bu^n_3SnH \longrightarrow R{-}H + Bu^n_3Sn\cdot$ *etc.*

2. 

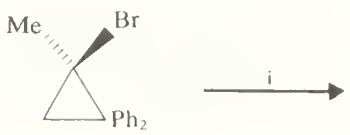
+ Bu^n_3SnH $\xrightarrow{i, ii}$ 

(97%)

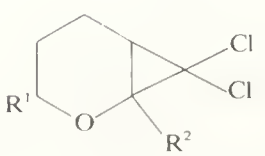
i, $Me_2C(CN){-}N{=}N{-}C(CN)Me_2$ (AIBN) (radical initiator); ii, toluene, 60 °C.

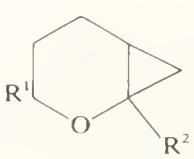
SCHEME 31

Examples of other methods of reduction[88] are shown in Scheme 32. These involve electrolysis, treatment with metals in protic solvents, and reactions with organometallic compounds.

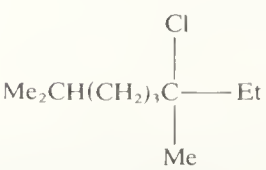
1. 

(Ref. 93)

2. 



(Ref. 94)

3. 

$Me_2CH(CH_2)_3CHEt$ (Ref. 95)
|
Me

(retention of configuration)

4. $CCl_4 + Mg + Pr^iOH \longrightarrow CH_4$ (47%) (Ref. 87)

5. $CCl_4 + Pr^iOH + RuCl_2(PPh_3)_3 \xrightarrow{iv} CHCl_3$ (98%) (Ref. 96)

6. $Bu^n_2C{=}CHI + Pr^iMgCl \xrightarrow{v} Bu^n_2C{=}CH_2$ (90%) (Ref. 97)

i, Electrolysis, MeCN, Hg cathode; ii, Li, NH_3, $PhCO_2Na$; iii, Na, NH_3; iv, 140 °C, sealed tube under N_2; v, 1% Mn(II), THF.

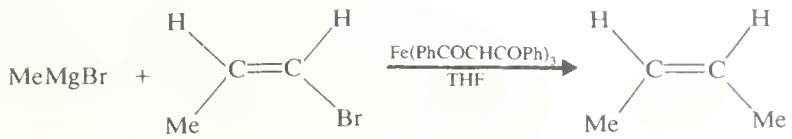
SCHEME 32

3.3.5 Displacement by metals

Displacement of halogens by metals to form organometallic compounds is a subject which is well documented elsewhere[98] and attention is drawn here to only a few points of interest.

The process for formation of Grignard reagents has been investigated by ^1H n.m.r. spectroscopy through CIDNP and appears to be radical in nature[99] (equation 59). Reactions of Grignard reagents may be modified by addition of transition-metal compounds[100] (equation 60).

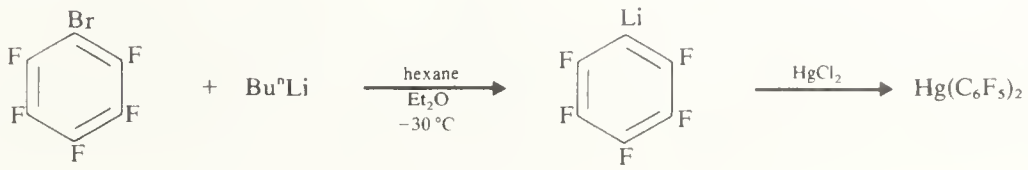
$$RX + Mg \longrightarrow RX^- + Mg^+ \longrightarrow R\cdot + \cdot MgX \longrightarrow RMgX \qquad (59)$$



(99%) (60)

Organolithium reagents[101] are now commercially available and in many cases are more convenient to use than Grignard reagents, *e.g. via* exchange reactions, as in equations (61) and (62).

$$Bu^nX + 2Li \xrightarrow{\text{hexane}} Bu^nLi + LiX \ (e.g.\ X = Br) \qquad (61)$$



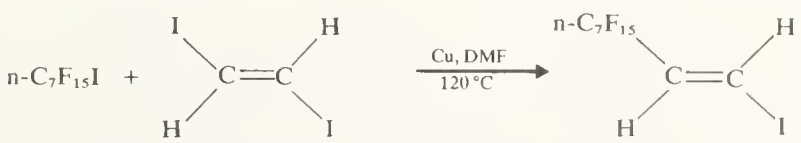
(62)

$$CCl_4 + Li \xrightarrow{800\text{–}1000\,^\circ C} CLi_4 + C_2Li_4 \xrightarrow{D_2O} CD_4 + C_2D_4 \qquad (63)$$

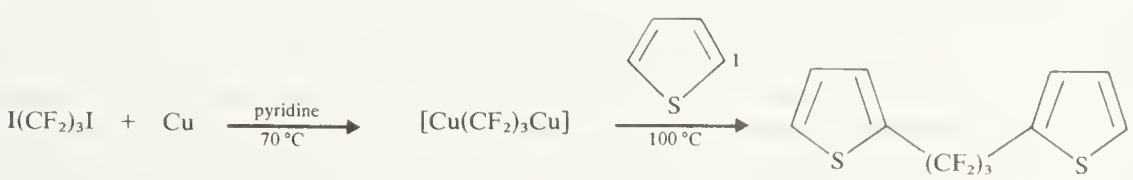
$$C_2Cl_6 + Li \xrightarrow{800\text{–}1000\,^\circ C} C_2Li_6 \xrightarrow{D_2O} C_2D_6 \qquad (64)$$

Formation of polylithio derivatives is a fascinating and little explored subject.[102] Two examples are given in equations (63) and (64).

Organocopper reagents have found greater use in recent years and these are generally formed *via* Grignard or lithium derivatives but in some cases may be obtained directly,[103,104] as shown in equations (65) and (66).



(65)



(66)

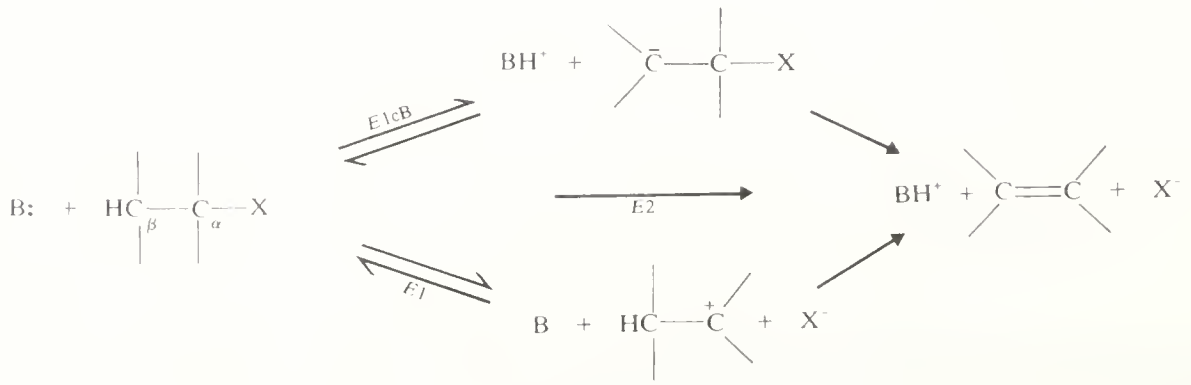
$$(CF_3)_2CFI + Ag\ (vapour) \xrightarrow[-196\,^\circ C]{MeCN} (CF_3)_2CFAg + AgI \qquad (67)$$

Perfluoroalkylsilver compounds have been obtained in reactions of metal atoms, but solvent is required for stabilization[105] (equation 67).

3.3.6 Eliminations[106,107]

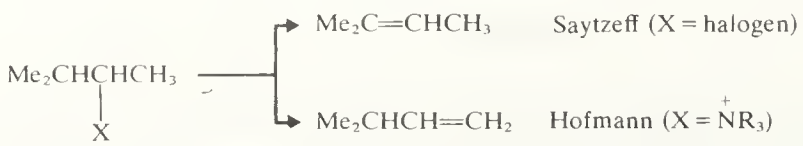
3.3.6.1 β-Eliminations

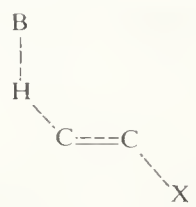
A familar mechanistic outline of base-induced β-eliminations of hydrogen halides is as shown in Scheme 33 and, as may be expected, leaving group ability has a significant effect on the processes involved. One of the most vexed questions in mechanistic organic



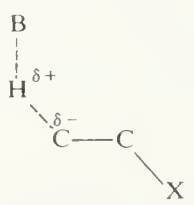
SCHEME 33

chemistry has been the rationalization of the old empirical orientation rules for predicting the products in olefin-forming elimination reactions. According to the Saytzeff rule, which referred to reactions of alkyl halides, elimination occurs giving, preferentially, the olefin with the greatest number of alkyl groups attached to the double bond (the most thermodynamically stable isomer) while, conversely, the Hofmann rule, which refers to alkylammonium ions, indicates that the least substituted olefins are obtained preferentially:



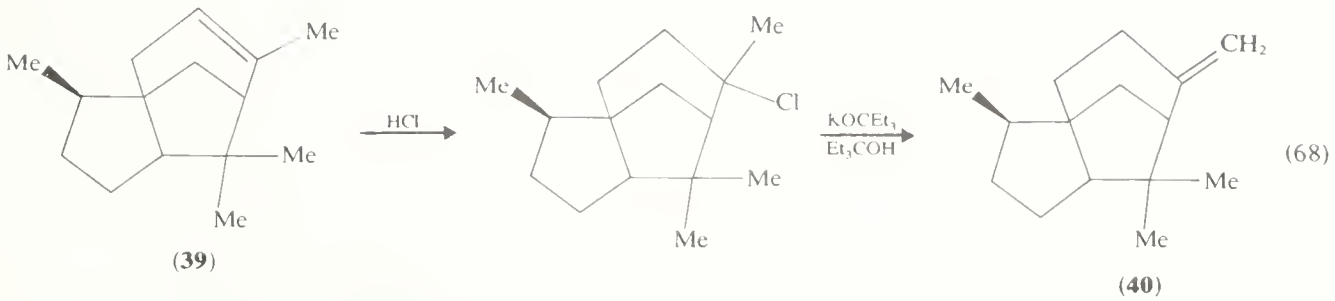


(**37**) (Saytzeff)



(**38**) (Hofmann)

The current consensus of opinion is probably that the basis of the two rules lies in the amount of negative charge developed at the β-position, in the transition state for *E*2 elimination. When X is a good leaving group, then a concerted transition-state like (**37**) is encouraged, whereas with poorer leaving groups like $\overset{+}{N}R_3$, the generation of negative charge at the β-carbon is encouraged as in (**38**) and, consequently, alkyl groups at this position are not favoured. The results in Table 11 support this model, the increasing ρ value showing the increased negative charge developed, in the transition-state, with decreasing efficiency of the leaving group, for the halogens. Apparently, the high ρ value for $\overset{+}{N}Me_3$ is due to a combination of low mobility and the acidifying influence of the charged group on the β-hydrogen. The results presented in Table 12 show, however, that there is not such a sharp distinction between halides and alkylammonium salts as the orientation rules would imply, because Hofmann-type orientation occurs with alkyl



(39) (40) (68)

fluorides. Furthermore, Hofmann-type orientation may be induced even with iodides, if a stronger base than methoxide is used. It seems that a stronger base moves the transition-state more towards (**38**). This use of very strong bases is applied to the synthesis of less thermodynamically stable isomers of certain olefins,[108] *e.g.* the conversion of α-cedrene (**39**) to β-cedrene (**40**)[109] in equation (68). Saytzeff-type products are, of course, observed in *E*1 eliminations.

TABLE 11

*E*2 Elimination from $RC_6H_4CH_2CH_2X$ Derivatives at 30 °C with EtO^- in EtOH[107]

X	*Relative rate*	ρ
I	26 600	2.07
Br	4100	2.14
Cl	392	2.27, 2.50
F	1	3.12
$\overset{+}{N}Me_3$	760	3.77

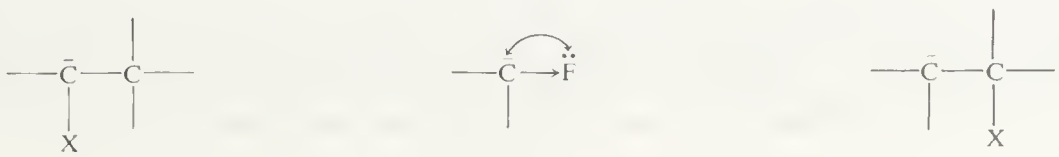
TABLE 12

Eliminations from 2-Hexyl Halides at 100 °C[107]

Halogen	NaOMe–MeOH (% *hex-1-ene*)	NaOBu^t–Bu^{t}OH (% *hex-1-ene*)
I	19	69
Br	28	80
Cl	33	88
F	70	97

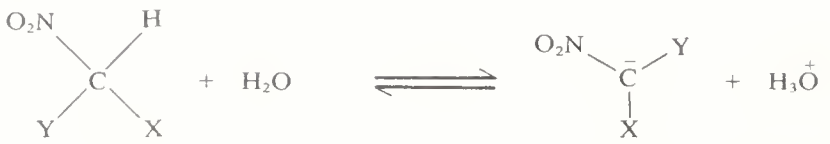
3.3.6.2 Halocarbanions[7]

The presence of halogen in an organic molecule has a significant acidifying influence on the remaining C—H bonds, but the effectiveness of fluorine depends on its location with respect to the developing carbanionic centre. Much of the information in this area comes from kinetic acidity measurements[110] for base-catalysed hydrogen–deuterium or –tritium exchange and, for halogen attached to the centre (**41**), the order of acidifying influence is I ≈ Br > Cl > F. Participation by *d*-orbitals and relief of crowding could be factors which are important for iodine and bromine, but the fact that fluorine is least effective in the series implies that, in this case, electron-pair repulsion effectively offsets inductive withdrawal (**42**). The acidifying influence of chlorine and fluorine may also be compared by means of the ionization constants for the nitromethanes shown in Table 13. It is difficult to compare the effects of different halogen atoms at sites adjacent to the carbanion centre (**43**) because of the ease with which β-elimination occurs. Nevertheless, fluorine is at least as effective as chlorine in these situations.



(41) (42) (43)

TABLE 13
Apparent Ionization Constants for Substituted Nitromethanes (in Water at 25 °C)



Y	X	pK_a
CO_2Et	Cl	4.16
CO_2Et	H	5.75
CO_2Et	F	6.28
NO_2	Cl	3.80
NO_2	H	3.57
NO_2	F	7.70

3.3.6.3 Eliminations from carbanions

Polyhalogenoalkanes are often sufficiently acidic (see equation 69) to promote the *E*1cB process, although there is often extreme difficulty in making a distinction between this and a concerted elimination. The orientation of elimination of hydrogen halides from highly halogenated systems is governed by: (i) the relative acidities of hydrogen atoms within the molecule, (ii) the mobility of leaving halogen, and (iii) the mobility of fluorine from carbon which decreases in the series $CH_2F > CHF_2 > CF_3$.[7] The following examples in equations (70)–(72) illustrate these effects where orientation of elimination from (**44**)–(**46**) is governed by the acidity of the hydrogens shown bold-faced. In (**47**) in equation (73), removal of chlorine from CCl_3 is easier than from CF_2Cl.

$$CF_3CHCl_2 + MeO^- \longrightarrow MeOH + CF_2{=}CCl_2 \cdot + F^- \quad (69)$$

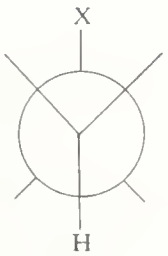
$$CF_3C\mathbf{H}_2CHBrMe \xrightarrow[EtOH]{KOH} CF_3CH{=}CHMe \quad (70)$$
(**44**)

$$CF_2ClC\mathbf{H}ClCH_2Cl \longrightarrow CF_2ClCCl{=}CH_2 \quad (71)$$
(**45**)

$$C\mathbf{H}Cl_2CCl_2CHF_2 \longrightarrow CCl_2{=}CClCHF_2 \quad (72)$$
(**46**)

$$CCl_3CH_2CF_2Cl \xrightarrow{KOH} CCl_2{=}CHCF_2Cl \quad (73)$$
(**47**)

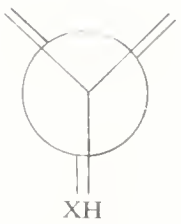
(*i*) *Stereochemistry.* It now seems established, from the work of DePuy and his co-workers,[106,107] that coplanarity of the groups being eliminated in the transition state of an *E*2 process, *i.e.* (**48**) and (**49**), is the preferred relationship. This seems to be the important factor but, given this relationship, *anti* is preferred over *syn* elimination. On this basis the well-known resistance to non-coplanar *anti* elimination of HCl from β-hexachlorocyclohexane (**50**) may be understood, as well as the faster coplanar *syn* elimination from (**51**) than non-coplanar *anti* elimination from (**52**). It is quite clear, however, that *syn* eliminations are more common, even in acyclic systems, than was once thought and, in this context, change of mechanism, *e.g.* towards an *E*1cB process, and the nature of the solvent, may have profound effects. Some examples of β-eliminations are given in Table 14.



(**48**)

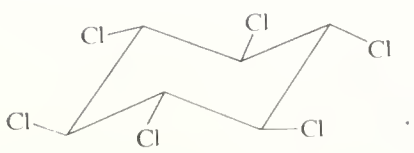
anticoplanar

X = halogen

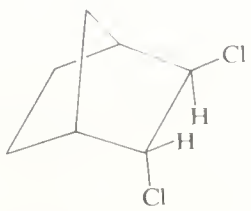


(**49**)

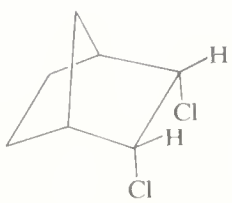
syncoplanar



(**50**)



(**51**)

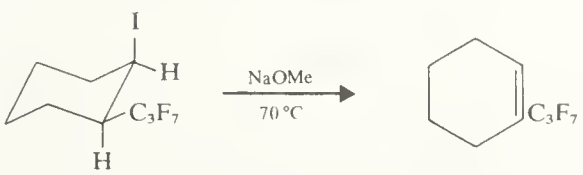


(**52**)

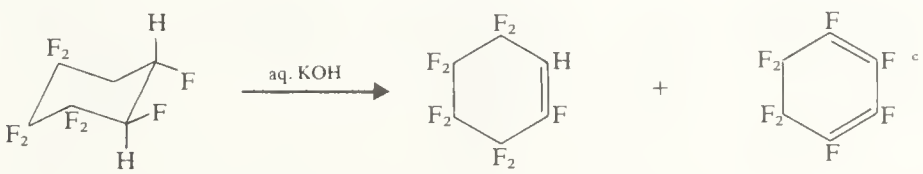
TABLE 14

β-Eliminations

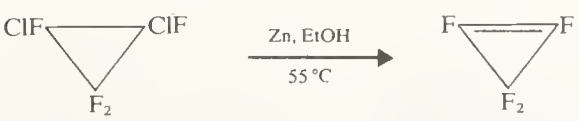
1. $C_3F_7CH_2CF_2I \xrightarrow{LiCl,\ DMF} C_3F_7CH{=}CF_2$ (91%)[a]

2. 

(77%) [b]

3. 

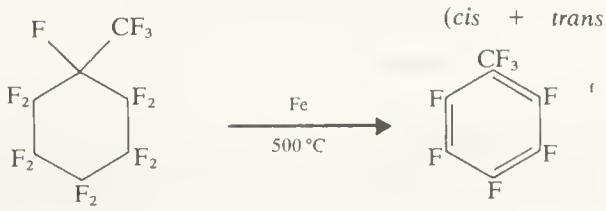
[c]

4. 

(85%) [d]

5. $CF_3CF_2CCl_2CF_3 \xrightarrow{P(OBu)_3} CF_3CF{=}CClCF_3 + (BuO)_2PFO$ [e]

(*cis* + *trans*)

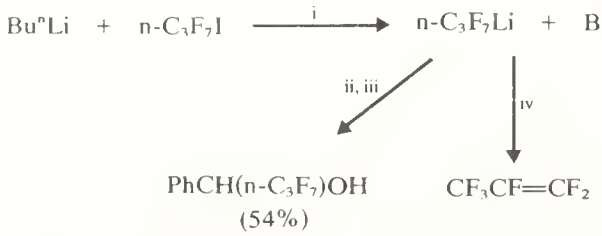
6. 

[f]

[a] M. Hauptschein and R. E. Oesterling, *J. Amer. Chem. Soc.*, 1960, **82,** 2868. [b] N. O. Brace, *ibid.*, 1964, **86,** 2428. [c] R. P. Smith and J. C. Tatlow, *J. Chem. Soc.*, 1957, 2505; S. F. Campbell, F. Lancashire, R. Stephens, and J. C. Tatlow, *Tetrahedron*, 1967, **23,** 4435. [d] P. B. Sargeant and C. G. Krespan, *J. Amer. Chem. Soc.*, 1969, **91,** 415. [e] A. W. Frank and C. F. Baranauckas, *J. Org. Chem.*, 1965, **30,** 3970. [f] B. Gething, C. R. Patrick, M. Stacey, and J. C. Tatlow, *Nature*, 1959, **183,** 588.

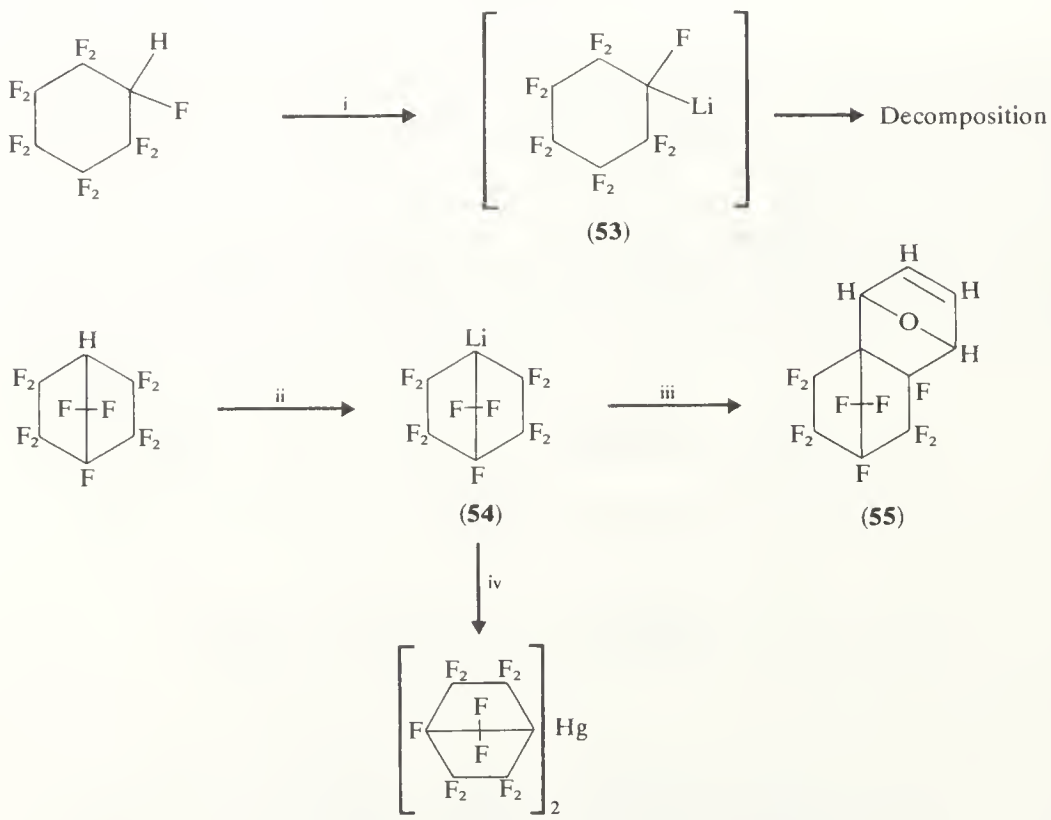
3.3.6.4 β-Elimination from organometallic compounds

The effective use of perhaloalkyl-lithium derivatives or Grignard reagents is limited (see Scheme 34) by the competing elimination of metal halides.[7,111,112] A contrast in stability occurs between perfluorocyclohexyl-lithium (**53**) — an easy elimination path is available — which decomposes at very low temperatures[113] and lithio derivatives of fluorinated bicyclic systems,[113,114] *e.g.* (**54**), where formation of a bridgehead olefin is a higher-energy process (see Scheme 35). Nevertheless, evidence for elimination was obtained by trapping with furan to give (**55**).



i, Et_2O, −78 °C; ii, PhCHO; iii, H_2SO_4; iv, −LiF.

SCHEME 34



i, MeLi, −90 °C; ii, Bu^{n}Li, −78 °C; iii, furan, 20–30 °C; iv, $HgCl_2$, −78 to 15 °C.

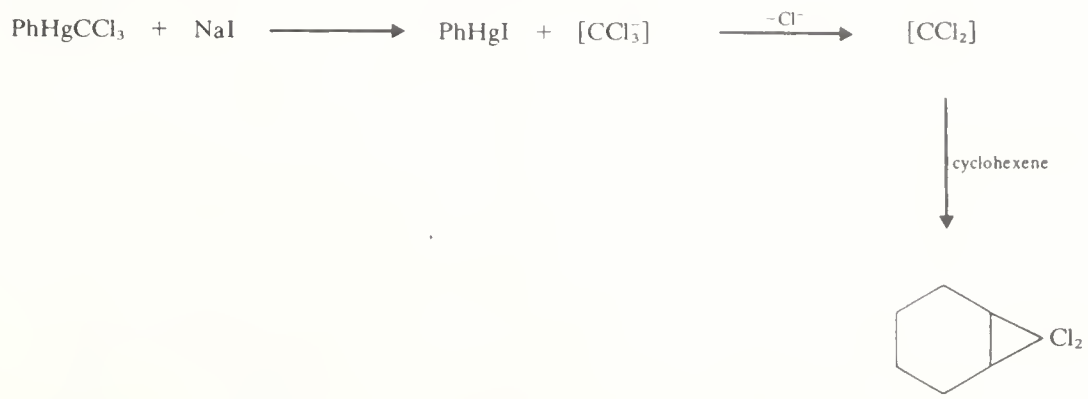
SCHEME 35

3.3.6.5 α-Elimination (*generation of carbenes*)

This subject has been discussed at length in other books.[115,116] We may roughly divide the generation of carbenes into the following categories:

(i) Decomposition of halocarbanions, which may occur in concert with a step in which the carbanion is generated, *e.g.* decarboxylations (see Table 15). The mechanism can be represented:

Carbanions are intermediates in the very versatile carbene transfer agents developed by Seyferth and co-workers.[117] An example is:



(ii) Fragmentation reactions.
(iii) Decomposition of diazo compounds.
Examples to illustrate these processes are shown in Table 15.

TABLE 15
α-Eliminations

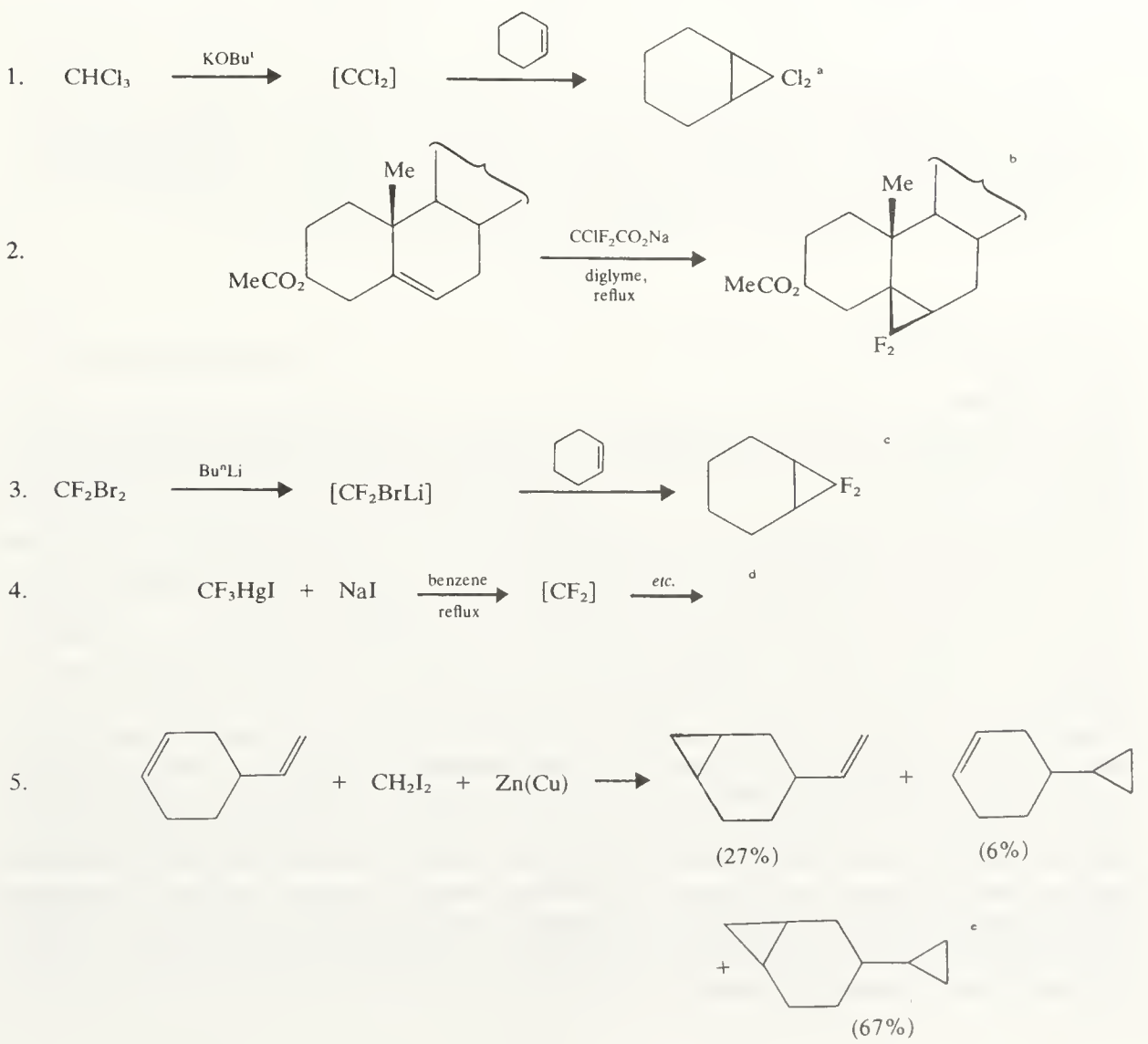
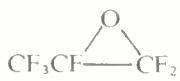
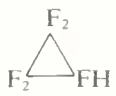
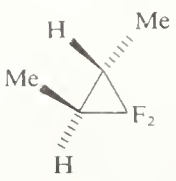
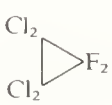
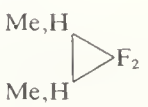


TABLE 15 (*continued*)

6. $(CF_3)_2PF_2 \xrightarrow[24\ h]{120\ °C} CF_2{=}CF_2$ (10%) +  (80%) + $(CF_2)_n$ (10%) [f]

7.  + $CF_2{=}CFH \xrightarrow{185\ °C}$  (65%) + CF_3COF [g]

8. *trans*-MeCH=CHMe +  $\xrightarrow{u.v.}$  (33%)[h]
(*trans*)

9. *cis*-MeCH=CHMe +  $\xrightarrow{\Delta}$  (*cis* 86%, *trans* 2%)[i]

[a] W. V. E. Doering and A. K. Hoffmann, *J. Amer. Chem. Soc.*, 1954, **76,** 6162. [b] L. H. Knox, E. Verlarde, S. Berger, D. Cuadriello, P. W. Landis, and A. D. Cross, *J. Amer. Chem. Soc.*, 1963, **85,** 1851. [c] V. Franzen, *Chem. Ber.*, 1962, **95,** 1964. [d] Ref. 117. [e] S. D. Koch, R. M. Kliss, D. V. Lopiekes, and R. J. Wineman, *J. Org. Chem.*, 1961, **26,** 3122; W. Mahler, *Inorg. Chem.*, 1963, **2,** 230. [g] P. B. Sargeant and C. G. Krespan, *J. Amer. Chem. Soc.*, 1969, **91,** 415. [h] R. A. Mitsch, *J. Amer. Chem. Soc.*, 1965, **87,** 758. [i] J. M. Birchall, R. N. Haszeldine, and D. W. Roberts, *Chem. Comm.*, 1967, 287.

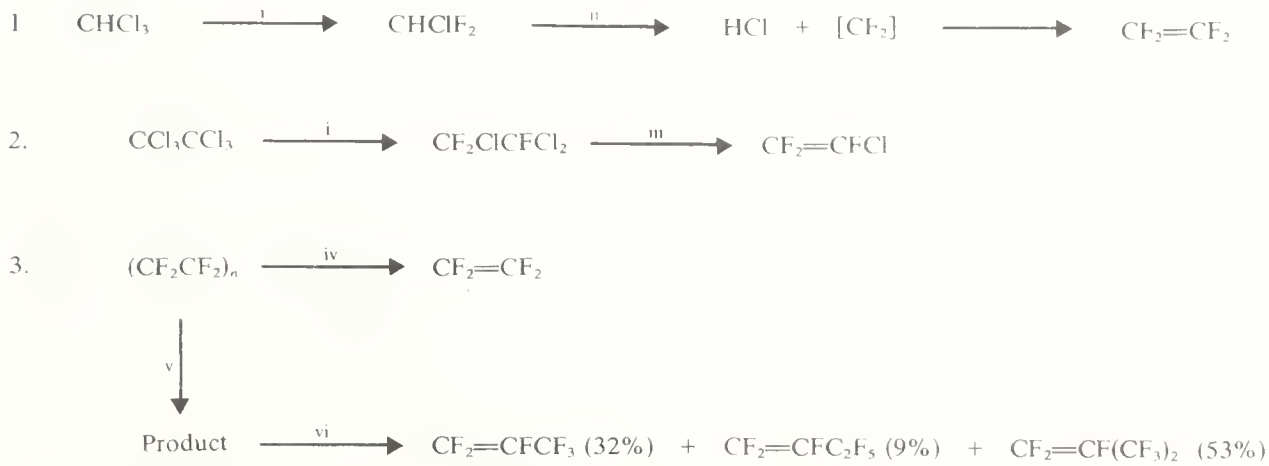
3.4 HALOALKENES

3.4.1 Synthesis

General methods for the introduction of halogen into an organic molecule were discussed in Section 3.2. Some specific syntheses of industrially significant systems are discussed in this section.

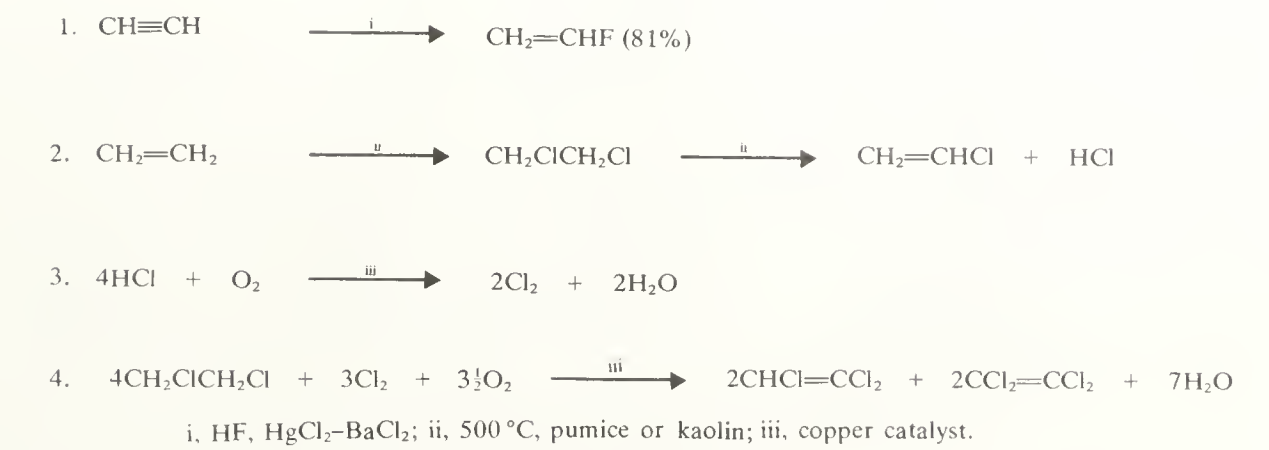
Fluoroalkenes are synthesized from chloroalkanes[118,119(i)] using hydrogen fluoride as the source of fluorine (see Scheme 36) although, in the laboratory, tetrafluoroethylene is most conveniently obtained by a simple and unusual thermal depolymerization.[119,(ii)] Perfluoropropene and -butenes may be obtained by pyrolysis of tetrafluoroethylene and the process apparently involves addition of difluorocarbene to the double bond followed by isomerization.

Vinyl fluoride, which in its polymeric form (PVF) is used as a protective coating for aluminium, is obtained (see Scheme 37) from acetylene.[120] However, ethylene-based routes are now preferred for the various chloroethylenes,[121] which are manufactured on an enormous scale. This has been made possible by the oxychlorination procedures[121,122] which have been developed (see Scheme 37), in which ethylene or dichloroethylene, together with chlorine and oxygen, are passed over a copper catalyst at elevated temperatures. In this way, chlorine is not wasted as hydrogen chloride. Trichloroethylene is used extensively as a solvent for metal degreasing, while perchloroethylene is used primarily as a dry-cleaning solvent.



i, HF, $SbCl_5$; ii, ~700 °C, Pt tube; iii, Zn, EtOH; iv, ~600 °C, vacuum; v, 450 °C; vi, 700 °C.

SCHEME 36

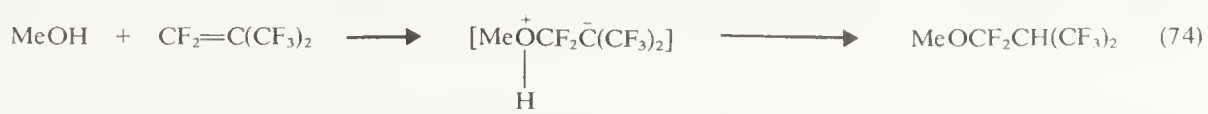


i, HF, $HgCl_2$–$BaCl_2$; ii, 500 °C, pumice or kaolin; iii, copper catalyst.

SCHEME 37

3.4.2 Nucleophilic attack[123]

In general, monohalo-alkenes and -arenes are unreactive towards nucleophilic substitution, unless other activating groups are also present in the molecule, whereas many polyhalo compounds are exceedingly reactive, *e.g.* perfluoroisobutene reacts with neutral methanol at room temperature (equation 74).



The nature of the products arising from nucleophilic attack on alkenes (see Table 16) may be regarded as dependent on the fate (see Scheme 38) of an intermediate carbanion (**56**): this can undergo (i) proton abstraction from the solvent to give (**57**), (ii) elimination of halide ion to give (**58**), or (iii) if the opportunity is available, an S_N2' process by loss of halide ion, giving (**59**).

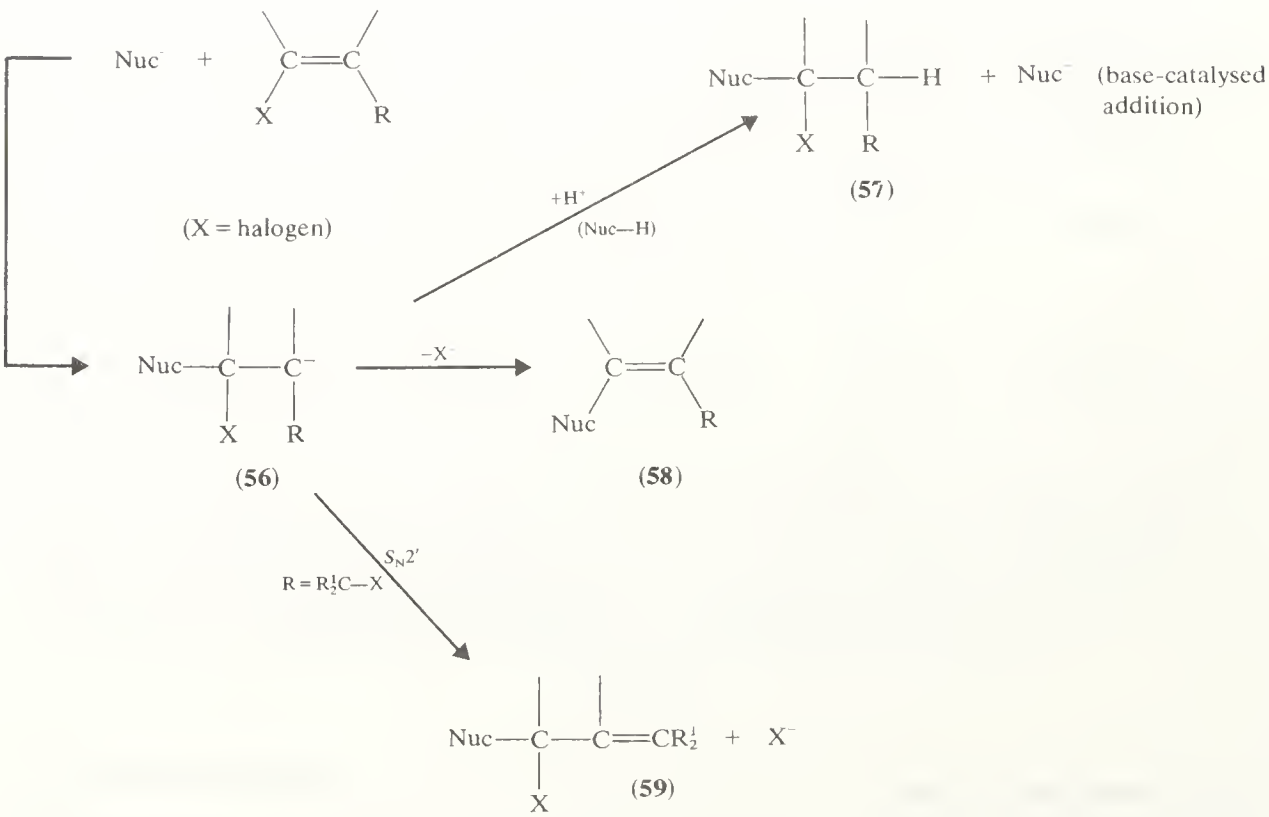
In other cases, elimination–addition reactions may occur and, in very special situations, preliminary ionization is possible and detailed discussions of these processes are available elsewhere.[124–127] There is a similarity between the mobility order of the halogens in displacements from vinylic positions and the well-established mobility order, F ≫ Cl, Br, for displacement from aromatic systems, although the comparisons which are contained in

TABLE 16

Substitution of Halogen[a] in p-$NO_2C_6H_4CH{=}CHX$ with PhS^- and MeO^- in MeOH at 25 °C[126]

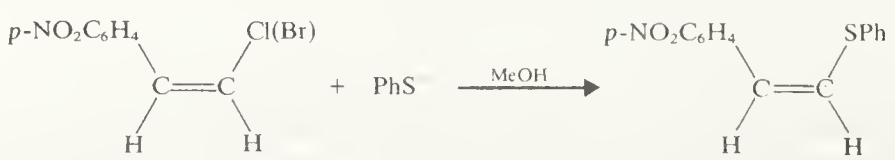
	PhS^-		MeO^-	
X	$k_{trans} \times 10^4$	$k_{cis} \times 10^4$	$k_{trans} \times 10^4$	$k_{cis} \times 10^4$
Br	22	6.9	0.016	Elimination
Cl	10.5	2.05	0.025	Elimination
F	111	22.3	7.21	1.68

[a] All values in $l\,mol^{-1}\,s^{-1}$.



SCHEME 38

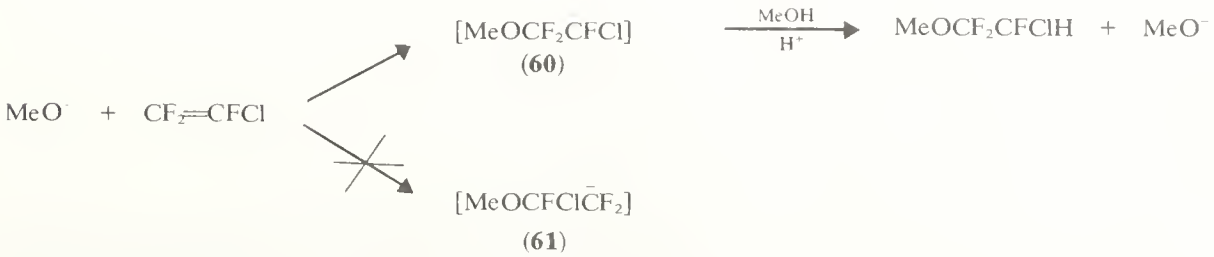
Table 16 indicate differences that are less dramatic than those which are normally encountered in aromatic systems. Frequently, substitution occurs in a highly stereospecific manner, *e.g.* equation (75), leading to retention of the configuration of the original olefin but there appears to be no clear cut case of true inversion.



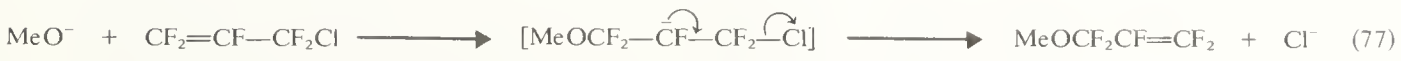
(75)

Regioselectivity for attack on highly halogenated olefins is apparently determined by the relative stabilizing influence of the halogen atoms on the intermediate carbanion. For example, reaction of methoxide ion with chlorotrifluoroethylene occurs exclusively at the difluoromethylene group (indeed all fluoro-olefins containing a difluoromethylene group undergo preferential attack at that position[123]) and this may be rationalized on the basis that intermediate (**60**) would be more stable than intermediate (**61**) in equation (76) because, in the situation $\bar{C}$—X, X corresponding to chlorine is more stabilizing than X

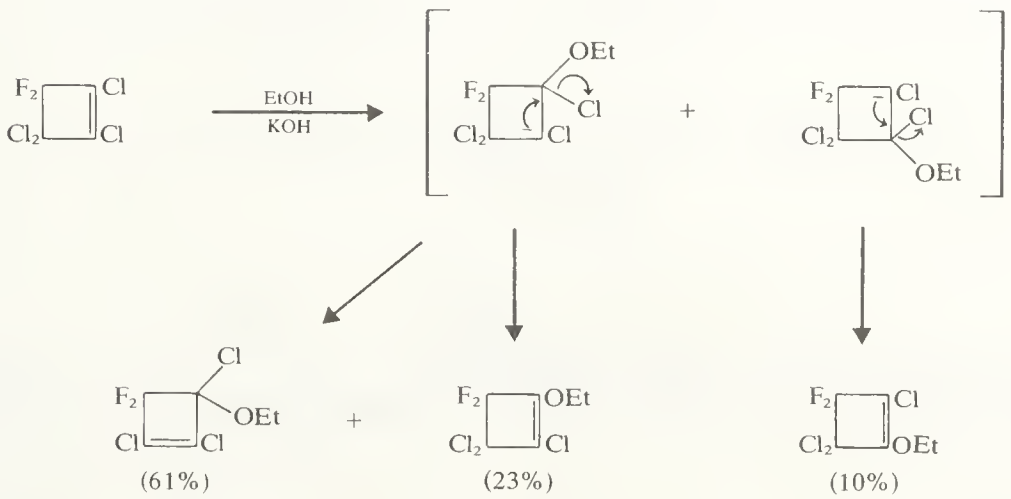
corresponding to fluorine. Similarly, the relative reactivities of polyfluoroalkenes reflect the carbanion-stabilizing influences of substituents, *e.g.* increasing reactivity in the series $CF_2{=}CF_2 < CF_2{=}CFCF_3 \ll CF_2{=}C(CF_3)_2$ and $CF_2{=}CF_2 < CF_2{=}CFCl < CF_2{=}CFBr$. The greater reactivity of tetrafluoroethylene over tetrachloroethylene is, however, a reflection of the lower mobility of chlorine than fluorine as the displaced group. A quite different situation obtains when there is a choice between loss of fluoride or, for example, chloride, as in equations (77) and (78), because here the order is the same as in an S_N2 process with fluoride being least readily lost. Thioaryl derivatives are formed from tetrachloroethylene and, eventually, all four chlorine atoms are displaced (equation 79) although only under drastic conditions.[129]



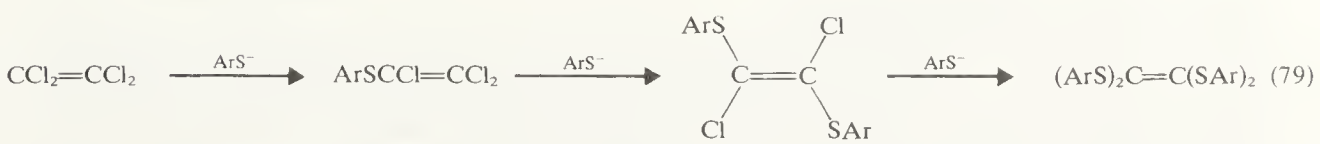
(76)



(77)



(78)[128]



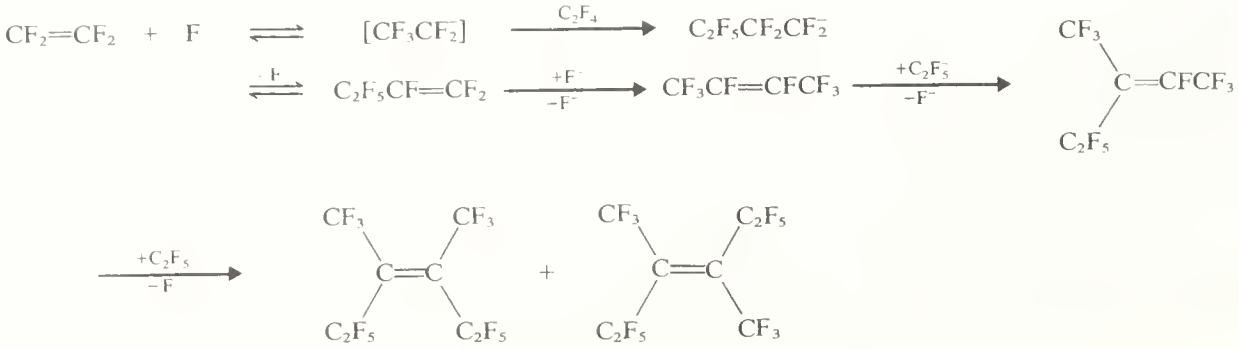
(79)

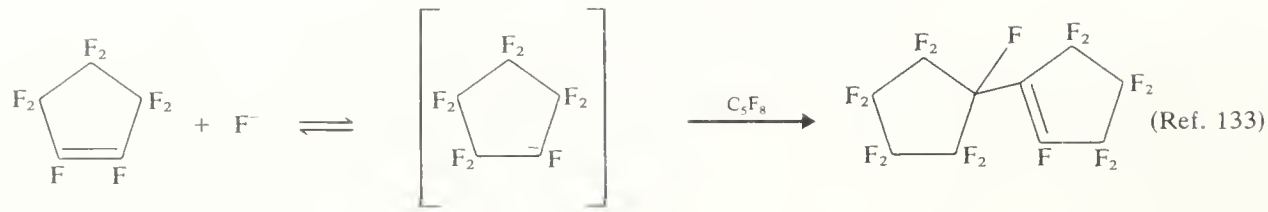
3.4.2.1 Fluoride ion induced reactions[130]

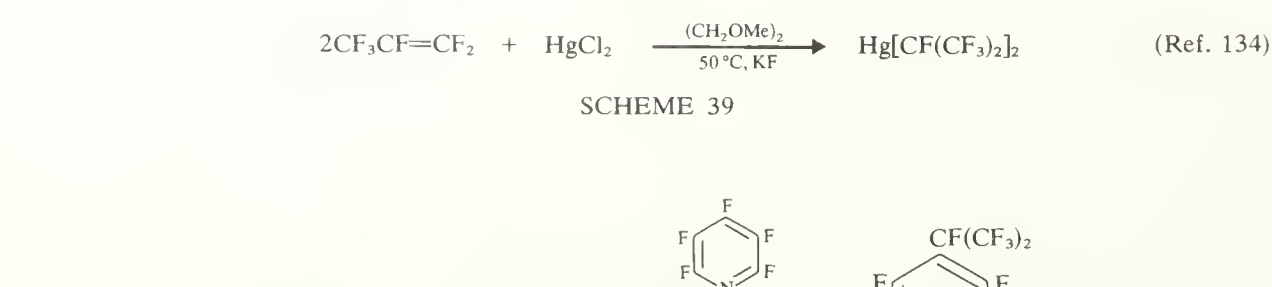
An analogy may be drawn between the role of fluoride ion in reactions with unsaturated fluorocarbons and the role of the proton in reactions with the corresponding unsaturated hydrocarbons. Carbanions can be generated by reaction of fluoride ion with a polyfluoroalkene and further reactions of carbanions generated in this way may be achieved, *e.g.* dimerization or oligomerization of the alkene, which mirror well-known proton-induced reactions of alkenes. See Scheme 39 for some examples. Polyfluoroalkylations may be achieved, using reactive aromatic systems (equation 80), in what may be regarded as the nucleophilic equivalent of the Friedel–Crafts reaction.

$$C_2F_4 \xrightarrow[\text{triglyme}]{\text{CsF, 99-100 °C}} C_8F_{16} + C_{10}F_{20} + C_{12}F_{24} + C_{14}F_{28} + \text{residue} \qquad \text{(Refs. 131, 132)}$$

	% composition				
5 psi	3	65	21	2	9
150–200 psi	6	21	25	42	6

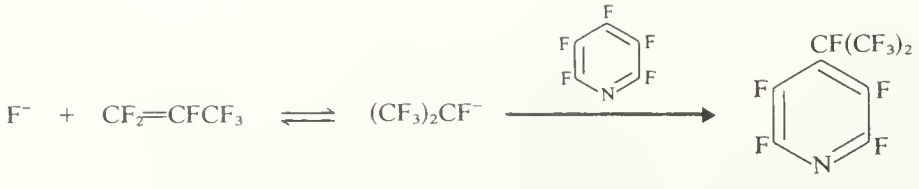






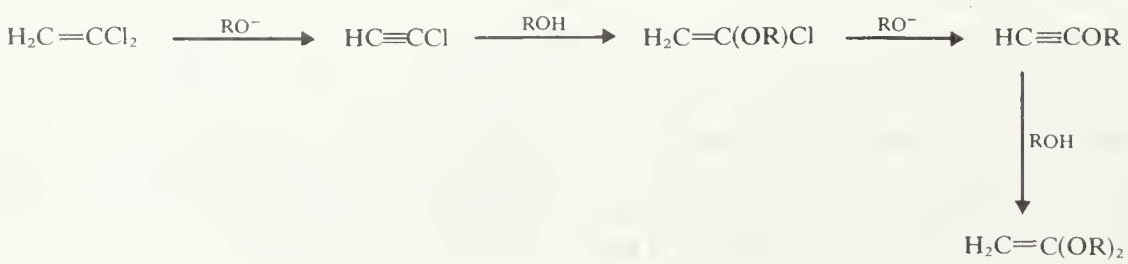
$$2CF_3CF{=}CF_2 + HgCl_2 \xrightarrow[50\,^\circ C,\ KF]{(CH_2OMe)_2} Hg[CF(CF_3)_2]_2 \qquad \text{(Ref. 134)}$$

SCHEME 39



3.4.2.2 *Other substitution processes*

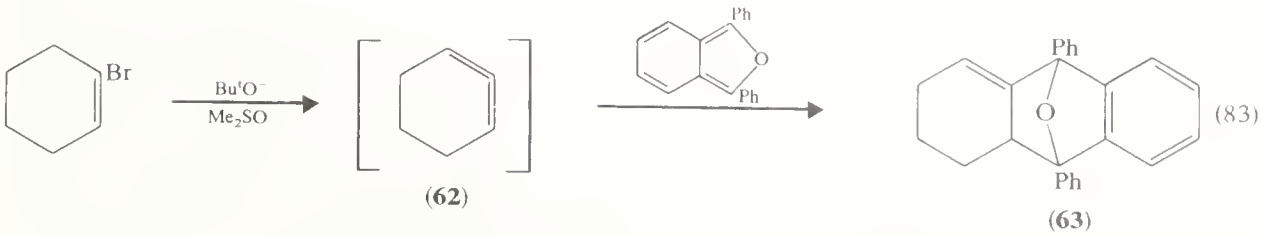
In certain cases the acidity of vinylic hydrogen is sufficient to allow β-elimination–addition processes to occur (equation 81). Elimination from both 1,1- and 1,2-dichloroethylene leads to chloroacetylene and so, understandably, in reaction with β-methoxyethoxide ion the same product is obtained from each olefin[137] (equation 82). Evidence for the formation of cyclohexa-1,2-diene (**62**) comes from a trapping experiment with 1,3-diphenylisobenzofuran, giving the Diels–Alder adduct (**63**)[138] (equation 83).



$$H_2C{=}CCl_2 \text{ or } cis\text{- or } trans\text{-}CHCl{=}CHCl \xrightarrow{MeOCH_2CH_2O^-} [HC{\equiv}CCl] \quad (82)$$

$$\downarrow$$

$$H_2C{=}C(OCH_2CH_2OMe)_2$$



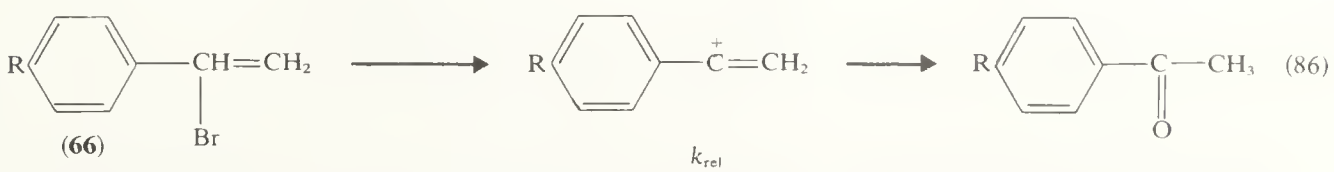
(62) (63) (83)

$$Ph_2C{=}CHF \; (\mathbf{64}) + EtO^- \longrightarrow Ph_2C{=}CHOEt \quad (84)$$

$$Ph_2C{=}CHCl(Br) \; (\mathbf{65}) + EtO^- \longrightarrow Ph_2C{=}CHOEt + PhC{\equiv}CPh \quad (85)$$

A comparison of the reactions (equations 84 and 85) of the fluoro compound (**64**) and either the corresponding chloro or bromo derivative (**65**) shows that, in the case of (**65**), α-elimination followed by rearrangement to diphenylacetylene competes successfully with addition–elimination.[126]

In special cases, rate-limiting ionization of vinyl halides occurs, as illustrated in equation (86) by the *para*-substituted bromostyrenes (**66**). Solvolysis in 80% aqueous ethanol leads to the corresponding acetophenones and it is clear from the relative rate constants that electron-donating substituents have powerful activation.[127]



(66) (86)

	k_{rel}
R = H	1
R = NH_2	5.5×10^8
R = MeO	8.5×10^3
R = MeCONH	2.2×10^3

Additional examples of reactions of nucleophiles with halo-olefins are shown in Table 17.

3.4.3 Radical additions

The generalized process can be described as shown below using the normal terminology to describe the various steps:

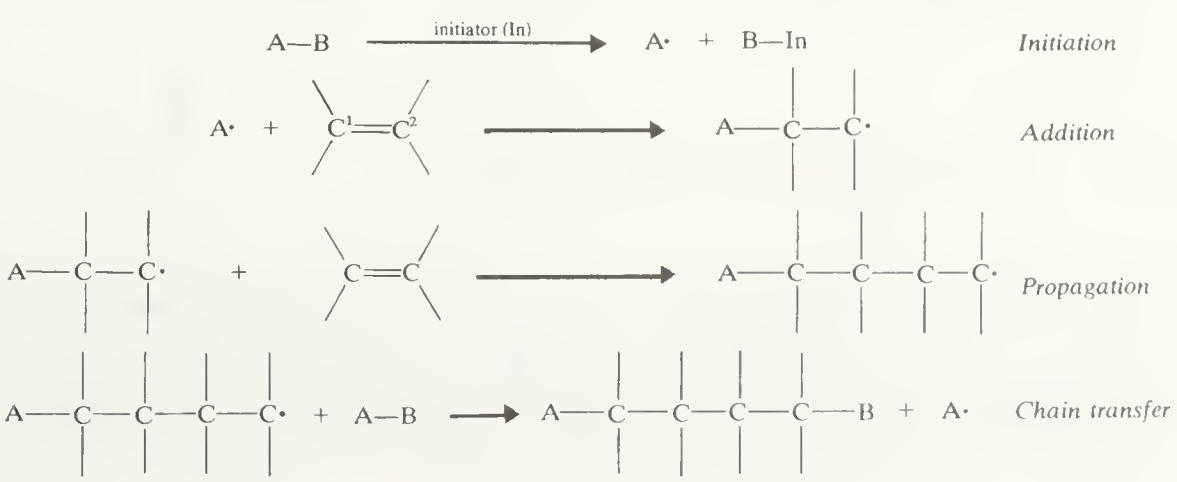
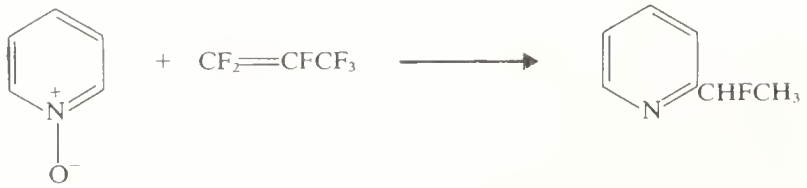


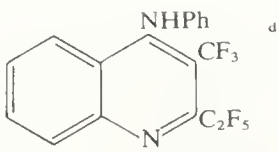
TABLE 17

Reaction of Nucleophiles with Haloalkenes

1. $CF{=}{=}CF_2 + MeO \xrightarrow[THF]{(MeO)_2CO} MeOCF_2CF_2CO_2Me\ (74\%) + (MeOCF_2CF_2)_2CO\ (12\%)$ [a]

2. $(CF_3)_2C{=}{=}CF_2 + NH_3 \xrightarrow[-60\,^\circ C]{Et_2O} (CF_3)_2CHCN\ (21\%) + (CF_3)_2CHCONH_2\ (13\%)$ [b]

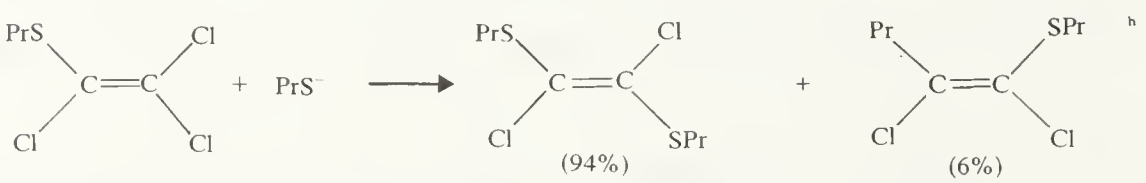
3.  [c]

4. $CF_3CF_2CF{=}{=}C(CF_3)_2 \xrightarrow{PhNH_2}$  [d]

5.  [e]

6.  [f]

7. $CF{=}{=}CFBr + RLi \longrightarrow RBr + [CF_2{=}{=}CFLi] \xrightarrow{HgCl_2} Hg[CF{=}{=}CF_2]_2$ [g]
(R = Me or Bu^n)

8.  [h]

[a] D. W. Wiley, *U.S. Pat.* 2 988 537 (1961); *Chem. Abs.*, 1962, **56,** 330. [b] I. L. Knunyants, L. S. German, and B. L. Dyatkin, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 1956, 1353; *Chem. Abs.*, 1957, **51,** 8037. [c] R. E. Banks, R. N. Haszeldine, and J. M. Robinson, *J.C.S. Perkin I*, 1976, 1226. [d] W. T. Flowers, R. N. Haszeldine, C. R. Owen, and A. Thomas, *J.C.S. Chem. Comm.*, 1974, 134; N. Ishikawa, A. Nagashima, and A. Sekiya, *Chem. Letters*, 1974, 1225. [e] A. W. Frank, *J. Org. Chem.*, 1965, **30,** 3663. [f] O. Scherer, G. Horlein, and H. Millauer, *Chem. Ber.*, 1966, **99,** 1966. [g] P. Tarrant, P. Johncock, and J. Savory, *J. Org. Chem.*, 1963, **28,** 839. [h] Ref. 129.

Obviously, if the bond A—B is weak, and the concentration of A—B is sufficiently high, then the main product will arise from addition to the double bond, *i.e.* chain transfer then competes successfully with propagation.

Generally, for the addition process, attachment of halogen atoms at C-1 is inhibiting towards radical attack, whereas attachment at C-2 has an activating effect. This is illustrated by the relative rate constants shown in Table 18, where the inhibiting effect of chlorine atoms at C-1 may be attributed to a combination of steric and polar effects on the approach of the bulky and electrophilic chlorine atom. In sharp contrast, however, fluorine atoms at C-1 do not have a pronounced inhibiting effect, at least arising from steric effects, and indeed, the heat of polymerization of tetrafluoroethylene is 71 kJ mol^{-1} *higher* even than the value for ethylene. This and other observations, such as the ready cycloaddition reactions of fluoroalkenes and the instability of 1-fluoroalkynes, have led to the suggestion that fluorine atoms de-stabilize these π-systems by electron-pair repulsions[7] between π-electrons in the C=C double bond and the non-bonding electrons on fluorine.

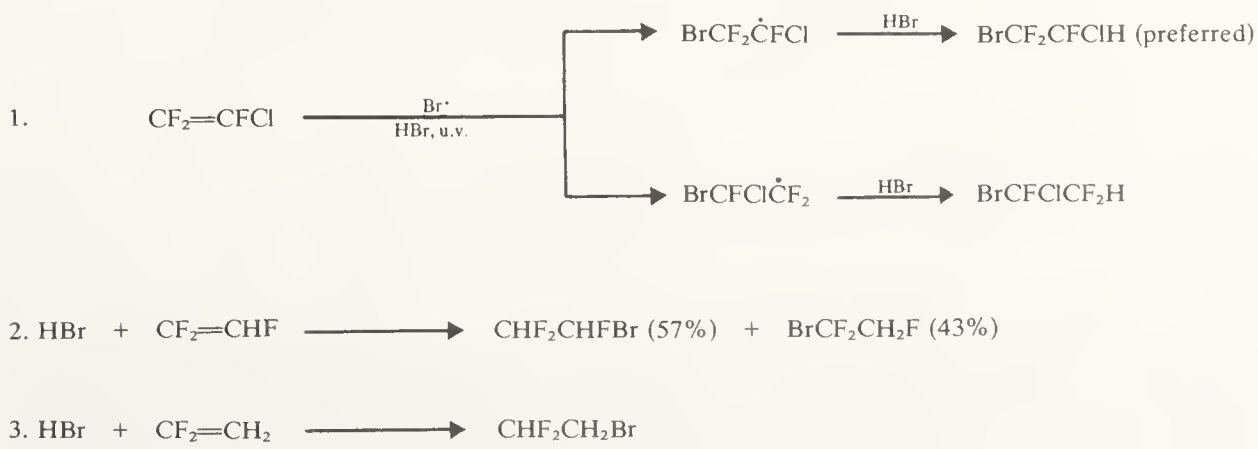
TABLE 18

Relative Rate Constants[18] for Addition of Chlorine Atoms to Chloro-olefins at 25 °C

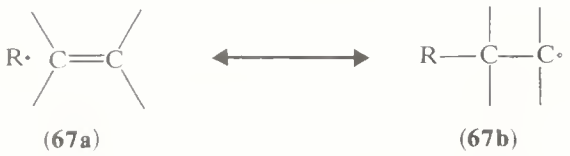
Olefin	k_{rel} (*non-complexing solvent*)	k_{rel} (CS_2)
$CH_2{=}CCl_2$	1.2	7.0
cis-CHCl=CHCl	0.6	0.9
trans-CHCl=CHCl	0.5[a]	0.5[a]
$CHCl{=}CCl_2$	0.7	0.9
$CCl_2{=}CCl_2$	0.2	0.03

[a] Other values relate to this.

In contrast to ionic reactions, radical additions to constitutionally unsymmetrical fluoro-olefins are frequently bi-directional, especially when electrophilic radicals are involved, although a general preference has been clearly established. The odd electron becomes situated on the carbon atom of the olefin with the substituents in the order of increasing preference, H < F < Cl,[139,140] as illustrated by additions of hydrogen bromide (see Scheme 40). It is now clear that the orientation of addition depends not only on the relative stabilities of the radicals produced on addition to an alkene, but also on the nature of the bond formed. In valence-bond terms this is equivalent to saying that the transition state should be represented as (**67a**)↔(**67b**), rather than just (**67b**), and it has been argued that too much emphasis has been placed on the latter in the past.



SCHEME 40



(67a) (67b)

Some examples of radical additions to halo-olefins are given in Table 19.

TABLE 19
Radical Reactions of Halo-olefins[7]

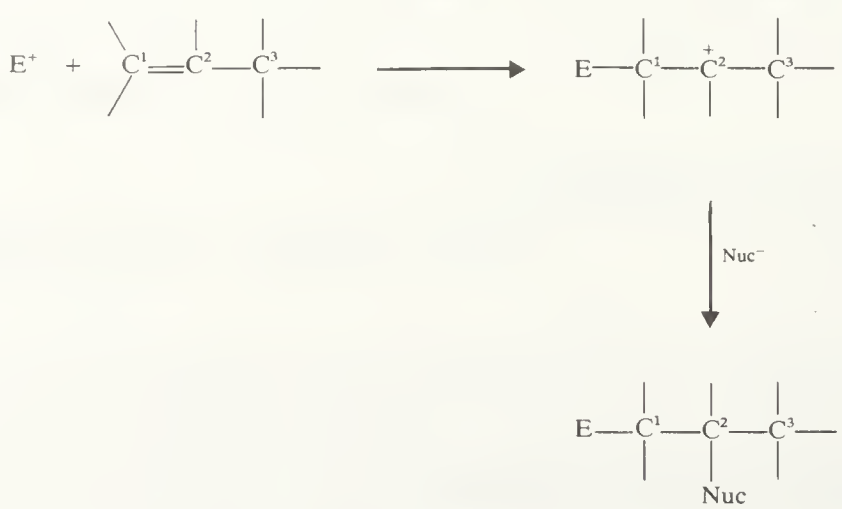
Olefin	*Reactants, etc.*	*Product*
$CF_2=CF_2$	CF_3I, $h\nu$	$CF_3(CF_2CF_2)_nI$
	PH_3	$CHF_2CF_2PH_2$ (53%)
		$(CHF_2CF_2)_2PH$ (7%)
		$H_2PCF_2CF_2PH_2$ (8%)
$CF_2=CCl_2$	Hg, $h\nu$	$CF_2ClCCl_2CCl_2CF_2Cl$
$CF_2=CFCF_3$	CF_3I, 194 °C	$CF_3[CF_2CF(CF_3)]_nI$ ($n = 1$–4)

The haloalkenes $CF_2=CF_2$, $CF_2=CFH$, $CF_2=CFCl$, and $CF_2=CFBr$ may be polymerized by radical processes to give useful homopolymers.[141] However, the extra steric constraints involved with hexafluoropropene mean that a homopolymer is produced only under quite drastic conditions (equation 87), although co-polymers with, for example, $CF_2=CF_2$ or $CF_2=CH_2$, may be obtained much more readily.

$$CF_2=CFCF_3 \xrightarrow[14\text{ h, }3000\text{ atm}]{(CF_3S)_2Hg,\ 225\,^\circ C} [CF_2CF(CF_3)]_n \qquad (87)^{142}$$

3.4.4 Electrophilic additions[22,143,144]

In the addition process in Scheme 41, halogen attached to the developing carbenium ion site, C-2, is able to interact conjugatively and thus offset inductive withdrawal. Therefore, as in electrophilic aromatic substitution, the resultant effect depends on the reagent used. It has been argued that the relative rate constants for addition of trifluoroacetic acid to 2-halopropenes listed in Table 20 provide good evidence for stabilization of the developing 2-fluoropropyl cation[78,145] by fluorine (equation 88).

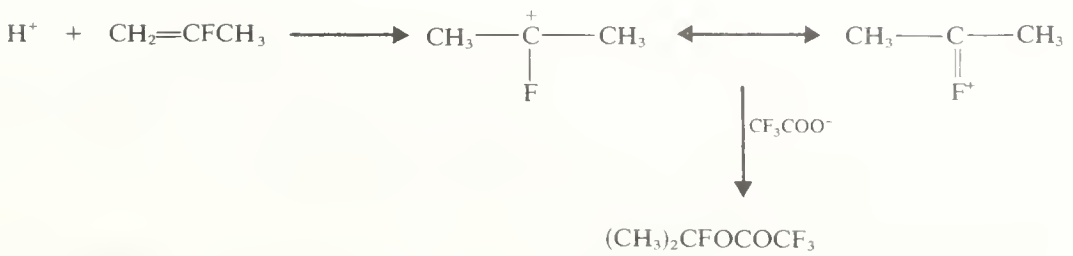


SCHEME 41

TABLE 20

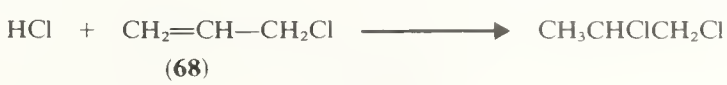
First-order Rate Constants for the Reaction of CF_3CO_2H with $CH_2{=}CXCH_3$ at 25 °C[145]

X	10^5k (s^{-1})	k_X/k_H
H	4.81	1
F	340	71
Cl	1.70	0.35
Br	0.395	0.082



(88)

Chlorine at C-3 (**68**) is deactivating but still results in Markownikov addition (equation 89), probably because chlorine bridges with the developing carbenium ion at C-2, whereas (**69**) apparently provides clear examples of anti-Markownikov addition (equation 90).



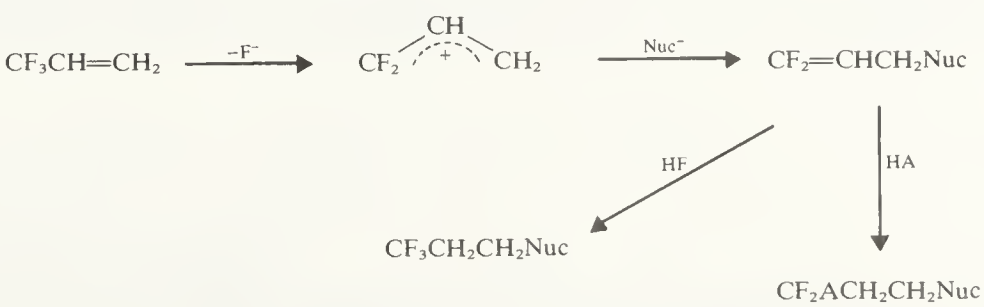
(89)

(**68**)

(90)

(**69**)

Nevertheless, doubt has been cast on the mechanism of electrophilic additions to (**69**) and, as a result of deuterium-labelling experiments, the mechanism of additions catalysed by strong acids, has been summarized as in Scheme 42. Equation (91) provides a specific example of this kind of addition.[146]



SCHEME 42

(91)

Polyhalo-olefins are relatively resistant to attack by the more common, or milder, electrophilic reagents. This is, of course, quite consistent with their established susceptibility towards nucleophilic attack. Nevertheless, with suitably reactive electrophiles, addition occurs (equations 92 and 93).

$$CF_2{=}CCl_2 + HF \xrightarrow{BF_3} CF_3CHCl_2 + \text{polymer} \quad (92)^{147}$$

$$AgF + CF_2{=}CFCF_3 \xrightarrow[125\,^\circ C]{HF} [AgCF(CF_3)_2] \xrightarrow{HF} HCF(CF_3)_2 + AgF \quad (93)^{148}$$

(47%)

A variety of interesting electrophilic additions has been developed where addition of XF (X = Cl, Br, I, NO_2, *etc.*) to polyhalo-olefins is achieved by reaction with a series of reagents in anhydrous hydrogen fluoride[144] (equations 94 and 95).

$$\text{N—Cl} + CF_2{=}CH_2 \xrightarrow[HF,\,-10\,^\circ C]{\text{hexachloromelamine}} CF_3CH_2Cl \quad (94)$$

$$CF_2{=}CF_2 \xrightarrow[20\,^\circ C]{HF,\,HNO_3} CF_3CF_2NO_2 \ (93\%) \quad (95)$$

The generation of long-lived carbenium ions by interaction of polyhalo-alkenes with Lewis acids was discussed in Section 3.3.3.5. Friedel–Crafts type alkylations have been achieved (see Scheme 43) *via* perfluorinated allyl cations.[149]

$$CF_2{=}CFCF_3 \underset{}{\overset{i}{\rightleftharpoons}} [CF_2{=}CF{=}CF_2]^+ \xrightarrow{ii} [C_6F_5CF_2CF{=}CF_2]$$

$$\overset{i}{\rightleftharpoons} [C_6F_5CF{=}CF{=}CF_2]^+ \xrightarrow{ii} [(C_6F_5)_2CF{-}CF{=}CF_2]$$

$$\overset{i}{\rightleftharpoons} [(C_6F_5)_2C{=}CF{=}CF_2]^+ \xrightarrow{iii} (C_6F_5)_2C{=}CFCF_3$$

i, SbF_5; ii, pentafluorobenzene; iii, $+F^-(SbF_6^-)$.

SCHEME 43

3.4.5 Cycloadditions

3.4.5.1 [2+2] *Cycloadditions*

An unusual aspect of the chemistry of fluoroalkenes is their tendency to form four-membered rings by dimerization (equations 96–98).[150–153] Alternatively, codimerization will occur not only between different fluoroalkenes, but also between fluoroalkenes and unsaturated hydrocarbons and, moreover, some of these mixed reactions proceed more readily than dimerization of the corresponding fluoroalkene.

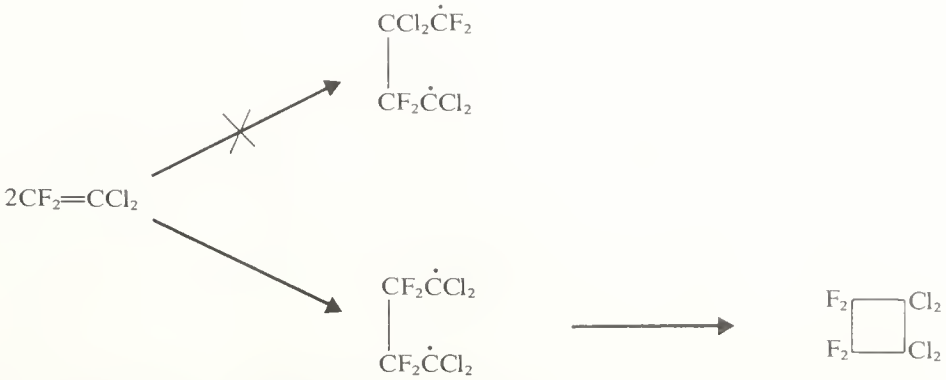
$$2CF_2{=}CF_2 \longrightarrow \begin{array}{cc} F_2 & F_2 \\ \square & \\ F_2 & F_2 \end{array} \quad (96)^{154}$$

$$CF_2{=}CF_2 + \begin{array}{cc} H & H \\ C{=}C & \\ D & D \end{array} \longrightarrow \begin{array}{cc} F_2 & HD \\ \square & \\ F_2 & HD \end{array} \quad (97)^{155,156}$$

(*cis* + *trans*)

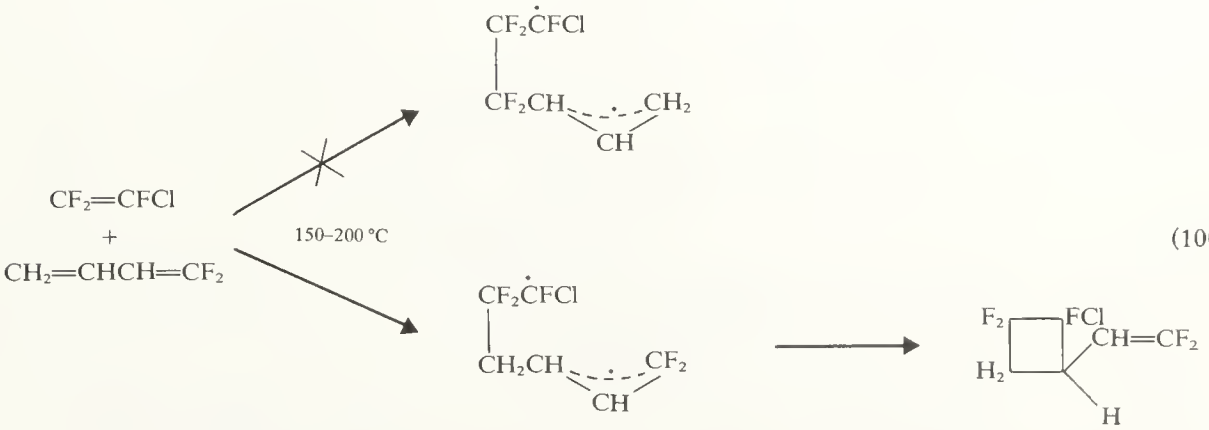
$$2CF_2{=}C{=}CF_2 \longrightarrow \begin{array}{ccc} & & CF_2 \\ & \diagup\!\diagdown & \\ F_2 & & \\ & \diagdown\!\diagup & \\ F_2 & & \\ & & CF_2 \end{array} \quad (98)^{157}$$

Thermally induced $[{}_{\pi}2_s + {}_{\pi}2_s]$ cycloadditions are formally forbidden as concerted processes and, indeed, the information available can only be rationalized on the basis of formation of diradical intermediates. For example, only head-to-head dimers are formed from 1,1-dichlorodifluoroethylene (equation 99) and both *cis* and *trans* products are obtained in the addition of tetrafluoroethylene to either *cis*- or *trans*-[1,2-$^2H_2$]ethylene.[156]

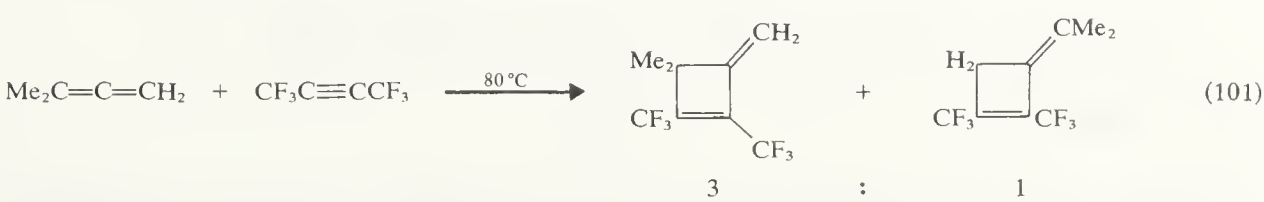


(99)

Product formation in alkene–diene reactions may also be rationalized on the basis of formation of the most stable (see Section 3.4.3) diradical intermediate (equation 100). Four-membered rings may also be produced from fluorinated alkynes[159] (equation 101).



(100)[158]

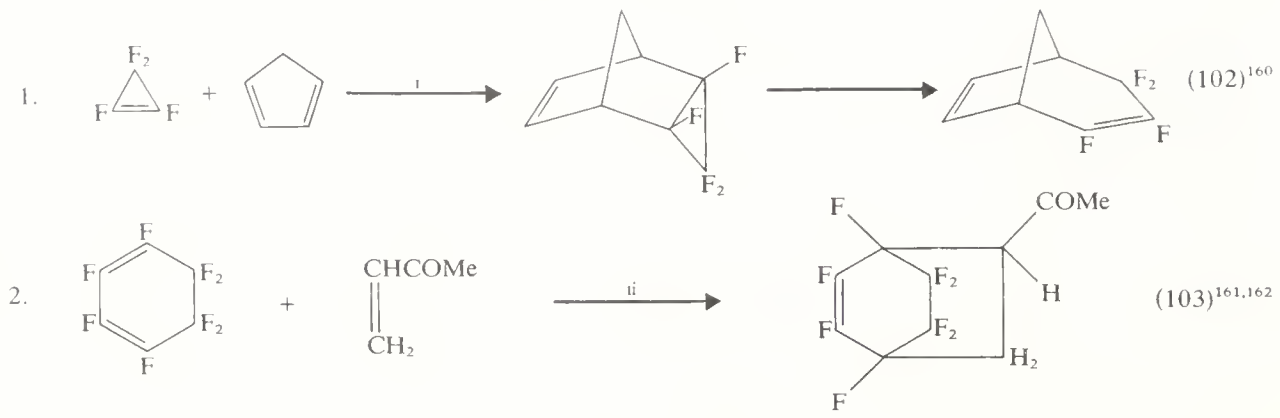


(101)

3.4.5.2 [4+2] Cycloadditions[150]

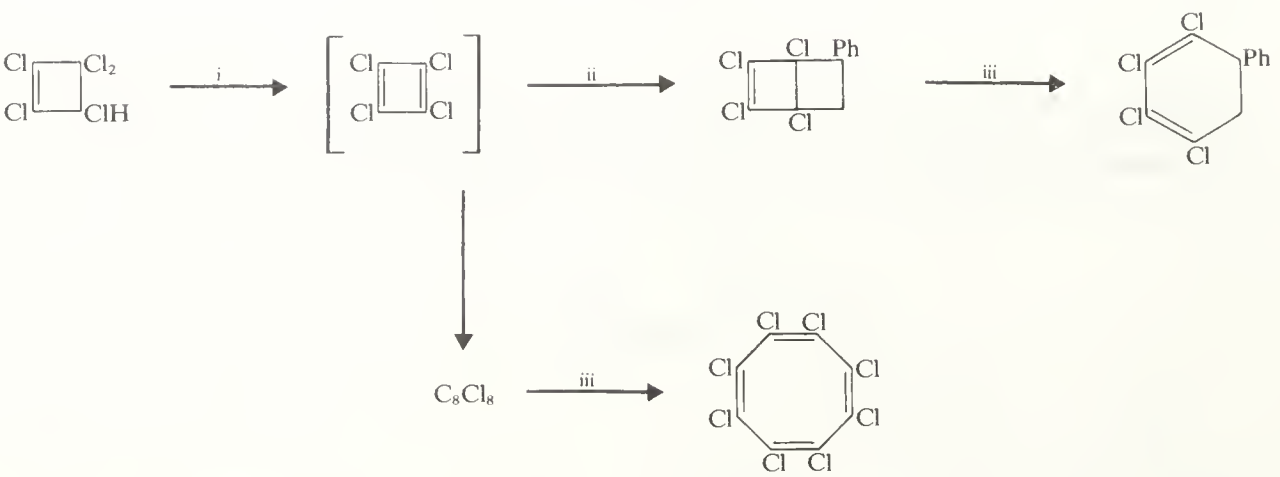
Although 1,2-cycloaddition products are unusually common in reactions of fluorinated alkenes, $[{}_{\pi}4_s + {}_{\pi}2_s]$ processes (Diels–Alder) are quite common and, indeed, 1,4-adducts may be the principal products, as shown in Scheme 44.

(*i*) *Reactions of cyclobutadienes.* Evidence has been presented for the formation of tetrachlorocyclobutadiene by trapping with styrene or cyclohexadiene;[163] in the absence of a trapping agent a dimer is formed which, on heating, gives octachlorocyclo-octatetraene, as depicted in Scheme 45. Generation of tetraiodo-[164] and tetrafluoro-cyclobutadienes[165] has also been reported (see Scheme 46).



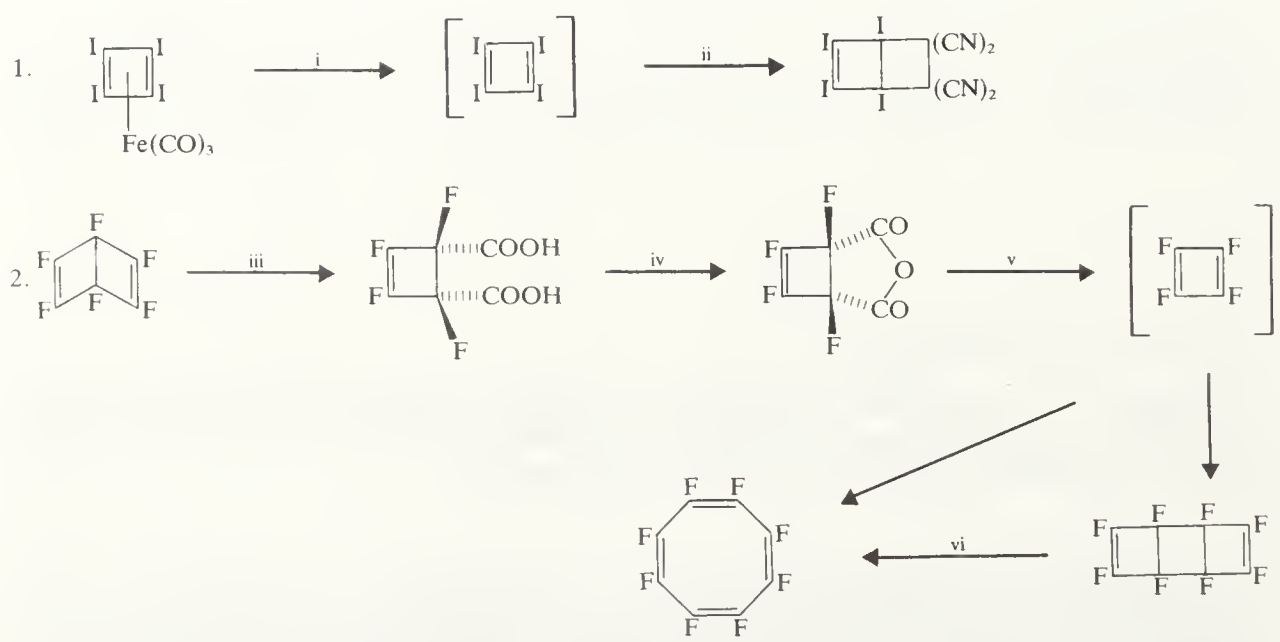
i, Room temp.; ii, 114 °C.

SCHEME 44



i, KOH; ii, styrene; iii, heat.

SCHEME 45

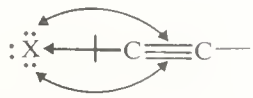


i, Ce^{2+}; ii, $C(CN)_2{=}C(CN)_2$; iii, O_3; iv, P_2O_5; v, $h\nu$; vi, Δ.

SCHEME 46

3.5 HALOALKYNES

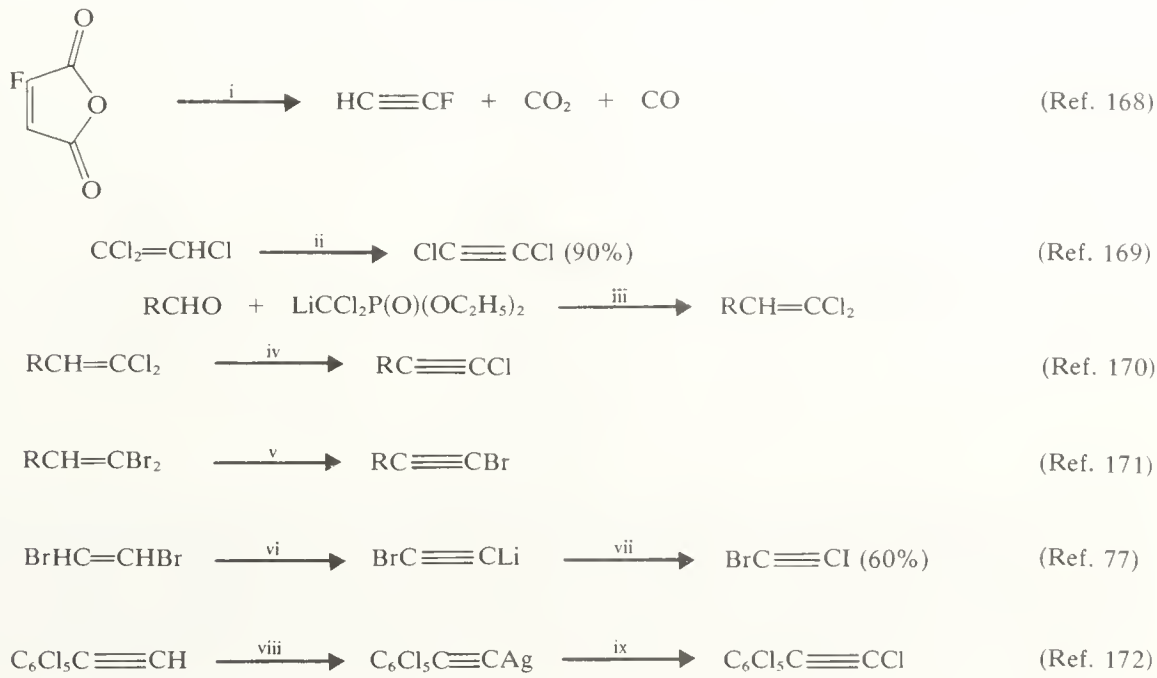
Fluorine and chlorine atoms directly attached to a triple bond are destabilizing,[166] the stability of haloalkynes increasing in the series F < Cl < Br, I. Obviously, electronegativity of the halogen will affect the strength of a carbon–halogen bond but the striking instability of fluoroalkynes is probably, principally, a manifestation of the effect of electron-pair repulsions, *i.e.* as shown in (**70**). The triple bond, having cylindrical symmetry, shows the



(**70**)

effects of electron-pair repulsions more than a double bond.[167] In contrast, however, $CF_3C{\equiv}CCF_3$ has none of the explosive instability associated with difluoro- or dichloroacetylene.

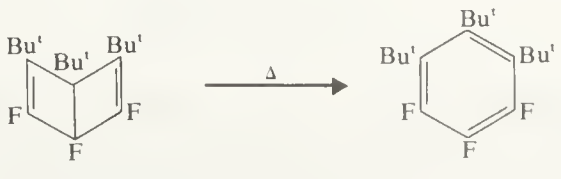
Some examples of the synthesis of halogenoalkynes are shown in Scheme 47.



i, 600 °C; ii, KOH, $(CH_2OH)_2$, 140 °C; iii, THF–Et_2O; iv, $LiNEt_2$, THF–Et_2O; v, $PhCH_2NMe_3OH$; vi, $LiNH_2$, NH_3; vii, I_2, −50 °C; viii, Ag^+, THF–H_2O; ix, Cl_2, CCl_4.

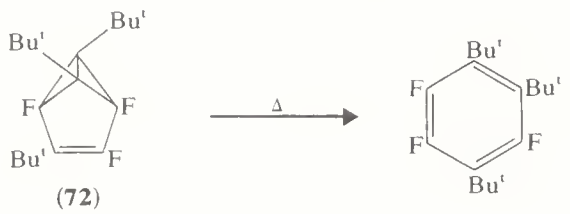
SCHEME 47

t-Butylfluoroacetylene may be stored at low temperatures but, remarkably, oligomers, which are mainly trimers, are formed even below 0 °C. Two of the trimers are valence isomers, a Dewar benzene (**71**) and a benzvalene (**72**), and each will aromatize on heating[166] (equations 104 and 105). Dichloroacetylene, which may be handled with reasonable safety in ether, will undergo cycloaddition reactions[169] (equations 106 and 107). Perchlorophenylacetylene will form a dimer and trimers if heated to 190–195 °C and the intermediacy of valence isomers has been postulated to account for the products[172] in equation (108).

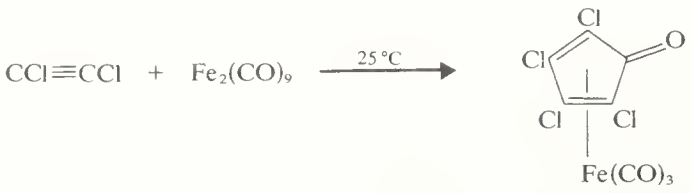


(104)

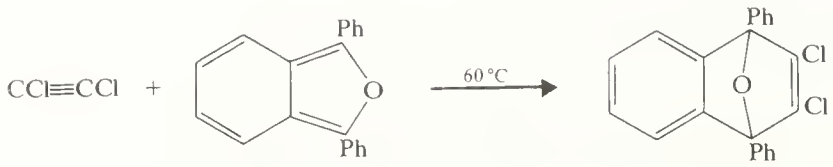
(**71**)



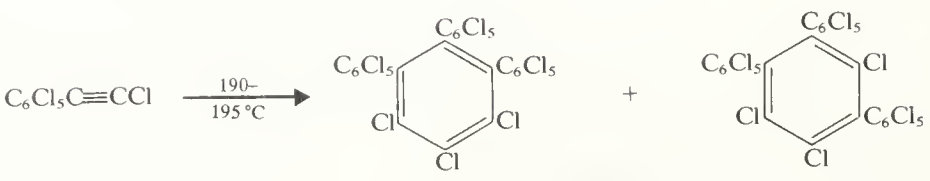
(72) (105)



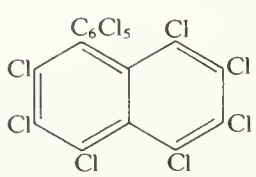
(106)



(107)



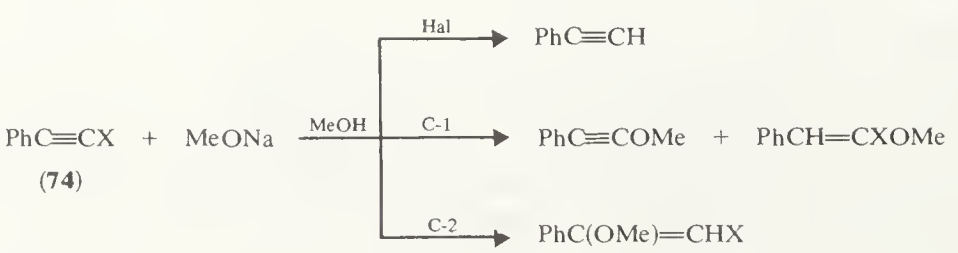
(108)



Nucleophilic substitutions take place in haloalkynes and, more recently, the variety of possible mechanisms for this process has been fully appreciated.[173] In principle, nucleophilic attack in (**73**) could take place at halogen, at C 1, or at C-2 and these possibilities are each observed in reactions of (**74**) with sodium methoxide in methanol[174] (equation 109). Some other examples of overall, nucleophilic substitutions are shown in Scheme 48, although some of the mechanisms are not at all clear.[173]

$$R—C^2{\equiv}C^1—Hal$$

(**73**)



(109)[174]

1. $Bu^tC{\equiv}CCl + PhS^- \xrightarrow{i} Bu^tC{\equiv}CSPh$

2. $R^1CH_2C{\equiv}CBr \xrightarrow{ii} [R^1CH{=}C{=}C{:}] \xrightarrow{iii} R^1CH{=}C{=}CHOR^2$ (+ other products) (Ref. 174a)

3. $R^1C{\equiv}CH + R^2C{\equiv}CBr \xrightarrow{iv} R^1C{\equiv}CC{\equiv}CR^2$ (Ref. 174b)

4. $R^1MgBr + R^2C{\equiv}CCl \xrightarrow{v} R^1C{\equiv}CR^2$

i, DMF; ii, R^2O^-; iii, R^2OH; iv, Cu^+; v, $CoCl_2$.

SCHEME 48

In contrast to the effect of fluorine directly attached to the triple bond, perfluoroalkyl groups lead to stable systems (see Scheme 49).

$CCl_2{=}CCl{-}CCl{=}CCl_2 \xrightarrow{i} CF_3CCl{=}CClCF_3 \xrightarrow{ii} CF_3C{\equiv}CCF_3$ (Ref. 175)

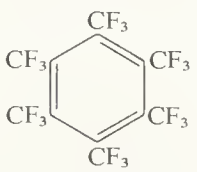
$R_FI + BrHC{=}CHPh \xrightarrow{iii} R_FCH{=}CHPh \xrightarrow{iv,\,v} R_FC{\equiv}CPh$ (Ref. 175a)

(R_F = perfluoroalkyl)

i, SbF_3, SbF_3Cl_2, 155 °C; ii, Zn, AcOH; iii, Cu, DMF; iv, Br_2; v, KOH.

SCHEME 49

Hexafluorobut-2-yne is the most extensively investigated example of these systems;[176] it will form a trimer but the severe conditions shown in equation (110) are required.[177] The triple bond is very susceptible to nucleophilic attack and in reaction with fluoride ion gives an unusual polymer (**77**)[178] (equation 111). The intermediate anions (**75**) and (**76**) may be trapped with suitably reactive systems,[178,179] as shown in equations (112) and (113).

$$3CF_3C{\equiv}CCF_3 \xrightarrow{375\,^\circ C}$$  (110)

$$F^- + CF_3C{\equiv}CCF_3 \underset{}{\overset{CsF,\ sulpholan}{\rightleftharpoons}} CF_3CF{=}\bar{C}CF_3 \xrightarrow{C_4F_6} CF_3CF{=}C(CF_3)C(CF_3){=}\bar{C}CF_3$$

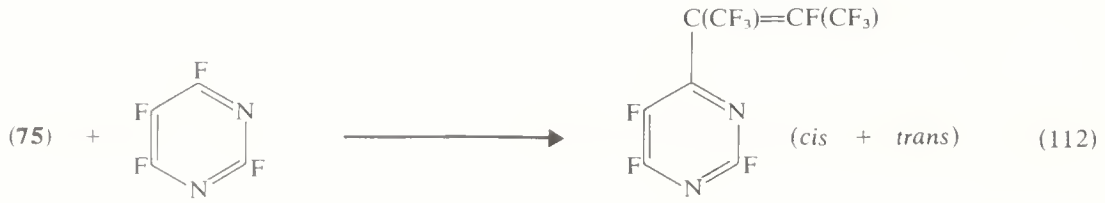
(**75**)

(**76**)

$\downarrow C_4F_6$ (111)

$F[C(CF_3){=}C(CF_3)]_n$

(**77**)

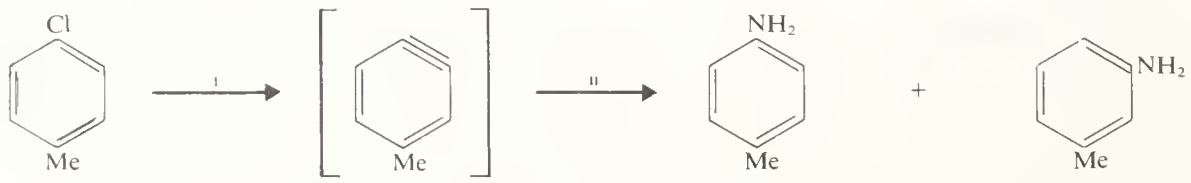


3.6 HALOARENES

3.6.1 Displacement of halogen

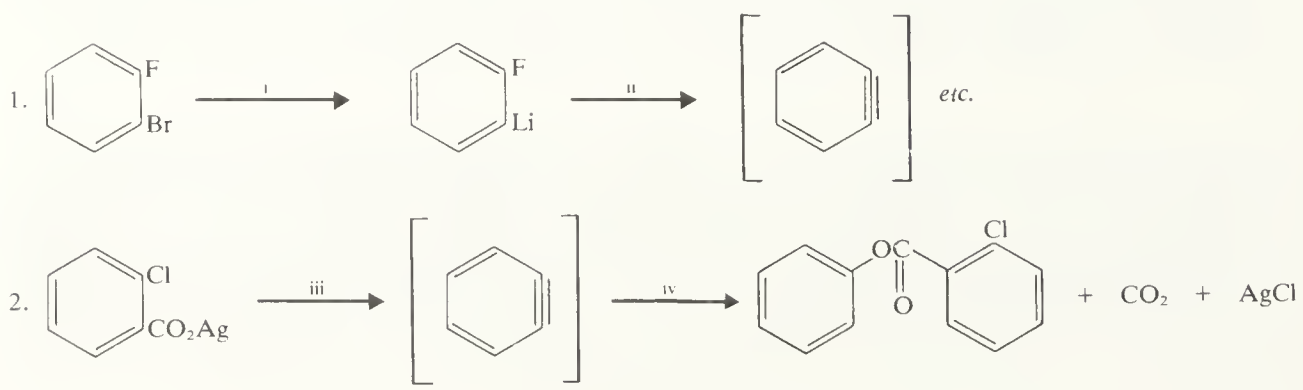
3.6.1.1 Elimination–addition

It is well-established that unactivated monohaloaromatic compounds are quite resistant to nucleophilic displacement of the halogen and that initial attack, by strong bases, will occur so as to remove a proton and hence cause elimination, giving an aryne[180] as shown in Scheme 50. Arynes may also be generated from dihalogenoaryls *via* formation of organo-lithium or 1-magnesium compounds, or by elimination from a silver salt of a carboxylic acid.[180–182] (see Scheme 51).



i, KNH_2, NH_3, −10 °C; ii, NH_3. *ca.* 1:1

SCHEME 50



i, Li; ii, −LiF; iii, Δ; iv, *o*-$ClC_6H_4CO_2$.

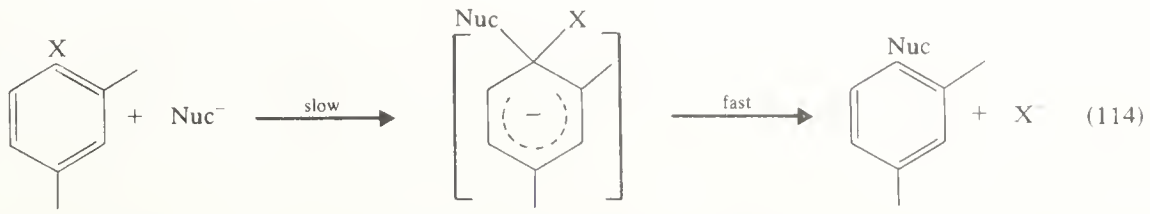
SCHEME 51

Reactions of arynes are discussed elsewhere (see Section 2.8.3.3).

3.6.1.2 Addition–elimination

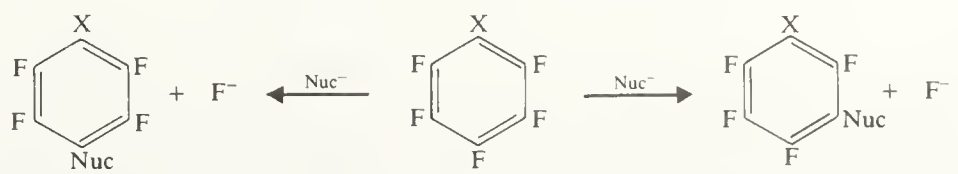
Nucleophilic displacement of halogen from activated systems most commonly occurs *via* a two-step addition–elimination mechanism.[183] The first step in equation (114) is usually,

but not always, rate-determining. Some of the most convincing evidence for this is that the mobility order of the halogens, established by the classic work of Bunnett and his co-workers,[184] is F ≫ Cl, Br, I. Since the carbon–fluorine bond is the strongest of the series, then there can be little bond breaking in the rate-determining step in systems where this order is observed. However, why the fluoro derivatives should be so much more reactive than the other halogens is more difficult to explain. It has been argued that the carbon–fluorine bond polarity $C^{\delta+}$—$F^{\delta-}$ is mainly responsible for this mobility order, *i.e.* making the carbon atom under attack more electrophilic in character, although the different steric requirements of the halogens probably make some contribution to the mobility order.



(114)

It is only with highly halogenated systems that problems arise about orientation of substitution, and these are analogous to the classical orientation problems of electrophilic aromatic substitution. The orientation of substitution and reactivity of polyhaloaromatic compounds has been a subject of much discussion and only recently has a clearer picture emerged[185,186] (see Scheme 52). In most cases for substitution in perfluorobenzenes, C_6F_5X, the main product (>90%) arises from displacement of a fluorine atom *para* to the substituent X (for example, where X = H, Me, SMe, CF_3, NMe_2, NO_2, *etc.*).[187,188] In a few cases (X = NH_2, O^-) replacement in the *meta* position predominates. The effect of substituents on rate constants is, however, in the direction expected for a nucleophilic aromatic substitution in that electron-donating groups deactivate (for example, $C_6F_5NH_2$ and $C_6F_5O^-$ are strongly deactivated) while withdrawing groups activate. Some relative rate constants[189] are shown in Table 21 illustrating that, as in electrophilic aromatic substitutions, these values vary greatly with different substituents. By contrast, the orientation pattern is relatively insensitive to the substituent.



(*e.g.* X = H, Me, CF_3) (X = NH_2, O^-)

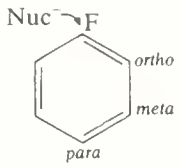
SCHEME 52

TABLE 21

Relative Rate Constants for Reaction with $NaOC_6F_5$ at 106 °C in *N,N*-Dimethylacetamide with C_6F_5X

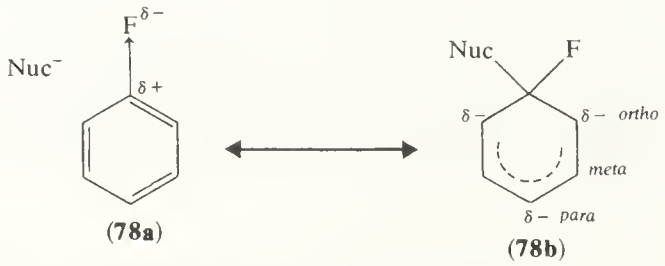
X	k_{rel}
CF_3	2.4×10^4
CO_2Et	2.9×10^3
C_6F_5	7.3×10^2
Br	39
Cl	32
H	1
F	0.91

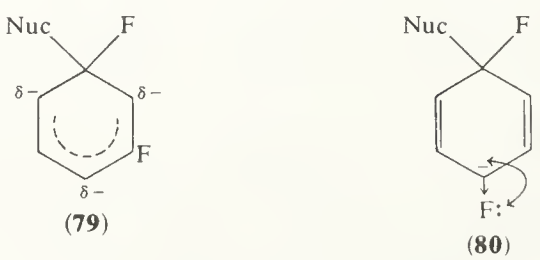
The basis of this unusual orientating effect of the halogens is the different activating influences of fluorine atoms which are *ortho*, *meta*, and *para* to the point of nucleophilic attack on the ring:



Activating influence of F, *meta* > *ortho* ≫ *para*

These separate activating influences have been established for reactions with methoxide in methanol;[186] the effect of a fluorine *para* to the reaction centre is little different to that of a hydrogen at the same site, whereas *ortho* and *meta* fluorines are strongly activating. An explanation of these effects has been advanced, based on (**78**) as a model for the transition state of the rate-determining step.[185,186] The activating influence of *meta* fluorine then is understandable, being adjacent to the centres of maximum charge delocalized into the ring (**79**). Likewise, the minor effect of a *para* fluorine is a consequence of competing inductive withdrawal and electron-pair repulsion (**80**). However, the significant activating influence of *ortho* fluorine is more difficult to account for since a model for the transition state of (**78b**) only would imply similar effects for both *ortho* and *para* fluorine. It is probable, therefore, that the *ortho* fluorine atom activates by enhancing the already electrophilic nature of the carbon atom under attack in the initial-state contribution (**78a**). Nevertheless, regardless of the basis of these activating effects for fluorine substituents, it is quite clear that nucleophilic attack usually occurs in C_6F_5X predominantly *para* to the substituent, because this maximizes the activating influence of fluorine atoms (see Figure 1).





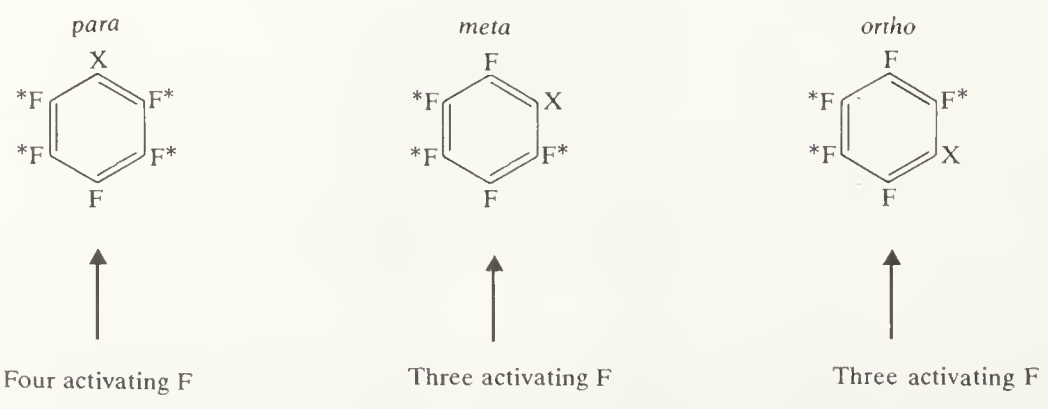
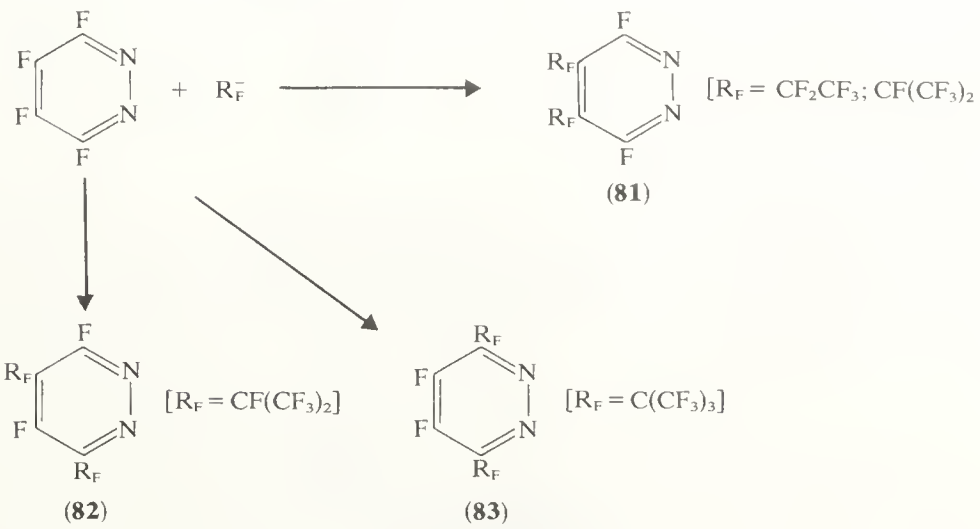


Figure 1 Nucleophilic attack in C_6F_5X

Orientation of substitution in polychloroaromatic compounds[12] is usually less specific than in polyfluorinated cases and this stems from the fact that a *para* chlorine is quite activating (see Table 21). Consequently, the differences in activating influences arising from the chlorine atoms, in say C_6Cl_5X, for attack *ortho*, *meta*, or *para* to the substituent X are significantly less than the corresponding differences in C_6F_5X.

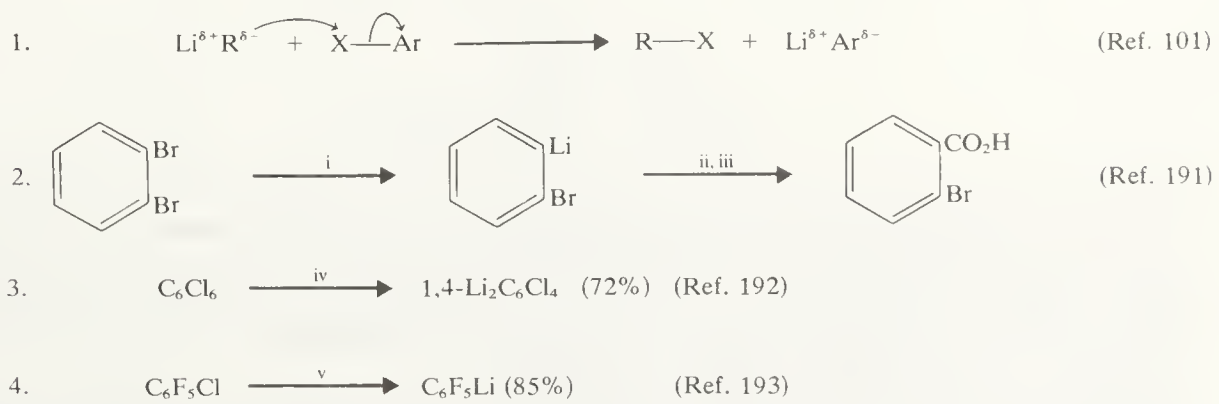
Perfluoroalkyl anions, generated by reaction of fluoride ion with a perfluoroalkene, will react with activated fluoroaromatic compounds in what may be regarded as the negative equivalent of Friedel–Crafts reactions.[135] Polysubstitution raises some complications for three reasons: (i) after polyfluoroalkyl groups are present these can, in some cases, control the position of further substitution, (ii) some of the reactions are reversible, and (iii) substitution at the position most activated to attack sometimes results in crowding and is, therefore, not the most thermodynamically stable system. This can lead to an interesting competition between kinetic (**81**) and thermodynamic (**82**) or (**83**) control of reaction products,[190] as shown in Scheme 53.



SCHEME 53

3.6.1.3 Nucleophilic attack on halogen

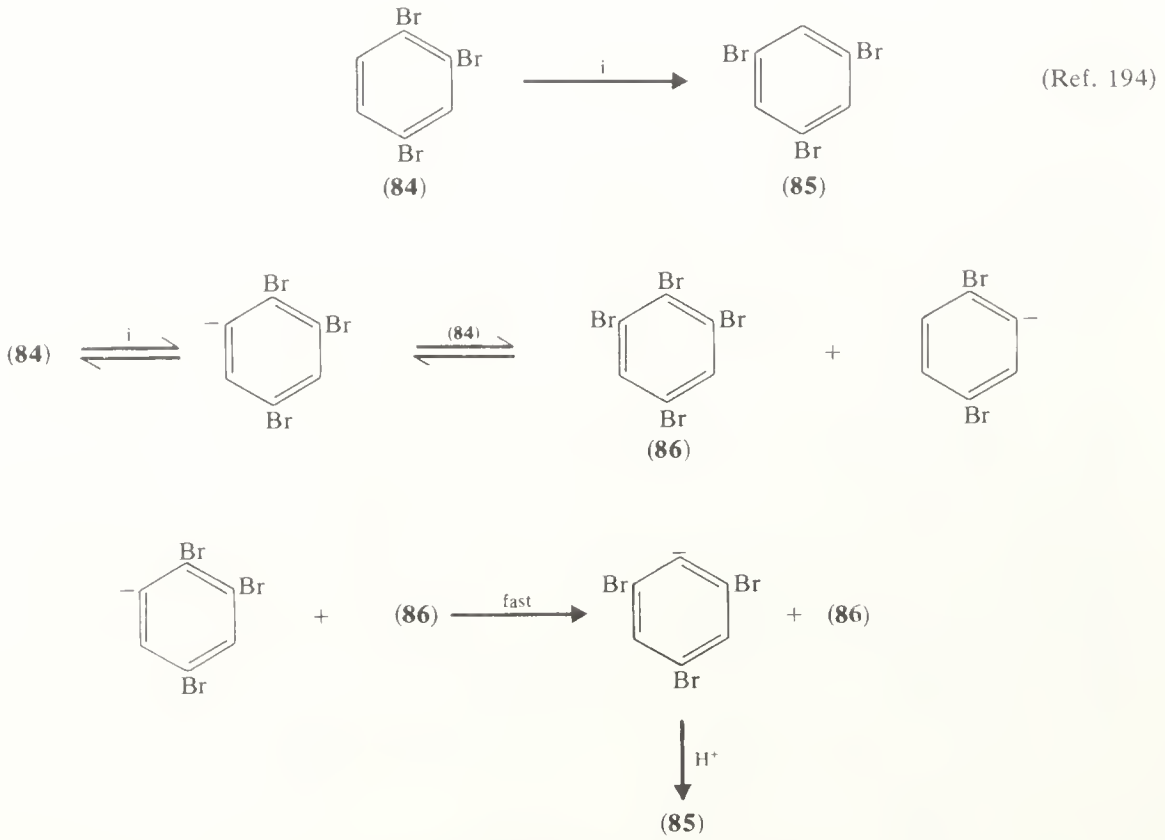
The simplest examples of this type involve metal exchange of a haloaromatic compound Ar—X with, for example, an alkyl-lithium[101] (see Scheme 54). In general the ease of exchange decreases in the series X = I > Br > Cl ≫ F, the fluoro compounds generally being much more susceptible to nucleophilic attack on carbon than on halogen.



i, BuLi, Et_2O, −110 °C; ii, CO_2; iii, H^+; iv, BuLi, THF, −70 °C; v, BuLi, Et_2O, −70 °C.

SCHEME 54

Nucleophilic attack on bromine occurs, rather than aryne formation, accounting for the fascinating halogen-dance mechanism for the conversion of (**84**) to (**85**), catalysed by (**86**) as shown in Scheme 55. There are, of course, many other examples of nucleophilic attack on halogen.[22]



i, PhNHK, liq. NH_3.

SCHEME 55

3.6.1.4 Electron transfer

Following the discovery of a radical chain mechanism ($S_{RN}1$) for substitutions in *p*-nitrobenzyl chloride (see Section 3.3.3.6), Bunnett and co-workers[195] have proposed a similar mechanism to account for the surprisingly easy substitution in some so-called unactivated aryl halides, by nucleophiles:

$$\text{Electron donor} + \text{Ar—X} \rightarrow \text{Nuc}^{\bullet}[\text{ArX}]^{\bullet-} \rightarrow [\text{Ar}]^{\bullet} + \text{X}^{-}$$

(X = Halogen)

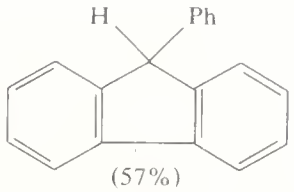
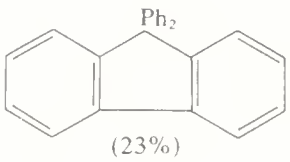
$$[\text{Ar}]^{\bullet} + \text{Nuc}^{-} \rightarrow [\text{Ar—Nuc}]^{\bullet-}$$

$$[\text{Ar—Nuc}]^{\bullet-} + \text{ArX} \rightarrow \text{ArNuc} + [\text{ArX}]^{\bullet-}, \textit{etc.}$$

Evidence that some of the reactions involve radical chain processes includes suppression of rates of reaction by addition of radical inhibitors as well as accleration of rates of reaction by photostimulation.[195,196] Much of the successful work so far has involved alkali metals in liquid ammonia for the non-photochemical reactions, while liquid ammonia and a range of other solvents have been used for photochemically induced processes.[196] Some examples of these reactions are given in Scheme 56.

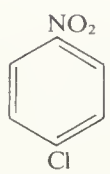
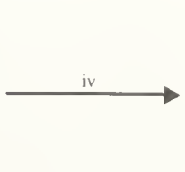
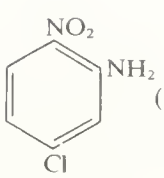
Generation of radical-anions from haloarenes may be achieved by electrochemical reduction (see Scheme 57) and the promotion of a radical chain mechanism for nucleophilic substitution has been claimed.[201]

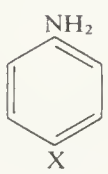
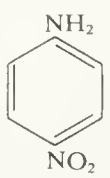
1. PhBr $\xrightarrow{\text{i}}$ $PhCH_2COMe$ (67%) + $PhCH_2CH(OH)Me$ (10%) (Ref. 195)

2. PhBr $\xrightarrow{\text{ii}}$  (57%) +  (23%) (Ref. 195)

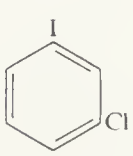
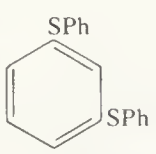
3. PhBr $\xrightarrow{\text{iii}}$ $PhCH_2COCMe_3$ + $Ph_2CHCOCMe_3$ (Ref. 197)

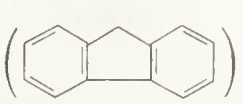
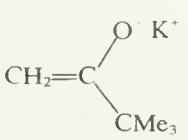
liq. NH_3	90:10
DMSO	87:9

4.   (45%) +  (11%) (Ref. 198)

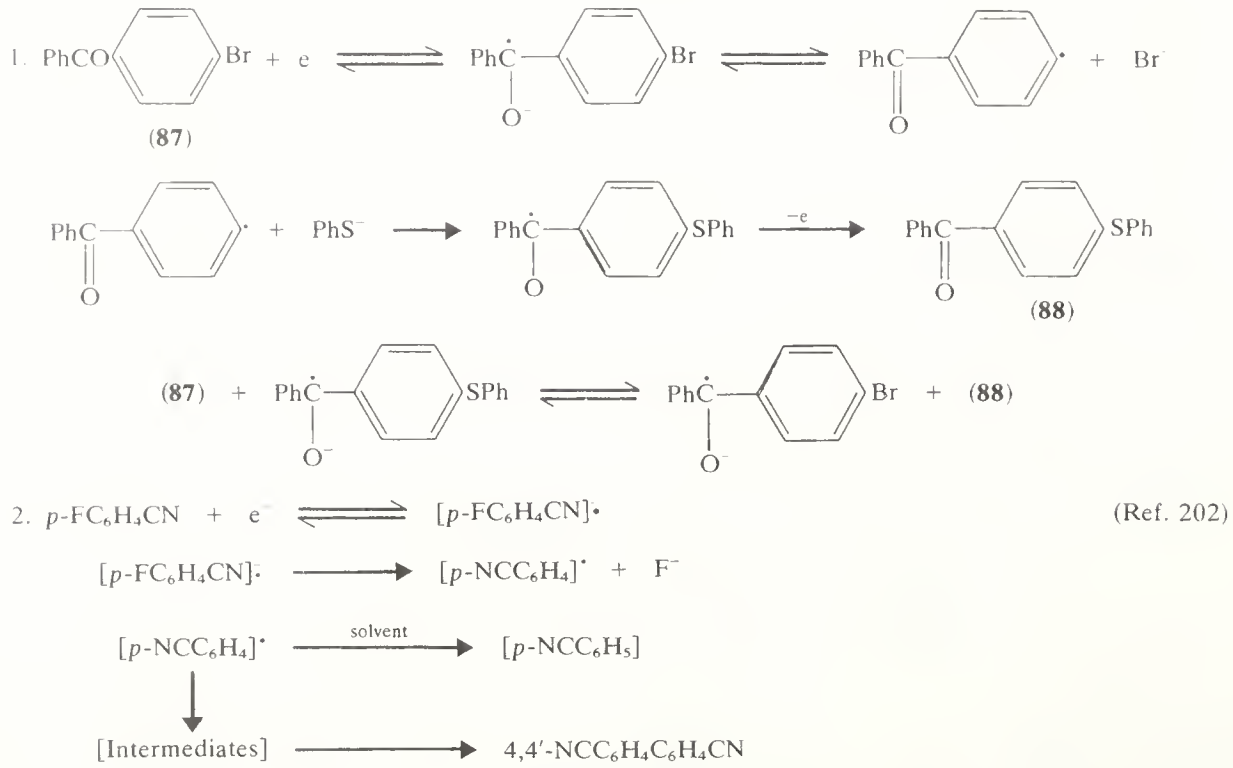
5.   (Ref. 199)

(X = F, Cl, Br, I) (Yields 18, 21, 20, and 10%, respectively)

6.   (91%) (Ref. 200)

i, $CH_2{=}C(Me)O^-\ K^+$, K, liq. NH_3; ii,  K^+, K, Liq. NH_3; iii,  , *hν*, solvent; iv, *hν*, liq. NH_3; v, *hν*, MeOH, H_2O, $NaNO_2$; vi, SPh , *hν*, liq. NH_3.

SCHEME 56



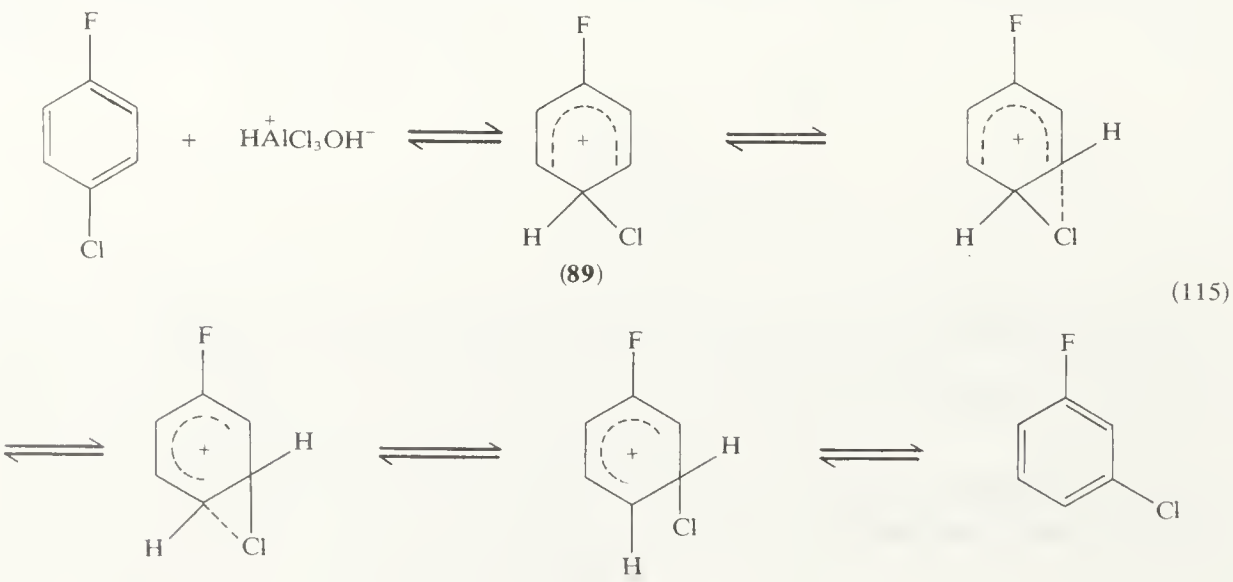
SCHEME 57

3.6.2 Rearrangements

3.6.2.1 Promotion by Lewis acids

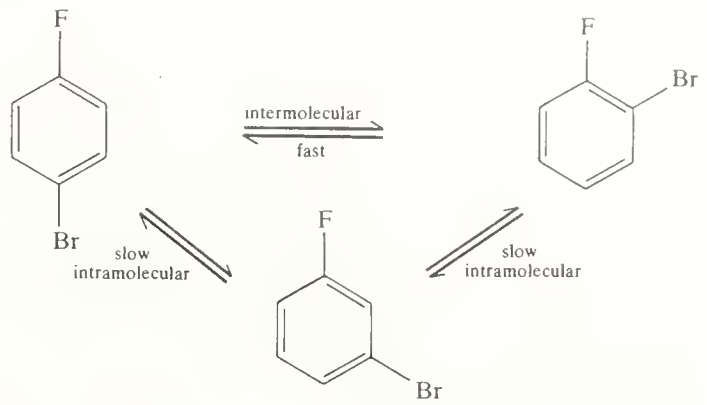
In the presence of Lewis acid catalysts, rearrangement and disproportionation are observed in halogenoaromatic compounds, just as they are in the alkylaromatics. In these reactions it is generally found that fluorine migration does not occur, migration of chlorine is most likely to be intramolecular, while migration of bromine may be both intra- and inter-molecular.[203] Iodoaromatics, under similar conditions, tend to disproportionate.[204]

For example, the water-promoted aluminium chloride catalysed isomerization of chlorofluorobenzenes takes place by an intramolecular 1,2-shift of the chlorine substituent in the intermediate σ-complex (**89**) in equation (115). The equilibrium mixture is 4% *o*-, 64% *m*-, and 32% *p*-chlorofluorobenzene.[205]



(115)

Similarly, water-promoted aluminium bromide catalysed isomerization of *m*-bromofluorobenzene takes place *via* a slow intramolecular 1,2-shift of bromine. However, isomerization of *o*- and *p*-bromofluorobenzene occurs *via* an initial fast intermolecular bromide migration (equation 116) followed by a considerably slower rearrangement to the equilibrium mixture of 5% *o*-, 63% *m*-, and 32% *p*-bromofluorobenzene.

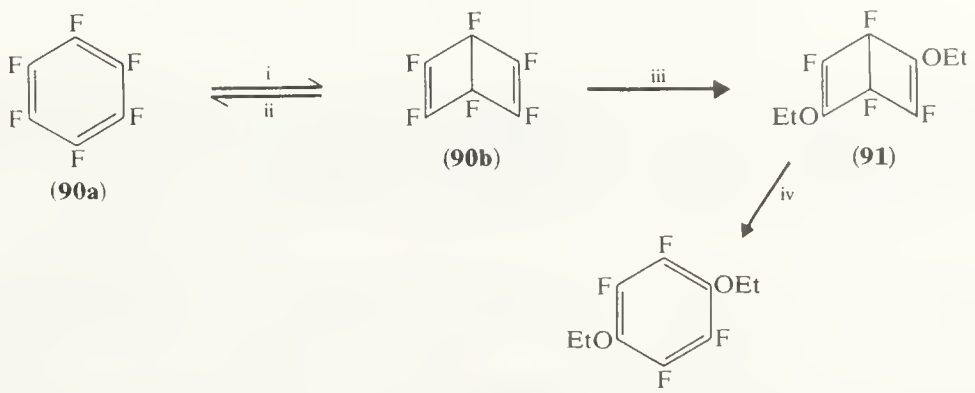


(116)

3.6.2.2 Formation of valence isomers

During the last decade, various valence isomers of aromatic systems, that had previously been thought of as only highly imaginative structures, have been isolated and characterized. Many of these isomers are very unstable and convert rapidly to the aromatic form, but some spectacular exceptions are now available, especially those with a number of perfluoroalkyl groups present in the molecule.[206,207]

Photolysis of hexafluorobenzene (**90**) at 254 nm produces (see Scheme 58) the *para*-bonded isomer (**90b**) which has been handled safely at temperatures below −15 °C but at higher temperatures may explode.[208] Isomer (**90b**) undergoes reactions (see Scheme 58) which are typical of a fluoroalkene.[206]

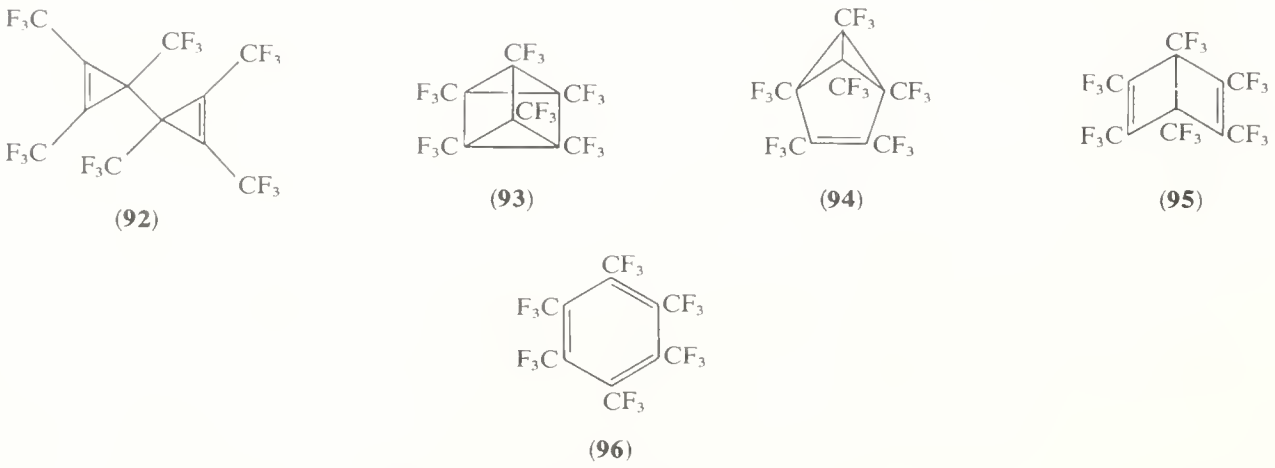


i, 254 nm, 10 h; ii, 80 °C, 4 h; iii, EtO^-; iv 195 °C, 3 h.

SCHEME 58

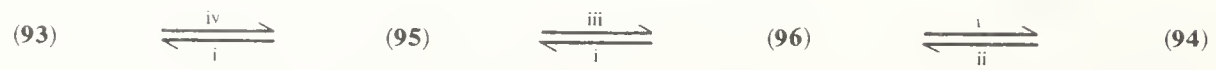
The system $C_6(CF_3)_6$ is quite remarkable in that it is the first case where a complete set of all of the benzene valence isomers has been isolated and characterized. The family is shown in Figure 2 and is numbered (**92**)–(**96**) in order of diminishing heat content. Isomers (**93**)–(**96**) may be obtained by photolysis of (**96**) in the gas phase or in solution,[209,210] as shown in Scheme 59. Kinetic and thermodynamic data for rearomatization of valence isomers[211,211a] indicated that a major difference between the $C_6(CF_3)_6$ and $C_6(CH_3)_6$ systems lies in the higher energy content of the benzene isomer containing CF_3

groups. It appears, therefore, that non-bonded interactions in the perfluoroalkyl compounds are at a maximum for the planar form. Indeed, at high temperatures (equation 117) the *para*-bond isomer (**98**) is obtained the benzene derivative (**97**).[212]



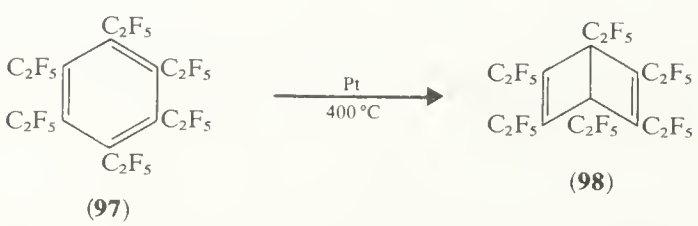
(**92**) (**93**) (**94**) (**95**) (**96**)

Figure 2 The valence isomers of $C_6(CF_3)_6$



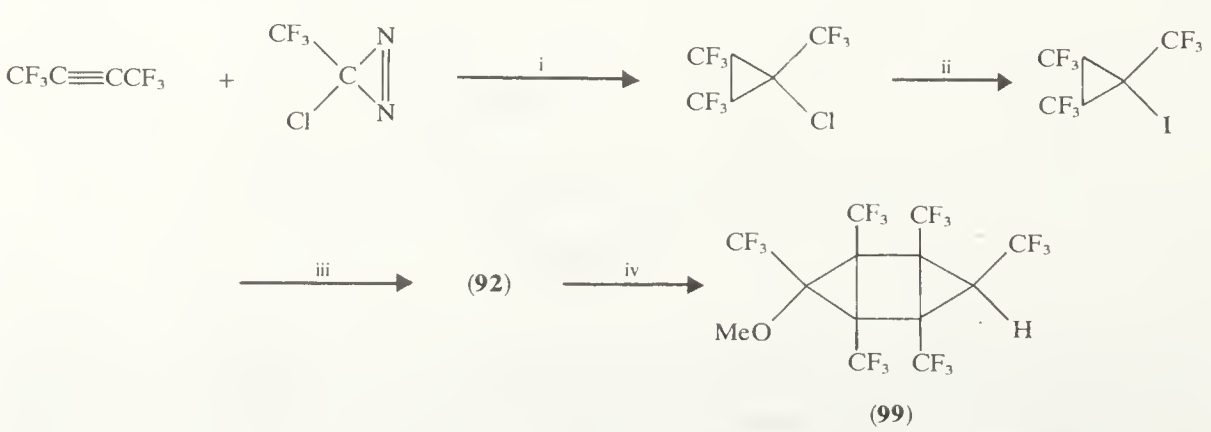
i, > 200 nm; ii, 170 °C, $t_{1/2}$, 9 h; iii, 170 °C, $t_{1/2}$, 135 h; iv, 170 °C, $t_{1/2}$, 29 h.

SCHEME 59



(**97**) (**98**) (117)

The bicyclopropenyl derivative (**92**) was obtained in a route starting with hexafluorobut-2-yne and reaction of (**92**) with methoxide ion results in a single stereoisomer of (**99**) by the fascinating cyclization process[213] shown in Scheme 60. Transformation of other perfluoroalkylbenzenes have been reported.[214]

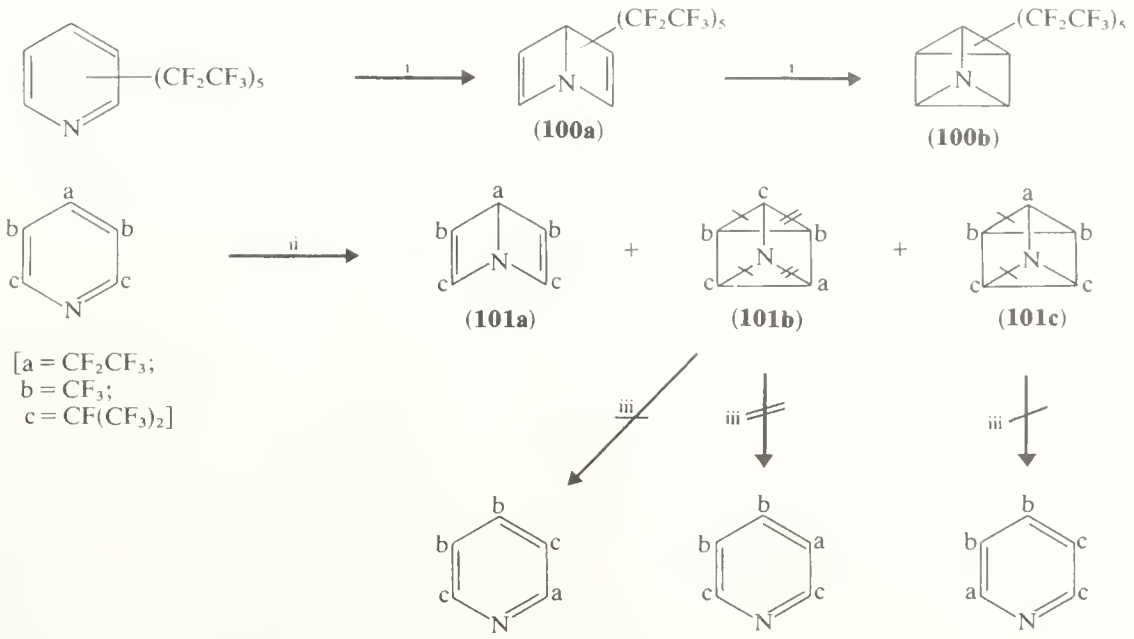


(**92**) (**99**)

i, 120 °C, gas phase; ii, NaI, MeCN; iii, $h\nu$, Hg; iv, MeOH, Et_2N.

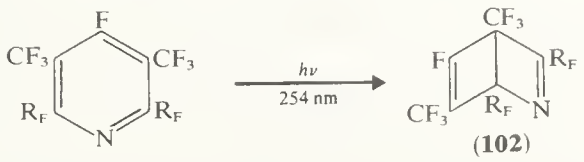
SCHEME 60

Stable valence isomers have also been isolated from perfluoroalkyl derivatives of aza-aromatic compounds. The presence of five perfluoroalkyl groups[215,216] leads (see Scheme 61) to a mixture of the 1-azabicyclohexadiene derivatives and remarkably stable azaprismanes, *e.g.* (**100a,b**) and (**101a–c**), whereas the presence of four or three perfluoroalkyl groups leads to stable derivatives of the 2-azabicyclohexadiene structure, *e.g.* (**102**) and (**103**)[217] in equations (118) and (119).

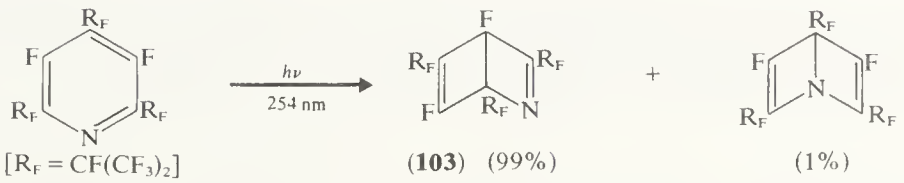


i, $h\nu > 200$ nm; ii, $h\nu$, 254 nm; iii, heat, cleavage as indicated.

SCHEME 61

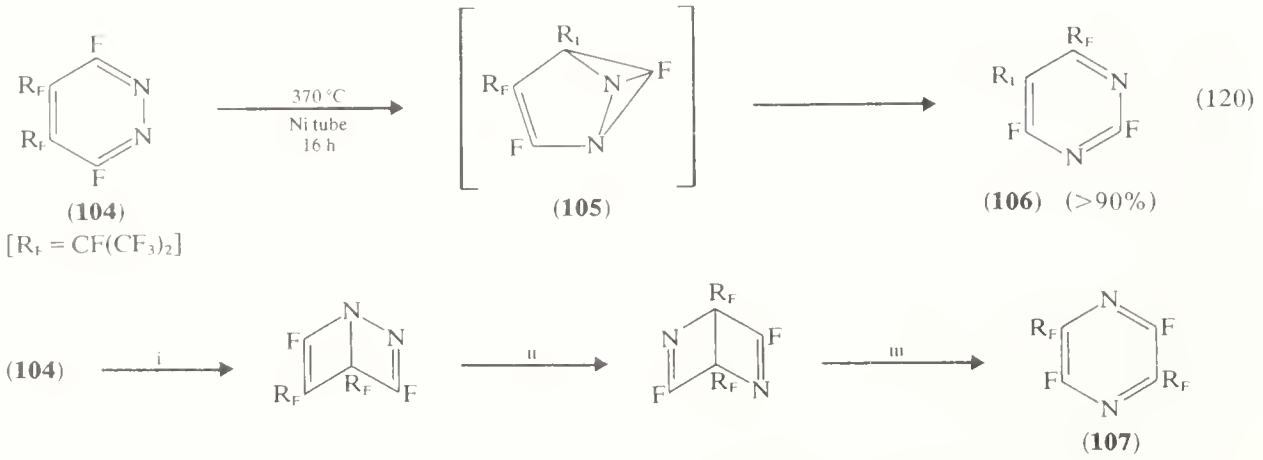


(118)

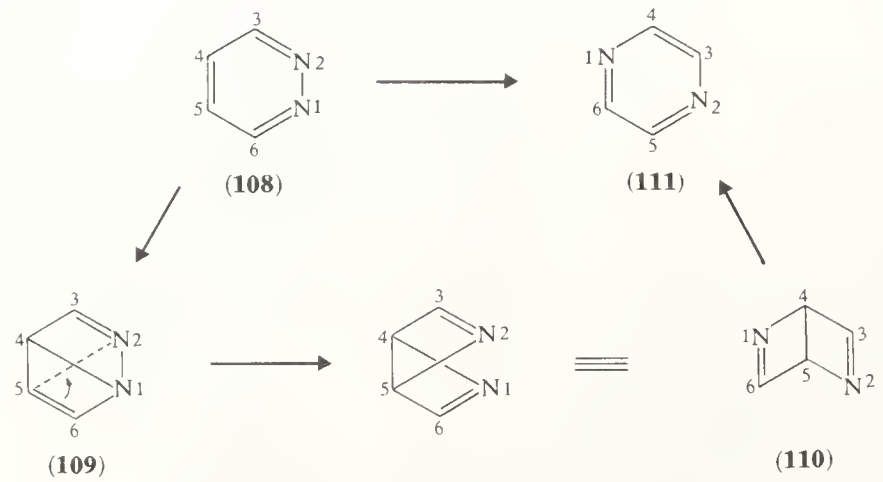


(119)

Pyrolysis[218] and photolysis[219,220] of fluorinated pyridazines has led to some quite remarkable rearrangements, as illustrated by (**104**). The very high conversion to a pyrimidine (**106**) on heating (equation 120) has been rationalized on the basis of an intermediate diazabenzvalene (**105**). The evidence for this is the highly specific substitution pattern in the product (**106**) and also in the pyrolysis products from other fluorinated pyridazines.[218] No intermediate valence isomers were isolated, however, which is in contrast to the photolysis of (**104**) and related pyrazines where relatively stable *para*-bonded species have been characterized and each stage in the conversion (see Scheme 62) of (**104**) to the pyrazine (**107**) has been identified. Examination of a variety of fluorinated pyrazines, coupled with trapping and characterization of corresponding intermediates, has allowed the novel rearrangement mechanism of (**108**) to (**111**) as shown in Scheme 62 to be established.

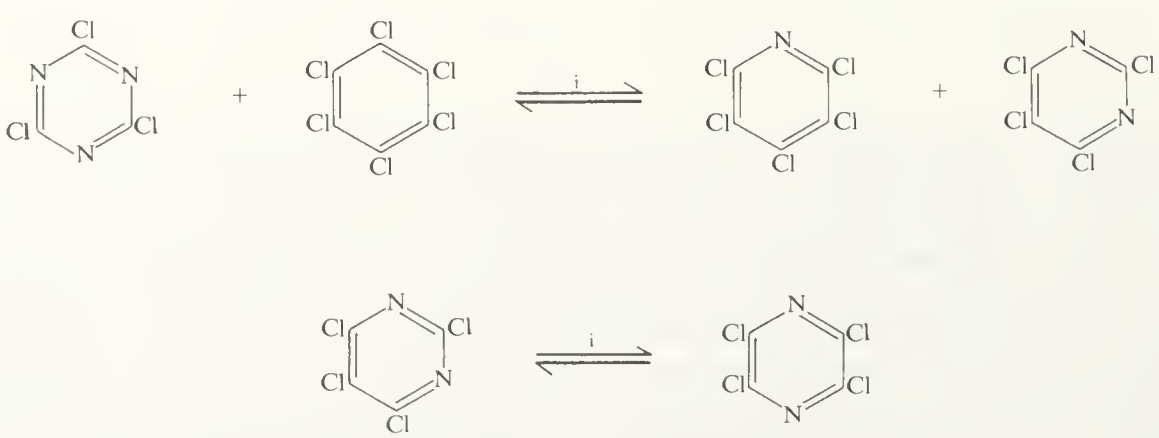


i, 300 nm, gas phase; ii, 100 °C, short contact; iii, 60 °C, $t_{1/2} = 9$ h.



SCHEME 62

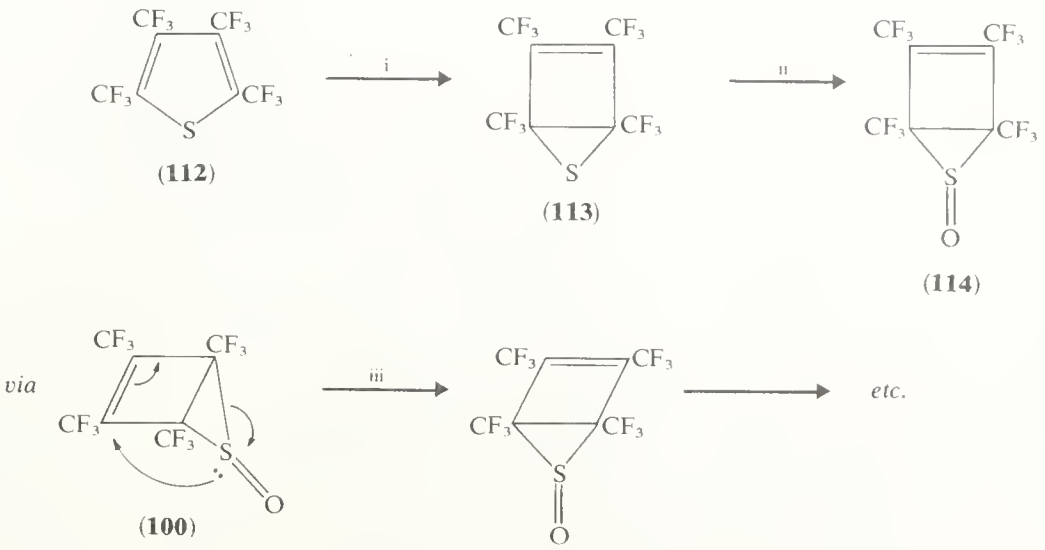
An interesting metathesis has been reported for some perchlorinated nitrogen heterocycles and near-equilibrium composition is observed (see Scheme 63) for the reaction between hexachlorobenzene and trichloro-1,3,5-triazine at 600 °C.[221]



i, 600 °C, gold tube.

SCHEME 63

Photolysis of perfluorotetramethylthiophen (**112**)[222] gave a valence isomer (**113**), which could be converted to a sulphoxide (**114**). This is a remarkable fluxional molecule, giving only one ^{19}F n.m.r. signal for the trifluoromethyl group even at −95 °C. This has been rationalized as shown in Scheme 64 in terms of an internal substitution process which involves a non-bonding electron-pair.[223] More recently, equilibration of trifluoromethyl groups in (**112**) has also been observed.[224]



i, *hν*, 254 nm, Hg; ii, CF_3CO_3H; iii, rapid.

SCHEME 64

References

1. 'The Chemistry of the Carbon–Halogen Bond', ed. S. Patai, Wiley, New York, 1973, (i) part 1, (ii) part 2.
2. 'Methoden der Organischen Chemie (Houben-Weyl)', Thieme, Stuttgart, 1962, Vol. 5/3, 'Fluor- und Chlor-verbindungen'.
3. 'Methoden der Organischen Chemie (Houben-Weyl)', Thieme, Stuttgart, 1960, vol. 5/4, 'Brom- und iod-verbindungen'.
4. 'Organic Chlorine Compounds', ed. E. H. Huntress, Wiley, New York, 1948.
5. 'Bromine and its Compounds', ed. Z. E. Jolles, Benn, London, 1966.
6. 'Encyclopedia of Chemical Technology (Kirk-Othmar)', Wiley-Interscience, (i) 1964, vol. 3, bromine, (ii) 1964, vol. 5, chlorine, (iii) 1966, vol. 9, fluorine, (iv) 1966, vol. 11, iodine.
7. R. D. Chambers, 'Fluorine in Organic Chemistry', Wiley-Interscience, New York, 1973.
8. W. A. Sheppard and C. M. Sharts, 'Organic Fluorine Chemistry', Benjamin, New York, 1969.
9. W. J. Feast, in 'Rodds Chemistry of Carbon Compounds, Supplement IAB, Aliphatic Compounds', ed. M. F. Ansell, Elsevier, Amsterdam, 1975.
10. M. Hudlicky, 'Chemistry of Organic Fluorine Compounds', Ellis-Horwood, Chichester, 1976.
11. Specialist Periodical Reports, 'Fluorocarbon and Related Chemistry', ed. R. E. Banks and M. G. Barlow, The Chemical Society, London, (i) 1971, vol. 1, (ii) 1974, vol. 2, (iii), 1976, vol. 3.
12. 'Polychloroaromatic Compounds', ed. H. Suschitzky, Plenum, New York, 1974.
13. (i) 'Biochemistry Involving Carbon–Fluorine Bonds', ed. R. Filler, A.C.S. Symposium Series No. 28, American Chemical Society, Washington, 1976; (ii) Ref. 1, p. 865; (iii) 'Carbon–Fluorine Compounds, Chemistry, Biochemistry, and Biological Activities', Ciba Foundation Symposium, Elsevier, Amsterdam, 1972.
14. M. L. Poutsma, in 'Methods in Free Radical Chemistry', ed. E. S. Huyser, Dekker, New York, 1969, vol. 1.
15. W. A. Thaler, in 'Methods in Free Radical Chemistry', ed. E. S. Huyser, Dekker, New York, 1969, vol. 2.
16. J. M. Tedder, *Quart. Rev.*, 1960, **14**, 336.
17. W. A. Pryor, 'Free Radicals', McGraw-Hill, New York, 1966.
18. D. C. Nonhebel and J. C. Walton, 'Free-Radical Chemistry', Cambridge University Press, 1974.
18a. C. M. Sharts and W. A. Sheppard, *Org. Reactions*, 1974, **21**, 125.
19. D. H. R. Barton, R. H. Hesse, R. E. Markwell, M. M. Pechet, and H. T. Toh, *J. Amer. Chem. Soc.*, 1976, **98**, 3034.
20. D. H. R. Barton, R. H. Hesse, R. E. Markwell, M. M. Pechet, and S. Rozen, *J. Amer. Chem. Soc.*, 1976, **98**, 3036.

21. J. Kollonitsch and L. Barash, *J. Amer. Chem. Soc.*, 1976, **98,** 5591.
22. P. B. D. de la Mare, 'Electrophilic Halogenation', Cambridge University Press, 1976.
23. S. J. Cristol and W. C. Firth, Jr., *J. Org. Chem.*, 1961, **26,** 280.
24. P. Gouverneur and J. P. Soumillion, *Tetrahedron Letters*, 1976, 133.
25. J. G. Traynham, *Tetrahedron Letters*, 1976, 2213.
26. H. L. Goering and D. W. Larsen, *J. Amer. Chem. Soc.*, 1959, **81,** 5937.
27. P. I. Abell and L. H. Piette, *J. Amer. Chem. Soc.*, 1962, **84,** 916.
28. 'Free Radicals' ed. J. K. Kochi, Wiley, New York, 1973, vol. 2.
29. G. A. Olah, *Chem. Technol.*, 1971, 566.
30. G. A. Olah, R. Renner, P. Schilling, and Y. K. Mo, *J. Amer. Chem. Soc.*, 1973, **95,** 7686.
31. P. B. D. de la Mare and R. Bolton, 'Electrophilic Additions to Unsaturated Systems', Elsevier, Amsterdam, 1966.
32. H. O. House, 'Modern Synthetic Reactions', 2nd edn., Benjamin, Menlo Park, California, 1972 (see chapter 8 for a comprehensive review of additions of hydrogen halides to alkenes).
33. C. A. Clarke and D. L. H. Williams, *J. Chem. Soc. (B)*, 1966, 1126 and refs. therein.
34. S. J. Cristol, F. R. Stermitz and P. S. Ramey, *J. Amer. Chem. Soc.*, 1956, **78,** 4939.
35. Ref. 22, p. 78.
36. V. Grakauskas, *J. Org. Chem.*, 1969, **34,** 2835; 1970, **35,** 723.
37. R. O. C. Norman and R. Taylor, 'Electrophilic Substitution in Benzenoid Compounds', Elsevier, Amsterdam, 1965.
38. Specialist Periodical Report, 'Aromatic and Heteroaromatic Chemistry', The Chemical Society, London, 1973–76, vols. 1–4.
39. C. L. Liotta and H. P. Harris, *J. Amer. Chem. Soc.*, 1974, **96,** 2250.
40. C. M. Starks and R. M. Owens, *J. Amer. Chem. Soc.*, 1973, **95,** 3613.
41. D. Landini, F. Montanari, and F. M. Pirisi, *J.C.S. Chem. Comm.*, 1974, 879.
42. H. Zollinger, 'Diazo and Azo Chemistry', Interscience, New York, 1961.
43. H. Suschitzky, *Adv. Fluorine Chem.*, 1965, **4,** 1.
44. K. L. Kirk and L. A. Cohen, *J. Amer. Chem. Soc.*, 1971, **93,** 3060.
45. G. A. Olah and J. Welch, *J. Amer. Chem. Soc.*, 1975, **97,** 208.
46. I. L. Knunyants, *Bull. Acad. Sci. U.S.S.R.*, 1974, **23,** 1046.
47. S. P. Anand, L. A. Quarterman, H. H. Hyman, K. G. Migliorese, and R. Filler, *J. Org. Chem.*, 1975, **40,** 807.
48. S. W. Tobey and R. West, *J. Amer. Chem. Soc.*, 1966, **88,** 2481.
49. J. L. Adcock, R. A. Beh, and R. J. Lagow, *J. Org. Chem.*, 1975, **40,** 3271.
50. R. J. Lagow, L. A. Shimp, D. K. Lam, and R. F. Baddour, *Inorg. Chem.*, 1972, **11,** 2568.
51. J. Burdon, J. R. Knights, I. W. Parsons, and J. C. Tatlow, *Tetrahedron*, 1976, **32,** 1041; M. Stacey and J. C. Tatlow, *Adv. Fluorine Chem.*, 1960, **1,** 166.
52. R. D. Chambers, D. T. Clark, T. F. Holmes, W. K. R. Musgrave, and I. Ritchie, *J.C.S. Perkin I*, 1974, 114.
53. A. T. Kuhn, *Encycl. Electrochem. Elem.*, 1975, **4,** 43.
54. R. D. Chambers, R. Daniels, W. K. R. Musgrave and P. L. Russell, *J.C.S. Perkin I*, 1976, 1069.
55. T. Chivers, in Ref. 1 (ii), p. 917.
56. See M. Ballester and S. Olivella, in Ref. 12, p.1.
57. D. E. Moore, J. F. Mills and J. A. Schneider, *U.S. Pat.* 3 845 146 (*Chem. Abs.*, 1975, **82,** 31 101).
58. W. Gottardi, *Monatsh.*, 1969, **100,** 42 (*Chem. Abs.*, 1969, **70,** 96 331).
59. B. Iddon, O. Meth-Cohn, H. Suschitzky, J. A. Taylor, and B. J. Wakefield, *Tetrahedron Letters*, 1976, 627.
60. L. Pauling. 'The Nature of the Chemical Bond', 3rd edn., Cornell University Press, New York. 1960, p. 314.
61. J. Hine, *J. Amer. Chem. Soc.*, 1963, **85,** 3239.
62. A. Eggleton, T. Cox, and D. Derwent, *New Sci.*, 1976, **70,** 402.
63. See Ref. 13 (i). Proceedings of American Societies for Experimental Biology.
64. D. H. R. Barton, R. H. Hesse, H. T. Toh, and M. M. Pechet, *J. Org. Chem.*, 1972, **37,** 329.
65. 'Basic Organic Chemistry. Part 5. Industrial Products', ed. J. M. Tedder, A. Nechvatal, and A. H. Jubb, Wiley, New York, 1975.
66. 'Halogenated Fire Suppressants', ed. R. G. Gann, A.C.S. Symposium Series 16, American Chemical Society, Washington, 1975.
67. C. K. Ingold, 'Structure and Mechanism in Organic Chemistry', 2nd edn., Cornell University Press, New York, 1969.
68. S. R. Hartshorn, 'Aliphatic Nucleophilic Substitution', Cambridge University Press, 1973.
69. R. A. Sneen, *Accounts Chem. Res.*, 1973, **6,** 46. For arguments against this approach see D. J. McLennan, *ibid*, 1976, **9,** 281.
70. Ref. 8, p. 43.
71. B. Capon, *Quart. Rev.*, 1964, **18,** 45; B. Capon and S. P. McManus, 'Neighbouring Group Participation', Plenum, New York, 1976, vol. 1.
72. G. D. Sargent, *Quart. Rev.*, 1966, **20,** 301.
73. H. C. Brown, *Accounts Chem. Res.*, 1973, **6,** 377.
74. 'Carbonium Ions', ed. G. A. Olah and P. von R. Schleyer, Wiley-Interscience, New York, (i) vol. 1, 1968, (ii) vol. 2, 1970, (iii) vol. 3, 1972.

75. G. A. Olah, 'Halonium Ions', Wiley, New York, 1975.
76. S. P. McManus and P. E. Peterson, *Tetrahedron Letters*, 1975, 2753.
77. G. M. Brook, 'Halogeno Compounds', in MTP International Review of Science, Organic Chemistry, Series One, vol. 2, 'Aliphatic Compounds', Butterworths, London, 1973.
78. P. E. Peterson, *Accounts Chem. Res.*, 1971, **4,** 407.
79. G. A. Olah and Y. K. Mo, *Adv. Fluorine Chem.*, 1973, **7,** 69; G. A. Olah and J. S. Staral, *J. Amer. Chem. Soc.*, 1976, **98,** 6290.
80. R. D. Chambers, A. Parkin, and R. S. Matthews, *J.C.S. Perkin I*, 1976, 2107.
81. B. E. Smart and G. S. Reddy, *J. Amer. Chem. Soc.*, 1976, **98,** 5593.
82. R. West, *Account Chem. Res.*, 1970, **3,** 130; J. S. Chickos, E. Patton and R. West, *J. Org. Chem.*, 1974, **39,** 1647.
83. N. Kornblum, *Angew. Chem. Internat. Edn.*, 1975, **14,** 734.
84. J. F. Garst, *Accounts Chem. Res.*, 1971, **4,** 400.
85. G. D. Sargent, C. M. Tatum, Jr., and S. M. Kastner, *J. Amer. Chem. Soc.*, 1972, **94,** 7174.
86. P. G. Gassman and J. L. Marshall, *Org. Synth.*, 1968, **48,** 68.
87. D. Bryce-Smith, B. J. Wakefield, and E. T. Blues, *Proc. Chem. Soc.*, 1963, 219.
88. Ref. 32, chapters 2, 3.
89. N. G. Gaylord, 'Reduction with Complex Metal Hydrides', Wiley-Interscience, New York, 1956.
90. H. M. Bell, C. W. Vanderslice, and A. Spehar, *J. Org. Chem.*, 1969, **34,** 3923.
91. E. J. Corey and J. W. Suggs, *J. Org. Chem.*, 1975, **40,** 2554.
92. T. Ishihara, E. Ohtani, and T. Ando, *J.C.S. Chem. Comm.*, 1975, 367.
93. J. L. Webb, C. K. Mann, and H. M. Walborsky, *J. Amer. Chem. Soc.*, 1970, **92,** 2042.
94. A. J. Duggan and S. S. Hall, *J. Org. Chem.*, 1975, **40,** 2238.
95. P. E. Verkade, K. S. de Vries, and B. M. Wepster, *Rec. Trav. chim.*, 1964, **83,** 367.
96. Y. Sasson and G. L. Rempel, *Tetrahedron Letters*, 1974, 3221.
97. G. Cahiez, D. Bernard, and J. F. Normant, *J. Organometallic Chem.*, 1976, **113,** 107.
98. G. E. Coates, M. L. H. Green and K. Wade, 'Organometallic Compounds', 3rd edn., Methuen, London, 1967.
99. B. J. Schaart, H. W. H. J. Bodewitz, C. Blomberg, and F. Bickelhaupt, *J. Amer. Chem. Soc.*, 1976, **98,** 3712.
100. S. M. Neumann and J. K. Kochi, *J. Org. Chem.*, 1975, **40,** 599.
101. B. J. Wakefield, 'The Chemistry of Organolithium Compounds', Pergamon, Oxford, 1974.
102. C. Chung and R. J. Lagow, *J.C.S. Chem. Comm.*, 1972, 1078; L. G. Sneddon and R. J. Lagow, *ibid.*, 1975, 302.
103. V. C. R. McLoughlin and J. Thrower, *Tetrahedron*, 1969, **25,** 5921.
104. P. L. Coe, N. E. Milner, and J. A. Smith, *J.C.S. Perkin I*, 1975, 654.
105. K. J. Klabunde, *J. Fluorine Chem.*, 1976, **7,** 95.
106. W. H. Saunders and A. F. Cockerill, 'Mechanisms of Elimination Reactions', Wiley, New York, 1973.
107. Ref. 1, chapter 9.
108. R. A. Bartsch and J. F. Bunnett, *J. Amer. Chem. Soc.*, 1969, **91,** 1376.
109. S. P. Acharya and H. C. Brown, *Chem. Comm.*, 1968, 305.
110. J. Hine, N. W. Burske, M. Hine, and P. B. Langford, *J. Amer. Chem. Soc.*, 1957, **79,** 1406.
111. O. R. Pierce, E. T. McBee, and G. F. Judd, *J. Amer. Chem. Soc.*, 1954, **76,** 474; Ref. 7, p. 118.
112. Ref. 1, p. 938.
113. S. F. Campbell, R. Stephens, and J. C. Tatlow, *Tetrahedron*, 1965, **21,** 2997.
114. F. Hardwick, A. E. Pedler, R. Stephens, and J. C. Tatlow, *J. Fluorine Chem.*, 1974, **4,** 9.
115. J. Hine, 'Divalent Carbon', Ronald, New York, 1964.
116. W. E. Kirmse, 'Carbene Chemistry', Academic. New York, 1964.
117. D. Seyferth, *Accounts Chem. Res.*, 1972, **5,** 65.
118. Ref. 7, p. 147.
119. Ref. 10, (i) p. 483, (ii) pp. 515–516.
120. A. E. Newkirk, *J. Amer. Chem. Soc.*, 1946, **68,** 2467.
121. Ref. 65, p. 166.
122. A. Campbell and R. Thompson, 'The Modern Inorganic Chemicals Industry', Special Publication No. 31, The Chemical Society, London, 1977.
123. R. D. Chambers and R. H. Mobbs, *Adv. Fluoride Chem.*, 1965, **4,** 50.
124. Z. Rappoport, *Adv. Phys. Org. Chem.*, 1969, **7,** 1; S. Patai and Z. Rappoport, 'The Chemistry of Alkenes', ed. S. Patai, Wiley, London, 1964, chapter 8.
125. Ref. 1, p. 466.
126. G. Modena, *Accounts Chem. Res.*, 1971, **4,** 73.
127. M. Hanack, *Accounts Chem. Res.*, 1976, **9,** 364.
128. J. D. Park, R. J. McMurtry, and J. H. Adams, *Fluorine Chem. Rev.*, 1968, **2,** 55.
129. W. E. Truce and R. Kassinger, *J. Amer. Chem. Soc.*, 1958, **80,** 6450; W. E. Truce, M. G. Rossmann, F. M. Perry, R. M. Burnett, and D. J. Abraham, *Tetrahedron*, 1965, **21,** 2899.
130. Ref. 7, p. 163.
131. H. C. Fielding and A. J. Rudge, *Brit. Pat.* 1 082 127 (1967); *Neth. Appl.* 6 604 357 (*Chem. Abs.*, 1967, **66,** 55 009).
132. D. P. Graham, *J. Org. Chem.*, 1966, **31,** 955.

133. R. D. Chambers, M. Y. Gribble, and E. Marper, *J.C.S. Perkin I*, 1973, 1710.
134. B. L. Dyatkin, S. R. Sterlin, B. I. Martynov, E. I. Mysov, and I. L. Knunyants, *Tetrahedron*, 1971, **27,** 2843.
135. R. D. Chambers, J. A. Jackson, W. K. R. Musgrave, and R. A. Storey, *J. Chem. Soc.* (*C*), 1968, 2221; R. D. Chambers, J. A. Jackson, S. Partington, P. D. Philpot, and A. C. Young, *J. Fluorine Chem.*, 1975, **6,** 5.
136. W. C. Kuryla and D. G. Leis, *J. Org. Chem.*, 1964, **29,** 2773.
137. W. C. Kuryla, *J. Org. Chem.*, 1965, **30,** 3926.
138. G. Wittig and P. Fritze, *Angew. Chem. Internat. Edn.*, 1966, **5,** 846.
139. Ref. 10, pp. 229, 425.
140. J. M. Tedder and J. C. Walton, *Accounts Chem. Res.*, 1976, **9,** 183.
141. 'Fluoropolymers', ed. L. A. Wall, Wiley-Interscience, New York, 1972.
142. H. S. Eleuterio, *U.S. Pat.* 2 958 685 (1960); *Chem. Abs.*, 1961, **55,** 6041.
143. P. B. D. de la Mare and R. Bolton, 'Electrophilic Additions to Unsaturated Systems', Elsevier, Amsterdam, 1966.
144. B. L. Dyatkin, E. P. Mochalina, and I. L. Knunyants, *Russ. Chem. Rev.*, 1966, **35,** 417; B. L. Dyatkin, E. P. Mochalina, and I. L. Knunyants, *Fluorine Chem. Rev.*, 1969, **3,** 45.
145. P. E. Peterson and R. J. Bopp, *J. Amer. Chem. Soc.*, 1967, **89,** 1283.
146. P. C. Myhre and G. D. Andrews, *J. Amer. Chem. Soc.*, 1970, **92,** 7596.
147. A. L. Henne and R. C. Arnold, *J. Amer. Chem. Soc.*, 1948, **70,** 758.
148. W. T. Miller, Jr., M. B. Freedman, J. H. Fried, and H. F. Koch, *J. Amer. Chem. Soc.*, 1961, **83,** 4105.
149. V. V. Brovko, V. M. Vlasov, L. I. Kann, T. D. Petrova, V. A. Sokolenko, and G. G. Yakobson, *Zhur. org. Khim.*, 1975, **11,** 1031.
150. D. R. A. Perry, *Fluorine Chem. Rev.*, 1967, **1,** 253.
151. W. H. Sharkey, *Fluorine Chem. Rev.*, 1968, **2,** 1.
152. P. D. Bartlett, *Quart. Rev.*, 1970, **24,** 473.
153. R. Huisgen, R. Grashey, and J. Sauer, in 'The Chemistry of Alkenes', ed. S. Patai, Wiley-Interscience, New York, 1964, p. 779.
154. D. D. Coffman, P. L. Barrick, R. D. Cramer, and M. S. Raasch, *J. Amer. Chem. Soc.*, 1949, **71,** 490.
155. J. L. Anderson, R. E. Putnam, and W. H. Sharkey, *J. Amer. Chem. Soc.*, 1961, **83,** 382.
156. P. D. Bartlett, G. M. Cohen, S. P. Elliott, K. Hummel, R. A. Minns, C. M. Sharts, and J. Y. Fukunaga, *J. Amer. Chem. Soc.*, 1972, **94,** 2899.
157. R. E. Banks, R. N. Haszeldine, and D. R. Taylor, *J. Chem. Soc.*, 1965, 978.
158. D. Lomas and P. Tarrant, *J. Org. Chem.*, 1969, **34,** 323.
159. B. E. Kirk and D. R. Taylor, *J.C.S. Perkin I*, 1974, 1844.
160. P. B. Sargeant, *J. Amer. Chem. Soc.*, 1969, **91,** 3061.
161. R. D. Chambers, W. K. R. Musgrave, and D. A. Pyke, *Chem. and Ind.* (*London*), 1965, 564.
162. L. P. Anderson, W. J. Feast, and W. K. R. Musgrave, *J. Chem. Soc.* (*C*), 1969, 211.
163. K. V. Scherer, Jr. and T. J. Meyers, *J. Amer. Chem. Soc.*, 1968, **90,** 6253; Abs. of Papers, 158th National Meeting, Amer. Chem. Soc., New York, 1969, No. ORGN-59.
164. G. Amiet, K. Nicholas, and R. Pettit, *Chem. Comm.*, 1970, 161.
165. M. J. Gerace, D. M. Lemal, and H. Ertl, *J. Amer. Chem. Soc.*, 1975, **97,** 5584.
166. S. Y. Delavarenne and H. G. Viehe, in 'Chemistry of Acetylenes', ed. H. G. Viehe, Dekker, New York, 1969, chapter 10.
167. Ref. 7, p. 144.
168. W. J. Middleton and W. H. Sharkey, *J. Amer. Chem. Soc.*, 1959, **81,** 803.
169. C. G. Krespan, *J. Org. Chem.*, 1975, **40,** 261.
170. J. Villieras, P. Perriot, and J. F. Normant, *Synthesis*, 1975, 458.
171. A. Gorgues and A. le Coq, *Bull. Soc. chim. France*, 1976, 125.
172. Ref. 12, p. 112.
173. S. I. Miller and J. I. Dickstein, *Accounts Chem. Res.*, 1976, **9,** 358.
174. R. Tanaka, M. Rodgers, R. Simonaitis, and S. I. Miller, *Tetrahedron*, 1971, **27,** 2651.
174a. C. D. Beard, J. C. Craig, and M. D. Solomon, *J. Amer. Chem. Soc.*, 1974, **96,** 7944.
174b. W. Chodkiewicz, *Ann. Chim.* (*France*), 1957, **2,** 819.
175. A. L. Henne and W. G. Finnegan, *J. Amer. Chem. Soc.*, 1949, **71,** 298.
175a. R. J. de Pasquale, C. D. Padgett, and R. W. Rosser, *J. Org. Chem.*, 1975, **40,** 810.
176. M. I. Bruce and W. R. Cullen, *Fluorine Chem. Rev.*, 1969, **4,** 79.
177. H. C. Brown, H. L. Gewanter, D. M. White, and W. G. Woods, *J. Org. Chem.*, 1960, **25,** 634.
178. R. D. Chambers, S. Partington, and D. B. Speight, *J.C.S. Perkin I*, 1974, 2673.
179. W. T. Miller, R. J. Hummel, and L. F. Pelosi, *J. Amer. Chem. Soc.*, 1973, **95,** 6850.
180. H. Heaney, *Chem. Rev.*, 1962, **62,** 81.
181. T. L. Gilchrist and C. W. Rees, 'Carbenes, Nitrenes and Arynes', Nelson, Bath, 1969.
182. R. W. Hoffmann, 'Dehydrobenzene and Cycloalkynes', Academic, New York, 1967.
183. J. Miller, 'Aromatic Nucleophilic Substitution', Elsevier, Amsterdam, 1968.
184. J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, 1951, **49,** 273; J. F. Bunnett, *Quart. Rev.*, 1958, **12,** 1.
185. R. D. Chambers, W. K. R. Musgrave, J. S. Waterhouse, D. L. H. Williams, J. Burdon, W. B. Hollyhead, and J. C. Tatlow, *J.C.S. Chem. Comm.*, 1974, 239.
186. R. D. Chambers, J. S. Waterhouse, and D. L. H. Williams, *J.C.S. Perkin II*, 1977, 585.

187. J. C. Tatlow, *Endeavour*, 1963, **22,** 89.
188. J. Burdon, *Tetrahedron*, 1965, **21,** 3373.
189. R. J. de Pasquale and C. Tamborski, *J. Org. Chem.*, 1967, **32,** 3163.
190. S. L. Bell, R. D. Chambers, M. Y. Gribble, and J. R. Maslakiewicz, *J.C.S. Perkin I*, 1973, 1716.
191. H. Gilman and R. D. Gorsich, *J. Amer. Chem. Soc.*, 1956, **78,** 2217.
192. I. Haiduc and H. Gilman, *Rev. Roumaine Chim.*, 1971, **16,** 907; *Chem. Abs.*, 1971, **75,** 76 908.
193. S. C. Cohen, M. L. N. Reddy, D. M. Roe, A. J. Tomlinson, and A. G. Massey, *J. Organometallic Chem.*, 1968, **14,** 241.
194. J. F. Bunnett, *Accounts Chem. Res.*, 1972, **5,** 139.
195. J. F. Bunnett, *J. Chem. Educ.*, 1974, **51,** 312.
196. J. Cornelisse and E. Havinga, *Chem. Rev.*, 1975, **75,** 353.
197. R. G. Scamehorn and J. F. Bunnett, *J. Org. Chem.*, 1977, **42,** 1449, 1457.
198. Ref. 196, p. 366.
199. A. V. El'tsov, O. V. Kul'bitskaya, and A. N. Frolov, *J. Org. Chem.* (*U.S.S.R.*), 1972, **8,** 76 (*Chem. Abs.*, 1972, **77,** 113 471); A. V. El'tsov, A. N. Frolov, and O. V. Kul'bitskaya, *J. Org. Chem.* (*U.S.S.R.*), 1970, **6,** 1943 (*Chem. Abs.*, 1970, **73,** 109 392).
200. J. F. Bunnett and X. Creary, *J. Org. Chem.*, 1974, **39,** 3611.
201. J. Pinson and J. M. Saveant, *J.C.S. Chem. Comm.*, 1974, 933.
202. M. R. Asirvathan and M. D. Hawley, *J. Amer. Chem. Soc.*, 1975, **97,** 5024.
203. H. J. Shine, 'Aromatic Rearrangements', Elsevier, New York, 1967.
204. P. H. Gore, S. Thorburn, and D. J. Weyell, *J. Chem. Soc.* (*C*), 1971, 2362.
205. G. A. Olah, W. S. Tolgyesi, and R. E. A. Dear, *J. Org. Chem.*, 1962, **27,** 3441, 3449, 3455; G. A. Olah and M. W. Meyer, *ibid.*, 1962, **27,** 3464.
206. Ref. 7, p. 328.
207. D. Bryce-Smith and A. Gilbert, 'Photochemical Reactions of Aromatic Compounds', in 'MTP International Review of Science, Organic Chemistry Series One', vol. 3, 'Aromatic Compounds', Butterworths, London, 1973; *Tetrahedron*, 1976, **32,** 1309.
208. G. Camaggi and F. Gozzo, *J. Chem. Soc.* (*C*), 1969, 489.
209. D. M. Lemal, J. V. Staros, and V. Austel, *J. Amer. Chem. Soc.*, 1969, **91,** 3373.
210. M. G. Barlow, R. N. Haszeldine, and R. Hubbard, *J. Chem. Soc.* (*C*), 1970, 1232.
211. D. M. Lemal and L. H. Dunlap, Jr., *J. Amer. Chem. Soc.*, 1972, **94,** 6562.
211a. A. M. Dabbagh, W. T. Flowers, R. N. Haszeldine, and P. J. Robinson, *J.C.S. Chem. Comm.*, 1975, 323.
212. E. D. Clifton, W. T. Flowers, and R. N. Haszeldine, *Chem. Comm.*, 1969, 1216.
213. M. W. Grayston and D. M. Lemal, *J. Amer. Chem. Soc.*, 1976, **98,** 1278.
214. M. G. Barlow, R. N. Haszeldine, and M. J. Kershaw, *Tetrahedron*, 1975, **31,** 1649, and earlier parts.
215. M. G. Barlow, R. N. Haszeldine, and J. G. Dingwall, *J.C.S. Perkin I*, 1973, 1542.
216. R. D. Chambers and R. Middleton, *J.C.S. Perkin I*, 1977, 1500.
217. R. D. Chambers and R. Middleton, *J.C.S. Chem. Comm.*, 1977, 154.
218. R. D. Chambers, M. Clark, J. R. Maslakiewicz, W. K. R. Musgrave, and P. G. Urben, *J.C.S. Perkin I*, 1974, 1513.
219. R. D. Chambers, J. A. H. MacBride, J. R. Maslakiewicz, and K. C. Srivastava, *J.C.S. Perkin I*, 1975, 396.
220. R. D. Chambers, J. R. Maslakiewicz, and K. C. Srivastava, *J.C.S. Perkin I*, 1975, 1130.
221. W. Mahler and T. Fukunaga, *J.C.S. Chem. Comm.*, 1977, 307.
222. H. A. Wiebe, S. Braslavsky, and J. Heicklen, *Canad. J. Chem.*, 1972, **50,** 2721.
223. J. A. Ross, R. P. Seiders, and D. M. Lemal, *J. Amer. Chem. Soc.*, 1976, **98,** 4325.
224. C. H. Bushweller, J. A. Ross, and D. M. Lemal, *J. Amer. Chem. Soc.*, 1977, **99,** 629.

PART 4

ALCOHOLS, PHENOLS, ETHERS, AND RELATED COMPOUNDS

4.1

Alcohols

S. G. WILKINSON
University of Hull

4.1.1 MONOHYDRIC ALCOHOLS 579
4.1.1.1 Introduction 579
4.1.1.2 General characteristics of the hydroxy group 582
4.1.1.3 Methods of preparation 587
4.1.1.4 Reactions 617

4.1.2 DIHYDRIC AND POLYHYDRIC ALCOHOLS 662
4.1.2.1 Introduction 662
4.1.2.2 General characteristics 664
4.1.2.3 Methods of preparation 666
4.1.2.4 Reactions 674

4.1.1 MONOHYDRIC ALCOHOLS

4.1.1.1 Introduction

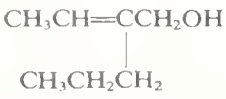
Monohydric alcohols (general formula ROH) are essentially aliphatic compounds in which the characteristic group (the hydroxy group) is attached to a saturated carbon atom. For the systematic treatment of both syntheses and reactions, the simple saturated alcohols (alkanols and cycloalkanols) are usefully classified as *primary* (RCH_2OH), *secondary* (R_2CHOH), and *tertiary* (R_3COH). The proximal presence of other functional groups gives rise to other important classes of alcohols with distinctive chemistries. Such classes considered in this section are benzylic (*e.g.* $ArCH_2OH$), allylic (*e.g.* $RCH{=}CHCH_2OH$), allenic (*e.g.* $RCH{=}C{=}CHCH_2OH$), alkynic (*e.g.* $RC{\equiv}CCH_2OH$), and halogeno (*e.g.* $RCHClCH_2OH$) alcohols.

Several types of nomenclature are accommodated within the IUPAC scheme (Rule C-201). Traditionally, *common* or *radicofunctional* names tend to be used for simple alcohols such as isopropyl alcohol (Pr^iOH), benzyl alcohol ($PhCH_2OH$), and cinnamyl alcohol ($PhCH{=}CHCH_2OH$). For general purposes, however, the versatile *substitutive* type of nomenclature is preferable. Saturated acyclic compounds for which the IUPAC priority rules define the hydroxy group as the principal group are thereby named as alkanols (and their derivatives). The prefix 'hydroxy-' is used in place of the suffix '-ol' in naming compounds for which the hydroxy group is not the principal group. Procedures for selecting and numbering the parent compounds, and for extending the system to unsaturated and cyclic compounds, are illustrated with compounds (**1**)–(**6**). Following British practice, all locants in the names given are placed immediately before the group or function indicated. Among other types of nomenclature, the *carbinol* system (in which acyclic alcohols are named as derivatives of carbinol, CH_3OH) is now archaic, but

conjunctive nomenclature is important in relation to the use of *Chemical Abstracts*. The nomenclature is applied to compounds such as (**7**) and (**8**), in which a hydroxyalkyl group is attached to a ring system (benzene generally being excepted). Sheer convenience often dictates the use of *trivial* names for complex natural alcohols, and the vocabulary of these compounds grows inexorably.

(**1**) Pentan-2-ol

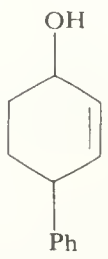
(**2**) 2-Ethyl-3-methylbutan-1-ol



(**3**) 2-Propylbut-2-en-1-ol

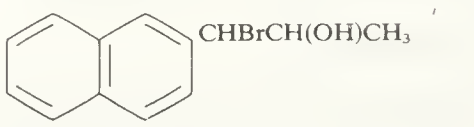
(**4**) 2-*N*,*N*-Dimethylaminoethanol

(**5**) 5-Hydroxyhexan-2-one



(**6**) 4-Phenylcyclohex-2-en-1-ol

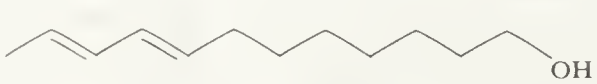
(**7**) Cyclopropanepropanol



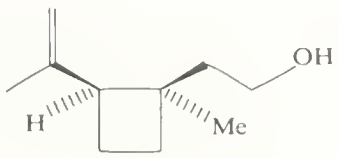
(**8**) β-Bromo-α-methyl-2-naphthalene-ethanol

The natural production of ethyl alcohol in the fermentation of carbohydrates by yeasts is widely known and appreciated. Many simple alcohols (free or esterified) also contribute to the pleasures of natural flavours and fragrances, while long-chain alcohols occur in the waxes of plants, insects, and some other animals. For example, phenethyl alcohol ($PhCH_2CH_2OH$) is the main volatile component of rose oil, cetyl alcohol ($n\text{-}C_{16}H_{33}OH$) is present in sperm-whale oil as the palmitate ester, and myricyl alcohol ($n\text{-}C_{30}H_{61}OH$) likewise in beeswax. Much recent interest in unsaturated alcohols has stemmed from the study of insect pheromones (behavioural stimulants). Examples of such compounds are codlelure (**9**), a sex attractant of the codling moth *Laspeyresia pomonella*, and grandisol (**10**), one of several monoterpene components of the aggregation pheromone from the male boll weevil *Anthonomus grandis*. More familiar terpenoid and steroid alcohols are geraniol (**11**), (−)-menthol (**12**), retinol or vitamin A (**13**), cholesterol (**14**), and ergocalciferol or vitamin D_2 (**15**). Since the hydroxy group is one of the most common functional groups, its chemistry has great significance for these and many other natural products.

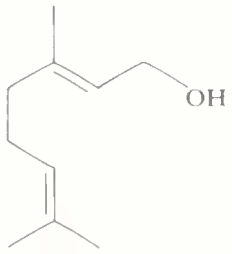
Both simple and complex alcohols are important industrially. Table 1 lists some of the



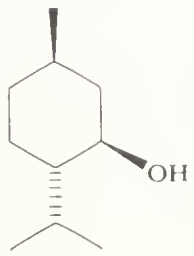
(**9**)



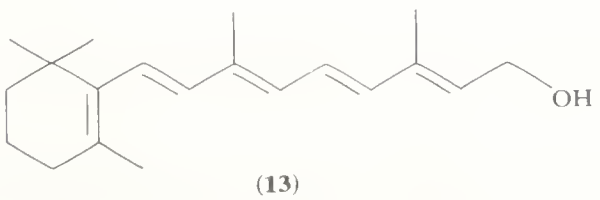
(10)



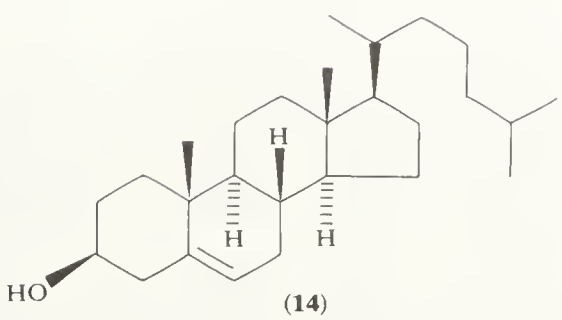
(11)



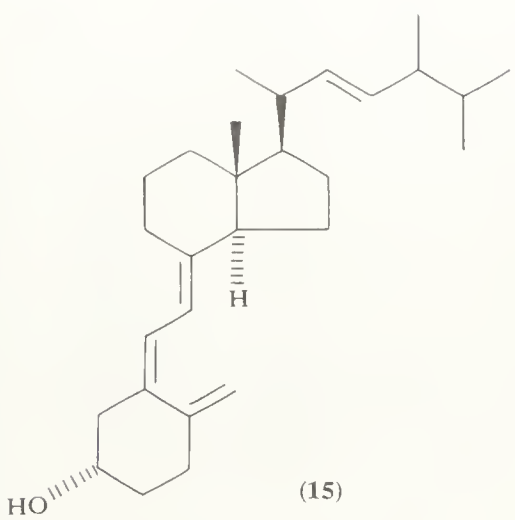
(12)



(13)



(14)



(15)

TABLE 1

Some Industrially Important Alcohols and their Applications

Alcohol	*Major production routes*	*Major applications*
MeOH	From synthesis gas ($CO + H_2$)	Production of HCHO, $MeCO_2H$, and MeCl. Solvent, fuels, methylations
EtOH	Hydration of ethylene (ethene) Fermentation	Solvent, ethylations. Production of MeCHO and diethyl ether
Pr^iOH	Hydration of propene	Solvent. Production of Me_2CO
Bu^nOH, Bu^iOH	Hydroformylation of propene Reduction of aldol (for Bu^nOH)	Solvents. Production of ester solvents and plasticizers
Primary C_6 to C_{10} alcohols	Hydroformylation. Aldol reactions (for $Bu^nEtCHCH_2OH$). Oxidation of aluminium alkyls	Production of ester plasticizers
Primary C_{12} to C_{18} alcohols	Hydroformylation. Oxidation of aluminium alkyls. Hydrogenation of fats	Production of surfactants
Secondary C_{12} to C_{18} alcohols	Autoxidation of alkanes	
Cyclohexanol	Autoxidation of cyclohexane Reduction of phenol	Production of caprolactam

simpler compounds in bulk production. The direct oxidation of saturated hydrocarbons by molecular oxygen has considerable appeal but limited application (*e.g.* the production of cyclohexanol, 1-phenylethanol, and long-chain secondary alcohols). Alkenes derived from light hydrocarbons and higher n-alkane waxes by cracking processes are the major raw materials. Alkenes of intermediate size are also produced by oligomerization of the C_3 and C_4 alkenes. The dominant modern processes for oxyfunctionalization are hydroformylation (the OXO reaction) and oxidation of the aluminium alkyls produced by telomerization of ethylene with triethylaluminium (the 'Alfol' process).

The confines of this chapter preclude the treatment of topics in depth. Apart from the standard works on organic chemistry, the monograph by Monick[1] and the two-part volume edited by Patai[2] do much to remedy this deficiency. The location of reviews on special topics is also facilitated by the Index of Reviews in Organic Chemistry produced for The Chemical Society, London (cumulative editions 1971 and 1976).

4.1.1.2 General characteristics of the hydroxy group

(i) Bonding and molecular geometry

The formal sp^3 hybridization of oxygen and the attached carbon produces approximately tetrahedral geometry at both atoms. Average bond lengths for the C—O and O—H bonds are 143 and 96 pm, respectively. Both bonds are extensively polarized by the electronegative oxygen atom. The polarity of hydroxy groups in relation to other isoelectronic groups is exemplified by the data in Table 2 for the dipole moments of the methane derivatives and for the calculated bond moments (to which the lone pairs contribute). In physical organic chemistry the electron-withdrawing inductive effect of the hydroxy group is often quantified by a constant such as σ_I (positive values are assigned to groups having a $-I$ effect according to the Ingold convention).

Table 2 also contains data for comparing the steric characteristics of hydroxy and other groups. Although hydroxy and methyl groups 'sweep' similar van der Waals volumes, the lack of spherical symmetry for the hydroxy group reduces its effective size (in the absence of association by hydrogen bonding). The greater conformational *freedom* of the hydroxy

TABLE 2

Polar and Steric Characteristics of Hydroxyl and Isoelectronic groups ($—XH_n$)

Parameter	$—CH_3$	$—NH_2$	—OH	—F
Dipole moment for $MeXH_n$ (D)[a]	0	1.31	1.70	1.85
Bond moment for X—H (D)[b]	0.3	1.3	1.5	—
Inductive constant (σ_I) for XH_n[c]	−0.01	0.17	0.24	0.54
van der Waals radius for XH_n (pm)[d]	227	220	216	147
Torsional barrier for $MeXH_n$ (kJ mol^{-1})[e]	12.26	8.28	4.48	—
A value ($-\Delta G°$) for cyclohexyl—XH_n (kJ mol^{-1})[f]	1.70	1.20	0.97	0.25
Steric constant (υ) for XH_n[c]	0.52	0.35	0.32	0.27

[a] Gas phase values, C. W. N. Cumper, *Tetrahedron*, 1969, **25**, 3131. [b] O. Exner, 'Dipole Moments in Organic Chemistry', Georg Thieme, Stuttgart, 1975, p. 33. [c] M. Charton, personal communication (1977). [d] Maximum values, calculated as the sum of the X—H bond length and the van der Waals radius for H (except for F). [e] L. Radom, W. J. Hehre, and J. A. Pople, *J. Amer. Chem. Soc.*, 1972, **94**, 2371. [f] For axial⇌equatorial equilibrium, J. A. Hirsch, *Topics Stereochem.*, 1967, **1**, 199; F. R. Jensen and C. H. Bushweller, *Adv. Alicyclic Chem.*, 1971, **3**, 139.

group is also reflected in the relatively low torsional (C—O) barrier for methanol. Interactions that may lead to a preferred conformation include[3] intramolecular hydrogen bonding, *gauche* (synclinal) interactions between lone pairs and/or polar bonds, and the *trans* (antiperiplanar) lone-pair effect (the preferred *trans* arrangement of oxygen lone pairs and α-C—H bonds). Although the separation of steric from other effects is often difficult, the relatively low steric *demand* of the hydroxy group is indicated, for example, by the positions of conformational equilibria for cyclohexane derivatives (Table 2) and by the barriers to t-butyl rotation in $Bu^tC(OH)Me_2$ (36 kJ mol^{-1})[4] and hexamethylethane (estimated at 40–42 kJ mol^{-1}). The effective size of a group may be expressed as the value for a steric constant such as υ (Table 2).

(*ii*) *Physical properties of alcohols*

The physical properties of the lower alcohols are largely determined by the polarity of the hydroxy group and its capacity for hydrogen bonding, which lead to relatively high dielectric constants, boiling points, and water solubilities (Table 3). The extensive use of

TABLE 3

Physicochemical Constants of Some Simple Alcohols[a]

Alcohol	*M.p.* (°C)	*B.p.* (°C)	*Density*[b] ($g\ cm^{-3}$)	*Refractive index*[b]	*Dielectric constant*[c]	*Water solubility*[d] (wt. %)
Methyl	−97.7	64.7	0.7866	1.3265	32.7	∞
Ethyl	−114.1	78.3	0.7850	1.3594	24.6	∞
n-Propyl	−126.2	97.2	0.7998	1.3837	20.3	∞
Isopropyl	−88.0	82.3	0.7813	1.3752	19.9	∞
n-Butyl	−88.6	117.7	0.8060	1.3973	17.5	7.5
Isobutyl	−108	107.7	0.7978	1.3939	17.9	10
s-Butyl	−114.7	99.6	0.8026	1.3950	16.6	12.5
t-Butyl	25.8	82.4	0.7812	1.3851	12.5	∞
Allyl	−129	97.1	0.8421	1.4090	21.6	∞
Cyclohexyl	25.2	161.1	0.9684	1.4648	15.0	3.8
Benzyl	−15.3	205.5	1.0413	1.5384	13.1	0.08

[a] Data adapted from J. A. Riddick and W. B. Bunger, 'Techniques of Chemistry. Vol. II. Organic Solvents', 3rd edn., Wiley-Interscience, New York, 1970. [b] At 25 °C, except for allyl alcohol (30 °C). [c] At 25 °C, except for allyl alcohol (15 °C) and benzyl alcohol (20 °C). [d] At 25 °C, except for s-butyl alcohol and benzyl alcohol (both 20 °C).

alcohols as solvents and co-solvents has the same physical basis. Even with the hydrophobic higher alcohols (*e.g.* hexadecan-1-ol, water solubility 4.1×10^{-6} wt.% at 25 °C), the hydroxy group can manifest its characteristic affinities, as in the formation of directed monolayers at the air–water interface.

Except for hindered alcohols (*e.g.* $Bu^t_2Pr^iCOH$), self-association in pure liquid alcohols and in concentrated solutions in non-bonding solvents is usually represented as the dynamic formation of linear multimers, in which each unit contributes one donor and one acceptor bond. The stabilization energy is about 20 kJ mol^{-1}. Self-association is suppressed in polar bonding solvents, and by increasing temperature and dilution in non-polar solvents, but small amounts of oligomers persist even at high dilution and in the vapour phase. The results of the numerous recent studies of the size (dimers, trimers, tetramers, or higher oligomers) and nature (linear or cyclic) of such units strike an impressive discord.

(*iii*) *Acidity and basicity*

Like water, the simple alcohols are weakly amphoteric: in Pearson terms,[5] they are hard acids and bases. The pK_a values determined or calculated for various alcohols in water

TABLE 4

The Acidity and Basicity of Alcohols

Alcohol	pK_a[a] (1)[b]	(2)[c]	*Proton affinity*[e] pK_{BH^+}[d]	(kJ mol^{-1})
MeOH	15.09	15.07	−2.18	753
EtOH	15.93	15.83	−1.94	782
Pr^{n}OH	16.1	15.92	−1.90	791
Bu^{n}OH	16.1	15.87	−1.87	791
Pr^{i}OH	17.1	16.57	−1.73	806
Bu^{t}OH	≥19	16.84	−1.47	828
CF_3CH_2OH	12.39	12.32	−4.35	703
$(CF_3)_3COH$	5.4	5.57	—[f]	—

[a] Values for aqueous alcohols at 25 °C. [b] J. Murto, in Ref. 2, p. 1106. [c] Values calculated[6] from the correlation with σ^*, the polar substituent constant. [d] Values calculated from the correlation with σ^*, taking pK_{BH^+} for H_3O^+ as −3.43, L. S. Levitt and B. W. Levitt, *Tetrahedron*, 1971, **27**, 3777. The value for EtOH agrees with the experimental value of D. G. Lee and R. Cameron, *J. Amer. Chem. Soc.*, 1971, **93**, 4724. [e] Negative of the enthalpy for gas-phase protonation. Value for CF_3CH_2OH from R. L. Martin and D. A. Shirley, *J. Amer. Chem. Soc.*, 1974, **96**, 5299, other values from Ref. 10. [f] No data available.

(Table 4) follow the trends expected from the operation of the accepted *inductive* effects. Acidity is decreased by electron-releasing groups (*e.g.* alkyl) and enhanced by electron-withdrawing groups (*e.g.* halogen), consistent with their influence on the polarity of the O—H bond and the stability of the alkoxide ion formed. The correlation is useful in allowing pK_a values to be predicted from the values for polar substituent constants.[6] However, recent developments in theoretical and gas-phase chemistry[7] reveal the intrinsic order of acidity for alkanols to be tertiary > secondary > primary > methanol. This order, and its inversion in solution, has been rationalized on the basis that proximal alkyl groups stabilize gas-phase anions through their *polarizability*, but destabilize anions in solution through *steric hindrance to solvation*. The phenomena have also been interpreted by using perturbational molecular orbital theory.[8]

In regard to basicity, the conflict between inductive and polarizability effects does not exist. Both in solution and in the gas phase, the order of basicity is tertiary > secondary > primary > methanol. The difficulty in obtaining pK_{BH^+} values for the conjugate acids has led to the use of other parameters such as the enthalpy of protonation in fluorosulphonic acid[9] and in the gas phase.[10] Proton affinities can also be compared through correlations with parameters such as polar and inductive substituent constants, ionization potentials for oxygen lone pairs, binding energies for oxygen 1*s* electrons, and spectral shifts. Representative sets of experimental and calculated data are included in Table 4. The low basicity and nucleophilicity, but high ionizing power, of fluoroalcohols such as CF_3CH_2OH makes them useful in studies of solvolysis. General aspects of the influences of solvent alcohols on chemical reactivity have been discussed by Dack.[11]

(*iv*) *Analysis*

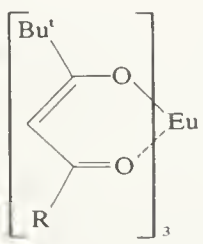
At least for research purposes, the classical methods[12] for the detection, characterization, and determination of hydroxy groups have largely been replaced by modern spectroscopic methods, of which the salient features are summarized here.

The presence of an alcoholic hydroxy group in a compound can usually be diagnosed from the infrared spectrum. The position and appearance of the O—H stretch band are sensitive to hydrogen bonding (and to structural effects). Intermolecular association produces a broad band (3200–3400 cm^{-1}), intramolecular association a sharp band (3450–3550 cm^{-1}) unaffected by dilution, and free O—H a dilution-dependent sharp band (3590–3650 cm^{-1}). Under favourable circumstances, the latter band and the bands (1050–1410 cm^{-1}) for coupled O—H bend and C—O stretch can be used to classify an alcohol.[13]

The ^1H nuclear magnetic resonance spectrum of a compound will often indicate both the presence and the location of a hydroxy group. Because of intermolecular hydrogen bonding and rapid exchange, the hydroxyl proton commonly gives a broad singlet with chemical shift (0.5–4.5 p.p.m. downfield from the protons of tetramethylsilane) highly dependent on the solvent, concentration, and temperature. Its recognition is facilitated by the upfield shift on dilution of a solution in a non-bonding solvent, the downfield shift on the addition of acid, and loss of the signal by deuterium exchange with ^2H_2O. The expected multiplicity of the signal for primary and secondary alcohols can be observed under conditions that retard proton exchange, *e.g.* rigorous purification of the alcohol, the existence of intramolecular hydrogen bonding, and dilute solution in a strongly bonding solvent such as dimethyl sulphoxide (DMSO). For alicyclic alcohols in DMSO, both the chemical shift and the coupling constant can be useful in assigning configurations.[14]

The location of a hydroxy group can also be inferred from its deshielding effect on neighbouring protons. The magnification of the downfield shifts when the hydroxy group is associated with a paramagnetic reagent — commonly one of the europium(III) derivatives (**16a**) and (**16b**), both hard Lewis acids — can greatly simplify the interpretation of ^1H n.m.r. spectra for complex alcohols.[15] Among other lanthanide shift reagents, the praseodymium analogue of (**16a**) is useful in producing upfield shifts, while the ytterbium compound is favoured in the rapidly expanding field of ^{13}C n.m.r. spectroscopy. As with ^1H n.m.r. spectra, the influence of hydroxyl on ^{13}C resonances is greatest at the α-position, the signal usually occurring 50–70 p.p.m. downfield from that for tetramethylsilane. Systematic studies of the ^{13}C n.m.r. spectra of simple alcohols have been made,[16] and the geometrical and stereochemical influences in alicyclic compounds are becoming apparent.[17]

The formation of derivatives, which is an integral part of the classical approach to identifying a compound, is also important in the chromatography and spectroscopy of alcohols. Reactions relevant to n.m.r. spectroscopy include esterification, etherification, and acetalation, which can provide structural information from distinctive resonances of the groups introduced or from shifts in the resonances (mainly α-hydrogen or α-carbon) for the alcohol residue. Esters which have proved useful include (**17**) and (**18**), while trimethylsilyl ethers (**19**) and hexafluoroacetone adducts (**20**) (monitored by using ^1H and ^{19}F n.m.r. spectra, respectively) provide more sensitive methods for the determination of hydroxy groups.

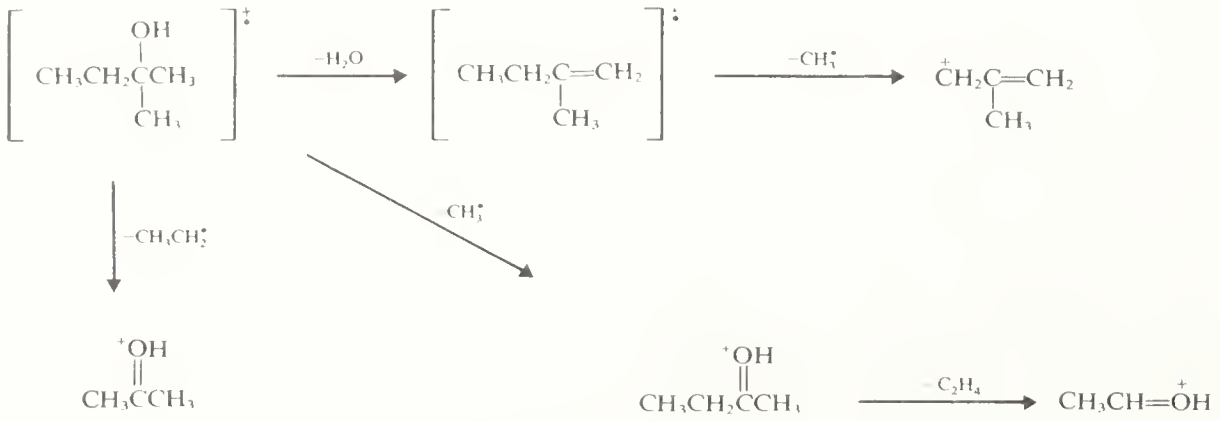


$CCl_3CONHCO_2R$
(**17**)

(**16a**) $Eu(dpm)_3$, $R = Bu^t$
(**16b**) $Eu(fod)_3$, $R = CF_3CF_2CF_2$

$CHCl_2CO_2R$ (**18**) $\quad$ Me_3SiOR (**19**) $\quad$ $(CF_3)_2C(OH)OR$ (**20**)

The electron-impact mass spectra of alcohols are generally characterized by α-cleavage, the elimination of water, and the elimination of an alkene. Such processes are shown in Scheme 1 for the fragmentation of 2-methylbutan-2-ol. The loss of water from the higher alkanols usually occurs by 1,4-elimination. The characteristics of the corresponding processes in cyclic and unsaturated alcohols remain under active study.[18] Because alcohols give little or no molecular-ion peak, and also tend to undergo *thermal* dehydration,



SCHEME 1

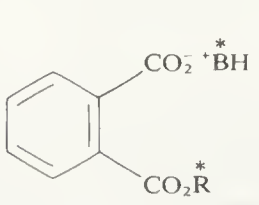
volatile derivatives such as (**19**) can often be used with advantage. The mass spectra usually contain prominent peaks for the molecular ion or a directly related fragment (*e.g.* $M-15$ for trimethylsilyl ethers, $M-57$ for t-butyldimethylsilyl ethers). Alternative solutions to the problem of determining the molecular weight are provided by the milder mass spectrometric techniques of chemical ionization and field ionization or desorption.

(*v*) *Chiral alcohols*

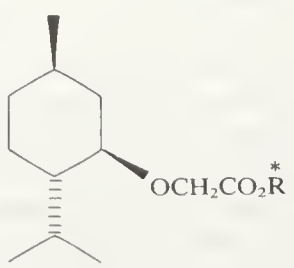
Stereochemical problems loom large in alcohol chemistry. The determination of configuration at the α-carbon is frequently necessary with natural secondary and tertiary alcohols, and the avoidance or resolution of racemates is equally important in synthesis.

Racemic alcohols are normally resolved *via* the preparation and separation (by fractional crystallization or chromatography) of diastereoisomeric derivatives.[19] The alkaloid salts of hydrogen phthalates (**21**) have been most widely used, but many other derivatives, *e.g.* (**22**) and (**23**), have been employed with success. Other methods of resolution, including kinetic resolution (the preferential formation or breakdown of one diastereoisomer) and the direct chromatography of racemates (in the presence of an optically active compound) are of less preparative interest.

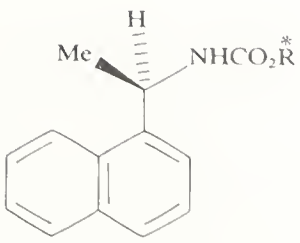
The following account of methods for the determination of configuration is restricted to some recent correlations which appear to have general utility. The special applications of n.m.r. spectroscopy and mass spectrometry to alicyclic alcohols, and classical methods such as those based on chemical interconversions, asymmetric syntheses (*e.g.* Prelog's rule for Grignard addition to chiral phenylglyoxylate esters), and the use of rotational rules (*e.g.* Brewster's rule for chiral benzoate esters) are covered in standard works on stereochemistry and structure determination. The lack of a convenient chromophore has restricted chiroptical studies of saturated alcohols, although significant Cotton effects have been detected below 200 nm. More usefully, chiral alcohols will induce circular dichroism in the electronic transitions of certain metals. The lanthanide reagent (**16b**) and copper(II) hexafluoroacetylacetonate have both been used to establish configurational models. The steric model (**24**) applies to isomers giving a negative Cotton effect at about 333 nm with the latter reagent.[20]



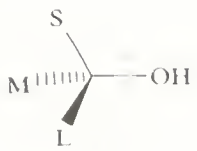
(**21**)



(**22**)



(23)

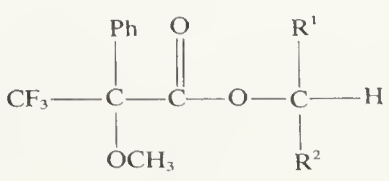


(24)

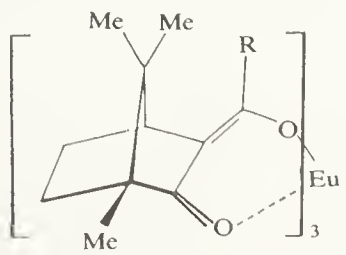
Groups: S, small
M, medium
L, large

Horeau's method, which has been used extensively, involves the kinetic partial resolution of (±)-2-phenylbutanoic anhydride during esterification with a chiral alcohol.[21] Alcohols with configuration (**24**; S = H) react more rapidly at the (*S*)-acyl group, liberating the (−)-(*R*)-acid in enantiomeric excess. In a highly sensitive adaptation of the method, the excess of anhydride is reacted with (+)-(*R*)-1-phenylethylamine (without kinetic resolution), and the proportions of the diastereoisomeric amides are determined by gas–liquid chromatography.

N.m.r. spectroscopy has also made substantial contributions to determinations of enantiomeric composition and configuration. Spectral differences between the members of diastereoisomeric pairs of esters from various acids have been characterized by several research groups. The stereochemical correlations have been most thoroughly studied for the esters (**25**) of 2-trifluoromethyl-2-methoxyphenylacetic acid (Mosher's reagent).[22] The availability of configurational models based on the relative chemical shifts of ^{19}F and ^{1}H (in both methoxy and alkyl groups) attached to the two chiral centres in (**25**) enhances the attraction of these esters. Even more attractive is the possibility of exploiting the spectral non-equivalence of enantiomers in asymmetric environments, provided by either a chiral solvent or a chiral shift reagent. During studies of diastereoisomeric solvation, Pirkle established that for alkylarylmethanols in (+)-1-(1-naphthyl)ethylamine, the resonance for the α-hydrogen was consistently at lower field for the enantiomer with configuration (**24**). More recently, the superior discrimination achieved by using chiral shift reagents has commanded attention. Such reagents, *e.g.* camphor derivatives (**26**), are excellent for the determination of enantiomeric composition of a partially resolved alcohol, but spectral–configurational correlations only seem to be reliable for closely related compounds.[23]



(25)



(26)

4.1.1.3 Methods of preparation

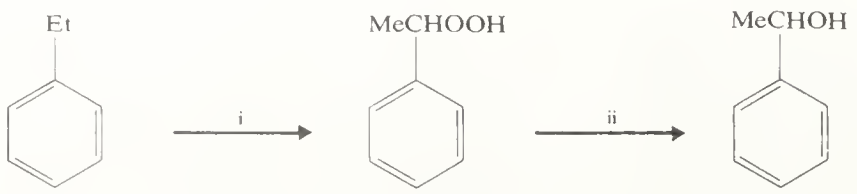
This section only attempts to summarize important general and specific methods, with minimal commentary. More comprehensive accounts are contained in encyclopaedic works such as 'Rodd' and 'Houben–Weyl' and the books by Buehler and Pearson,[24] while the accrescent literature is monitored in publications such as 'Theilheimer', the *Annual* and *Specialist Periodical Reports* of The Chemical Society, London, *Annual Reports in Organic Synthesis*, and the compendia of Harrison and Harrison.[25]

(i) *General methods*

(*a*) *Oxidation of hydrocarbons.* The direct oxidation of unactivated C—H to C—OH bonds can be achieved in various ways, but is not usually a reaction of choice. In general,

efficient non-biological oxidation is only possible for symmetrical hydrocarbons (*e.g.* cyclohexane) or compounds containing tertiary, allylic, or benzylic hydrogen.

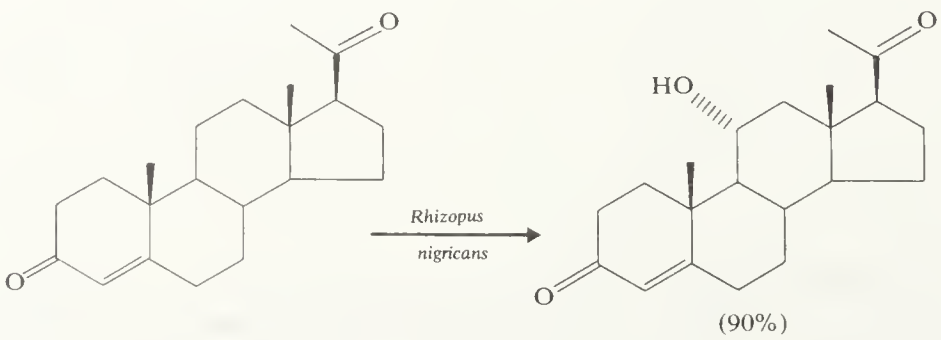
Autoxidation characteristically involves attack by a radical (generated chemically, thermally, or photochemically) on ground state molecular oxygen ($^3\Sigma$). The reaction is catalysed by one-electron redox agents (normally soluble salts or complexes of the transition metals Co, Cu, Fe, Mn, Rh, and Ir) through decomposition of the hydroperoxide produced. Industrial reactions (Table 1) are usually carried out in the liquid phase at modest temperature and pressure. In the Halcon process, reduction of the hydroperoxide (equation 1) is coupled to the production of propene oxide. In the Bashkirov reaction (autoxidation in the presence of boric acid), the formation of borate esters which resist further oxidation leads to improved yields of secondary alcohols.



(1)

i, O_2; ii, $MeCH{=}CH_2$, Mo naphthenate.

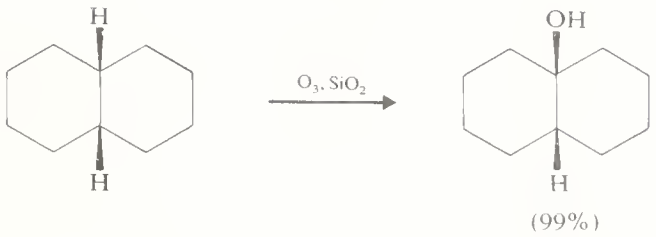
The ability of micro-organisms to use molecular oxygen for selective hydroxylations, particularly of steroids and other cyclic compounds, is extensively documented, and their lure as reagents is being recognized increasingly by chemists.[26] The efficient conversion of progesterone into its 11α-hydroxy derivative (equation 2) is a prime example of such an industrial process. The enzymes involved, termed mono-oxygenases or mixed-function oxidases, catalyse the incorporation of a single atom from molecular oxygen with retention of configuration. The desire to understand and emulate the action of mono-oxygenases has prompted many studies of the 'activation' of molecular oxygen.[27] Activation, usually regarded as the conversion of O_2 to an electrophilic peroxidic species, may occur in some transition metal–dioxygen complexes[28] and can be achieved by formal two-electron reduction, *e.g.* with iron(II)–EDTA–ascorbic acid (the Udenfriend reagent). However, the results so far obtained with such model systems are mainly of mechanistic interest.



(2)

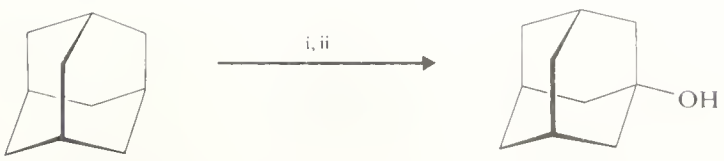
(90%)

Although the common oxidants chromic acid and alkaline permanganate can oxidize tertiary C—H in saturated hydrocarbons selectively and with high retention of configuration, over-oxidation is a serious problem,[29] so the search for better reagents goes on.[30] Some recent developments are exemplified in equations (3)–(5). Ozone adsorbed on silica is a mild and selective reagent for the small-scale preparations of tertiary alcohols (equation 3) and lead(IV) acetate in trifluoroacetic acid is also effective for the oxidation of bridgehead C—H bonds (equation 5). In contrast, trifluoroperacetic acid shows promise for the oxidation of secondary C—H bonds (equation 4), particularly in acyclic compounds containing electronegative groups (which discourage proximal hydroxylation).[30d]



(99%) (3)

(78%) (4)

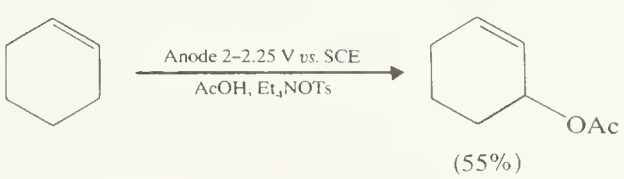


(89%) (5)

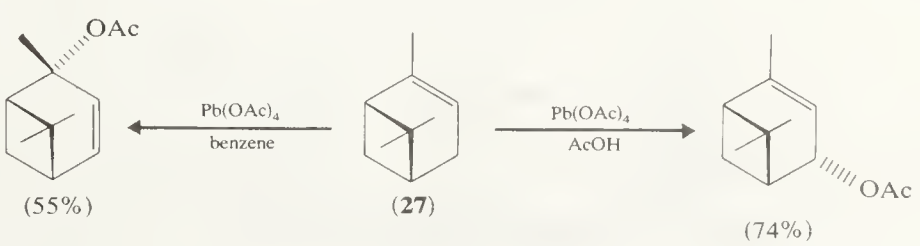
i, $Pb(OAc)_4$, CF_3CO_2H, LiCl; ii, OH^-,

The facile allylic oxidation of alkenes is usually complicated by the possibility of alternative points of attack and the formation of rearranged products. An important group of formally similar but mechanistically diverse reactions involves acyloxylation, followed by hydrolysis or reduction of the ester products. Good yields are often obtained in the copper(I)-catalysed reaction of an alkene with a peroxy ester (the Kharasch–Sosnovsky reaction[31]). Terminal alkenes give mainly 3-acyloxy derivatives (equation 6), but rearrangements are more striking with other classes. Alternative routes are provided by anodic acetoxylation (equation 7) and by reactions with various metal acetates.[32] Of the latter, lead(IV) acetate is effective in some benzylic and allylic substitutions, *e.g.* equation (8) for α-pinene (**27**), but generally gives inferior yields with acyclic alkenes.[32,33] Cleaner substitution occurs in the Treibs reaction (equation 9), involving the milder reagent mercury(II) acetate. Secondary acetates are formed almost exclusively from alk-1-enes used in excess, but equilibration with the more stable primary acetates is caused by an excess of reagent. Selenium dioxide is another well-established reagent for selective allylic oxidation, and one for which the substitutive preferences are extensively documented.[34]

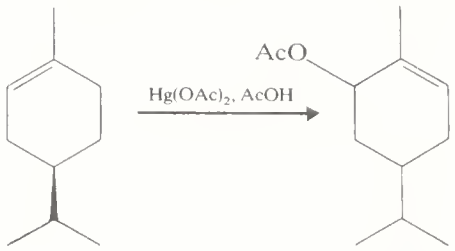
$$EtCH_2CH{=}CH_2 \xrightarrow{AcOOBu^t,\ CuCl} \underset{(78\%)}{EtCH(OAc)CH{=}CH_2} + \underset{(11\%)}{EtCH{=}CHCH_2OAc} \qquad (6)$$



(55%) (7)



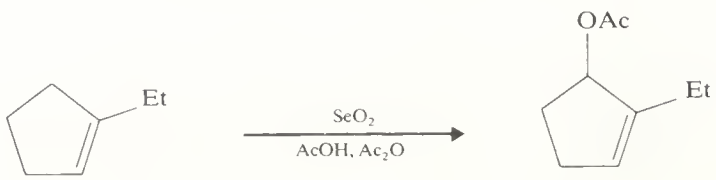
(55%) (**27**) (74%) (8)



(80%)

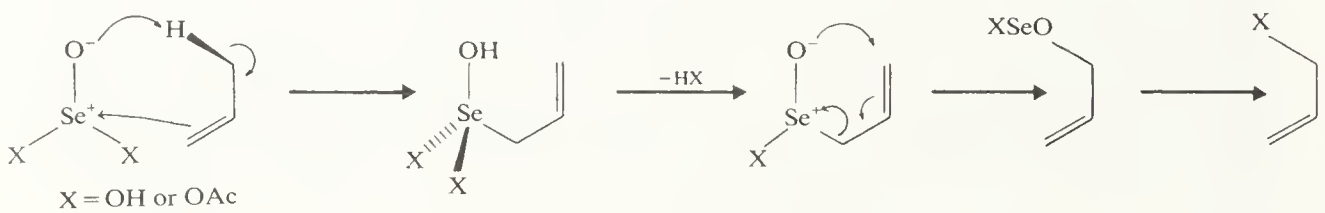
(Mixed racemates) (9)

Although alcohols can be obtained directly from reactions in the presence of water, preparation *via* the acetates (equation 10) is usually preferable. The reaction mechanism



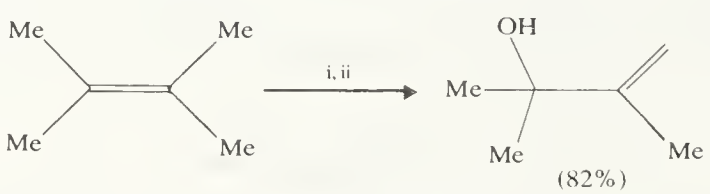
(40%) (10)

has been controversial, but recent studies by Sharpless point to 'ene' addition followed by elimination, a [2,3]-sigmatropic rearrangement of the intermediate allylseleninic acid, and solvolysis of the selenite ester (Scheme 2).



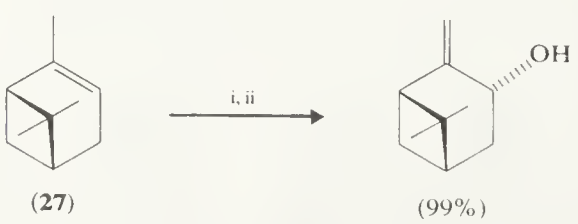
SCHEME 2

An interesting development in allylic oxidation is the use of singlet molecular oxygen ($^1\Delta$) for both laboratory and industrial reactions.[35] Photo-oxygenation sensitized by dyes (*e.g.* Rose Bengal, fluorescein, or Methylene Blue) is generally favoured, but the reagent can be generated in other ways (*e.g.* thermal decomposition of the triphenyl phosphite–ozone adduct, or the reaction of sodium hypochlorite with hydrogen peroxide). The yields of allylic hydroperoxides and the derived alcohols (equations 11 and 12) are often



(82%) (11)

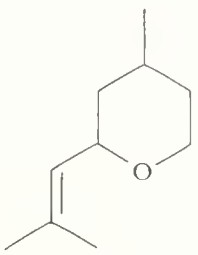
i, O_2, Rose Bengal, $h\nu$; ii, Ph_3P.



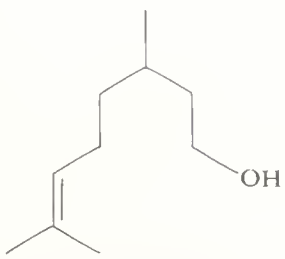
(**27**) (99%) (12)

i, O_2, Methylene Blue, $h\nu$; ii, $NaBH_4$.

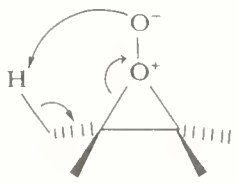
excellent and the products are complementary to those obtained by other methods. The reaction is exploited industrially as the first step in the production of rose oxide (**28**) from citronellol (**29**). The characteristics of the reaction, including shift of the double bond and stereospecific detachment of an allylic hydrogen, clearly differentiate it from radical autoxidation, but are consistent with either an 'ene' mechanism (analogous to step 1 in Scheme 2) or the formation of a peroxiran intermediate (**30**).



(**28**)



(**29**)

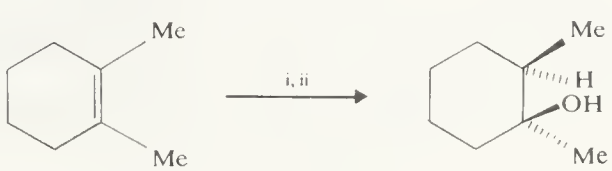


(**30**)

(*b*) *Addition reactions of alkenes.* Reactions in this category comprise some of the most important routes to alcohols in both industry and laboratory. Acid-catalysed hydration of a constitutionally unsymmetrical alkene, directly or *via* the formation and hydrolysis of an alkyl sulphate, follows the Markownikov orientation (equation 13). However, the value of the reaction for the preparation of secondary and tertiary alcohols is limited by the lack of stereospecificity and the well-known rearrangements that are consequential on a carbenium ion mechanism. These problems, and the strongly acidic conditions, are avoided in the alternative two-step conversion *via* an oxiran, to give *anti* hydration overall (equation 14). The same virtues characterize the hydration of simple alkenes *via* oxymercuration–demercuration. A highly convenient and efficient regime has been developed for this sequence,[36] in which the organomercurial adduct is reduced without isolation (equation 15). Potential side reactions are minimized by the speed of oxymercuration and by maintaining a low reaction temperature (25 °C or below). The marked sensitivity of the reaction to steric influences is exemplified by the stereoselective

$$Me_2C{=}CHMe \xrightarrow{\text{i, ii}} Me_2C(OH)CH_2Me \quad (74\%) \qquad (13)$$

i, 60% H_2SO_4, 25 °C; ii, H_2O



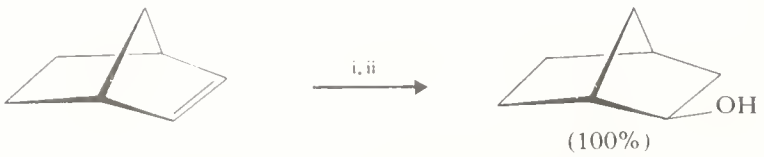
+ Enantiomer (14)

i, $PhCO_2OH$; ii, $LiAlH_4$.

$$Me_3CCH{=}CH_2 \xrightarrow{\text{i, ii}} Me_3CCH(OH)CH_3 \quad (94\%) \qquad (15)$$

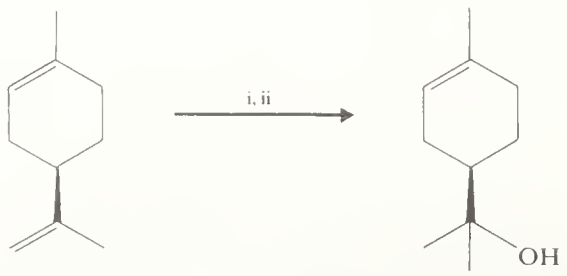
i, $Hg(OAc)_2$, THF, H_2O; ii, NaOH, $NaBH_4$.

formation of the *exo* alcohol from norbornene (equation 16), and by the preferential reaction of the disubstituted exocyclic double bond during the monohydration of limonene (equation 17). Although a 70% yield of the alcohol (**31**) was reported by Brown's group,[37a] extensive loss of product through further reaction was experienced by others.[37b]



(100%) (16)

i, $Hg(OAc)_2$, THF, H_2O; ii, NaOH, $NaBH_4$.



(**31**) (17)

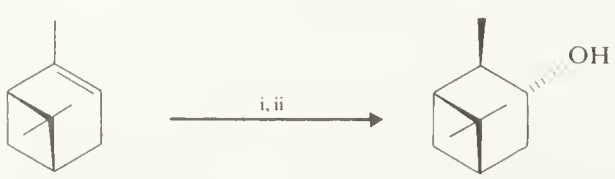
i, $Hg(OAc)_2$, THF, H_2O; ii, NaOH, $NaBH_4$.

The above methods for Markownikov hydration are powerfully complemented by the similarly mild and efficient method of hydroboration–oxidation with the reverse regioselectivity. The basic procedure[38] for the reaction of (di)borane with a simple alkene and the oxidation of the trialkylborane(s) without isolation is indicated by equation (18). The additional features of *syn* addition from the less-hindered side of the double bond, and the absence of rearrangement, are exemplified by the hydration of α-pinene (equation 19). The reaction of (di)borane with a hindered alkene like α-pinene may proceed only to a mono- or di-alkylborane, which can then be used as a less reactive and more selective hydroborating agent. Important examples of such reagents are thexylborane (**32**), disiamylborane (**33**), and 9-borabicyclo[3,3,1]nonane (**34**). Reagent (**34**), a crystalline compound with high thermal stability and tolerable stability to air, displays exceptional

$$Bu^nCH{=}CH_2 \xrightarrow{i} [R_3B] \xrightarrow{ii} \underbrace{Bu^nCH_2CH_2OH\ (94\%) + Bu^nCH(OH)Me\ (6\%)}_{\text{Isomer distribution}} \quad (18)$$

(Total yield 95%)

i, B_2H_6, diglyme; ii, NaOH, H_2O_2.

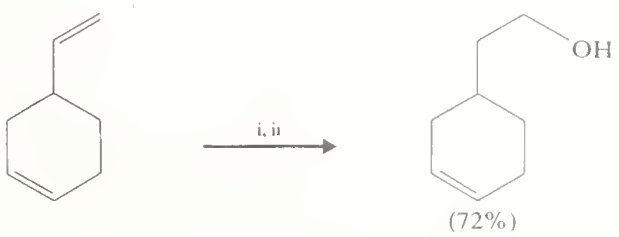


(**27**) (89%) (19)

i, B_2H_6, THF; ii, NaOH, H_2O_2.

(20)

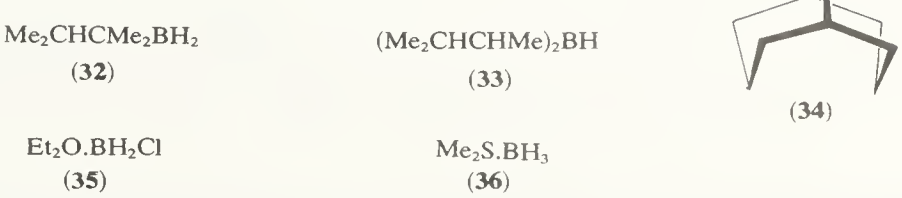
i, (**34**), THF; ii, NaOH, H_2O_2.



(21)

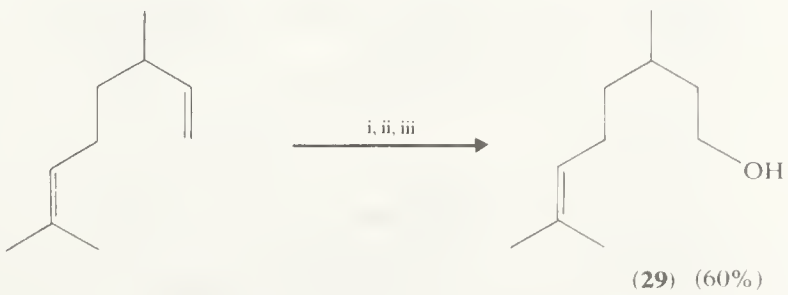
i, (**33**), THF; ii, NaOH, H_2O_2.

regioselectivity (equation 20). Reagent (**33**) is rather more sensitive to steric influences and less so to electronic (polar) ones: its use in a selective monohydration is shown in equation (21). The polar factor in the direction of hydroboration can be selectively exploited by using the etherate (**35**) of monochloroborane, which gives over 99.5% of the anti-Markownikov alcohol from hex-1-ene, compared with 94% when using borane in tetrahydrofuran (THF) or diethylene glycol dimethyl ether (diglyme) (equation 18). Among other innovations in the very active area of hydroboration are the introduction of the borane–dimethyl sulphide complex (**36**) as a stable, concentrated, and versatile



alternative to BH_3·THF, and trimethylamine *N*-oxide dihydrate as an alternative to alkaline hydrogen peroxide for oxidation of the organoborane adduct.

Although reactions analogous to hydroboration are known for other organometal hydrides (*e.g.* hydroalumination, hydrostannation, and, recently hydrozirconation), they have not yet found comparable synthetic utility. Hydroalumination has the same regio- and stereo-selectivity as hydroboration, but occurs less readily. Advantages are the facile displacement reactions of trialkylalanes (*e.g.* of isobutene from Bu^i_2RAl by the substrate alkene), which means that both di-isobutylaluminium hydride (**37**) and tri-isobutylaluminium (**38**) can be used as reagents (equation 22), and the ready oxidation of



(22)

i, (**37**) or (**38**); ii, O_2; iii, H_2O.

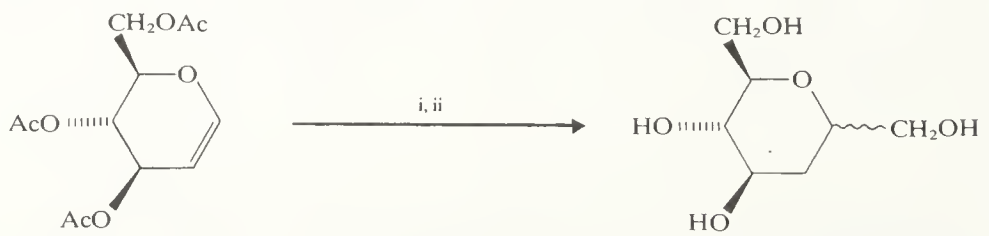
the products in air. As previously indicated (Table 1), the Ziegler telomerization of ethylene with triethylaluminium, followed by autoxidation, is a major industrial method for the production of n-alkan-1-ols.

The competing industrial process of hydroformylation–reduction also starts with hydrometallation of an alkene, by *syn* addition, though the hydroxyl-forming step is actually a carbonyl hydrogenation. The reaction is carried out under pressure with a Group VIII metal catalyst — conventionally a cobalt derivative such as $Co_2(CO)_8$ — and gives mainly unbranched alcohols from n-alk-1-enes (equation 23). The actual catalyst is apparently[39] a

$$RCH{=}CH_2 \xrightarrow{\text{i, ii}} \underbrace{RCH_2CH_2OH}_{3} + \underbrace{RCHMeCH_2OH}_{1} \quad \text{Isomer distribution} \qquad (23)$$

i, CO, H_2, $Co_2(CO)_8$; ii, H_2, catalyst.

hydrido species such as $CoH(CO)_4$ or $CoH(CO)_3$. Phosphine-containing catalysts, *e.g.* $(Bu^n_3P)_3CoH(CO)_3$, are more stable (permitting a lower operating pressure), better hydrogenation catalysts (giving a one-step process), and show greater regioselectivity (producing a higher proportion of unbranched alcohol). There is also intense interest[40] in rhodium-based catalysts, *e.g.* $(Ph_3P)_3RhH(CO)$. Although hydroformylation is primarily an industrial reaction, its laboratory applications include carbohydrate syntheses, *e.g.* equation (24).[41]

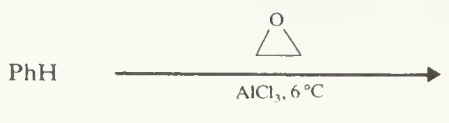


(24)

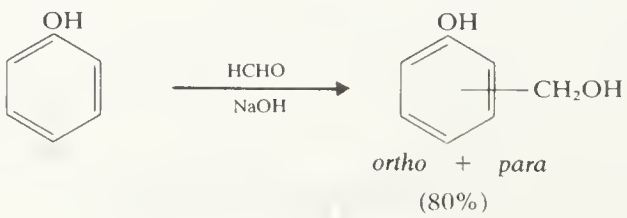
(Both epimers in equal amounts)

i, CO, H_2, $Co_2(CO)_8$; ii, NaOMe.

(*c*) *Substitution reactions (hydroxyalkylation) of alkenes and arenes.* Such reactions, involving carbonyl compounds or cyclic ethers, have rather limited synthetic scope. Even with simple oxirans and oxetans, the yields in Friedel–Crafts reactions, *e.g.* equation (25), are only modest. More important is the Lederer–Manasse reaction (equation 26), in which a phenol is hydroxymethylated by treatment with formaldehyde, usually in the presence of alkali at low temperature. Apart from the Prins reaction (Section 4.1.2.3), the reactions of formaldehyde with alkenes are less well known. However, homoallylic alcohols can be obtained in good yields from suitable alkenes, *e.g.* methylenecyclohexane or β-pinene

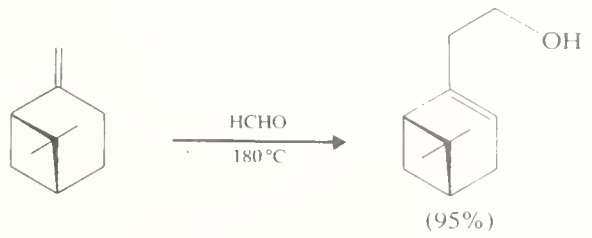


(25)

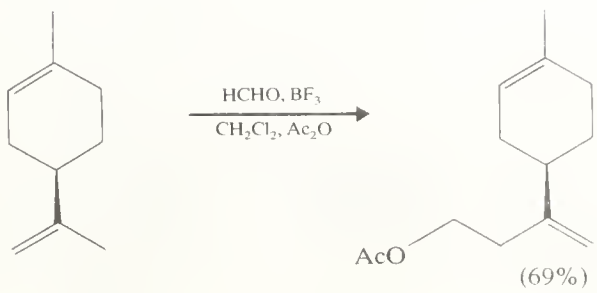


(26)

(equation 27), by the thermal or acid-catalysed 'ene' reaction[42] (a formal substitution). The major product obtained from limonene in a mild, Lewis-acid catalysed reaction is the exocyclic adduct (equation 28).



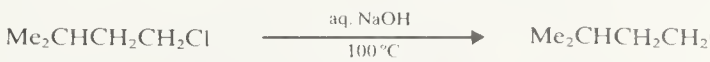
(27)



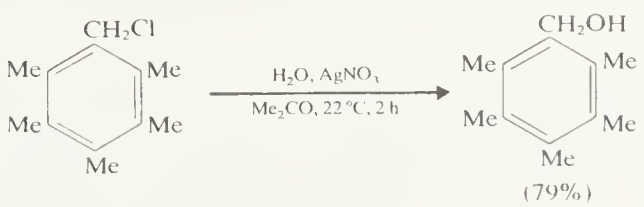
(28)

(*d*) *Hydrolysis and related reactions.* Reactions of this type are exemplified in equations (29)–(37). The preparative importance of the hydrolysis of alkyl halides and sulphonate esters does not match the mechanistic prominence of these nucleophilic substitutions. The transformation for halides is mainly relevant to compounds prepared directly from hydrocarbons. Hydrolysis with aqueous alkali is satisfactory for simple primary halides that react by the S_N2 mechanism (equation 29), but milder reagents (*e.g.* dilute sodium carbonate, silver(I) oxide, or water) are necessary or adequate for reactive halides (*e.g.* Ar_3CCl) and halides that readily undergo elimination (*e.g.* R_2CClCH_2R). Reactions are facilitated by the use of an inert co-solvent or a phase-transfer catalyst,[43] and by the presence of an electrophilic cation, normally silver(I) (equation 30) or mercury(II) (equation 31).[44]

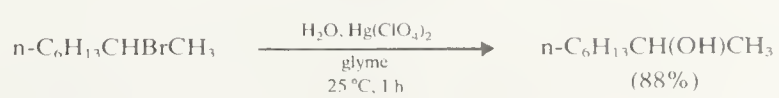
Competition from elimination can be minimized by following a two-step sequence: substitution with a weakly basic carboxylate anion (usually acetate or formate, as an alkali metal or quaternary ammonium salt), then hydrolysis or reduction of the ester formed. This is also the conventional method for epimerizing a chiral secondary alcohol (equation 32). More exotic derivatives of alcohols (*e.g.* alkoxybenzothiazolium salts[45]) that are also susceptible to S_N2 displacements, and are therefore suitable for epimerizations, are



(29)



(30)

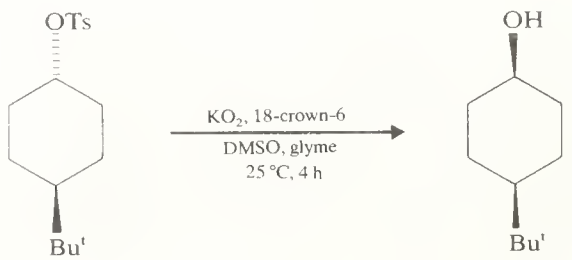


(31)

(32)

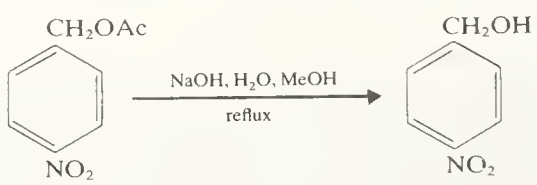
i, TsCl, pyridine; ii, R_4NOAc; iii, NaOH or $LiAlH_4$.

described in Section 4.1.1.4. Another novel and more direct alternative for the displacement step is the use of the superoxide radical-ion, a very powerful nucleophile.[46] The reaction of potassium superoxide in DMSO with a halide or sulphonate leads directly to the alcohol (equation 33), as the hydroperoxide intermediate is reduced by the solvent. Clean inversions are possible even with secondary allylic derivatives.[46b]



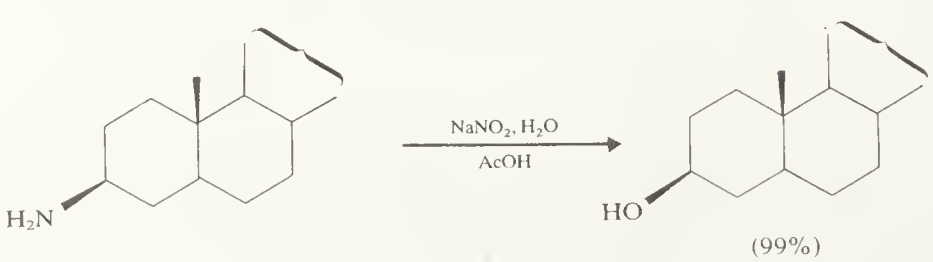
(95%) (33)

The formation or regeneration of hydroxy groups by the hydrolysis of carboxylate esters is a routine operation. Hydrolysis with aqueous or aqueous alcoholic alkali (equation 34) is most generally useful. Alcoholysis catalysed by either base (alkoxide or ammonia) or acid (mineral or Lewis) provides a milder alternative. Esters in which the carbonyl group is hindered towards nucleophilic attack may be degraded by alkyl–oxygen fission (*e.g.* by using Bu^{t}OK in warm DMSO, LiI in hot dimethylformamide (DMF), or LiSPr^n in hexamethylphosphortriamide (HMPT) at ambient temperature), but this is seldom a problem relevant to alcohol synthesis.

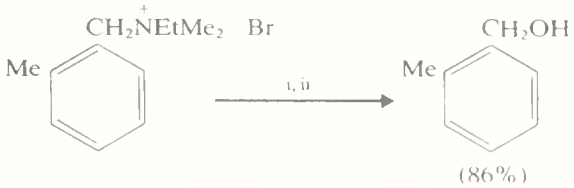


(71%) (34)

Routes to alcohols from amines are mostly synthetic by-ways. The potential complexity of aliphatic diazotizations limits preparative applications mainly to certain benzylic and alicyclic amines. The reaction is notably successful with compounds in which the amino group occupies an equatorial position in a rigid molecule, *e.g.* cholestan-3β-ylamine (equation 35). Other methods include nucleophilic displacements on those quaternary ammonium salts (equation 36) and sulphonimides (equation 37) that do not undergo preferential elimination.



(99%) (35)



(36)

i, AcOK, AcOH; ii, NaOH.

(37)

i, aq. HI, DMF, 125 °C; ii, KI, AcONa, HMPT, 115 °C
98% (R = H or HCO) > 95% (R = Ac)

(*e*) *Reduction of carbonyl compounds and cyclic ethers.* The reductive generation of hydroxyl from another oxygen-containing function is one of the most common and engaging of transformations. Its importance is reflected in the continuing spate of publications on new reagents and mechanistic studies. The most useful alcohol precursors are aldehydes, ketones, acids, esters, and oxirans. Examples of their reduction (equations 38–64) are grouped according to the principal methods in use or under investigation (Table 5). The incongruous brevity of the following discussion is excused by the fuller treatment of the topics elsewhere in this volume and in the leading references cited.

TABLE 5

Major Methods and Reagents for the Reduction of Carbonyl Compounds and Oxirans[a]

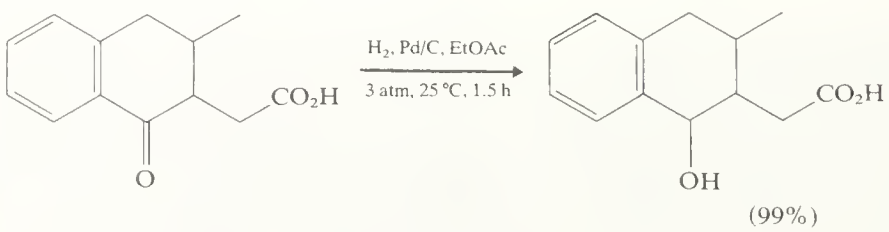
Method		*Representative reagents*
Catalytic hydrogenation	Insoluble catalysts[b]	Pt, Ru, Pd, Raney Ni, '$CuCr_2O_4$'
	Soluble catalysts[c]	$[(PhMe_2P)_2RhH_2\cdot(DMF)_2]ClO_4$, $(Ph_3P)_3IrH_3$–AcOH, $(Ph_3P)RhCl(C_8H_{12})$–$NaBH_4$
Catalytic hydrogen transfer[d]	Soluble catalysts	$IrCl_4$–$(MeO)_3P$, $(Ph_3P)_3RhCl$, $(Ph_3P)_3RuCl_2$, $(Ph_3P)_3CoH_3$
	Hydrogen donors	Pr^iOH, Pr^n_3N, 2,5-dihydrofuran
Catalytic hydrosilylation[e]	Soluble catalysts	$(Ph_3P)_3RhCl$, $(Ph_3P)_3RuCl_2$
	Organosilanes	Et_2SiH_2, Ph_2SiH_2, $PhMe_2SiH$
Ionic hydrogenation[f]	Catalysts	CF_3CO_2H, H_2SO_4, HCl, $ZnCl_2$, BF_3
	Organosilanes	Et_3SiH, Bu^nSiH_3
Reduction by metal hydrides[g]	Hydridoaluminates[h]	$LiAlH_4$, $LiAlH(OR)_3$(R = Me, Et, or Bu^t), $NaAlH_2Et_2$, $NaAlH_2(OCH_2CH_2OMe)_2$
	Hydridoborates[i]	MBH_4(M = Na, Li, Zn/2, or Bu^n_4N), MBH_3CN (M = Na, Li, or Bu^n_4N)
		$NaBH_2S_3$, $LiBHR_3$ (R = Et, Bu^s, or Pr^iCHMe), $KBHR_3$ (R = Bu^s or OPr^i)
	Boranes[j]	$BH_3\cdot THF$, $BH_3\cdot Me_2S$, thexylborane (**32**), disiamylborane (**33**), 9-BBN (**34**)
	Alanes[k]	AlH_3, $AlHCl_2$, Bu^i_2AlH, $Al_2H_3(OCH_2CH_2OMe)_3$
	Stannanes[l]	R_3SnH, R_2SnH_2 (R = Bu^n or Ph)
Meerwein–Ponndorf–Verley and related reductions		Pr^iOH–Pr^iOM (M = Al/3 or Li), Pr^iOH–Al_2O_3, Pr^i_2NLi, bornan-2-*exo*-ylaluminium dichloride (**48**), 'ate' complex (**49**), RMgX (hindered), Bu^i_3Al
Dissolved and dissolving metal reductions[m]		Na–EtOH (Bouveault–Blanc), Na or Li–NH_3–ROH (Birch), Li–RNH_2 (R = Me, Et, Pr^n or $NH_2CH_2CH_2$; Benkeser)

[a] For chemoselectivity see the text, Ref. 47, and references in the following footnotes. [b] P. N. Rylander, 'Catalytic Hydrogenation over Platinum Metals', Academic, New York, 1967; A. P. G. Kieboom and F. van Rantwijk, 'Hydrogenation and Hydrogenolysis in Synthetic Organic Chemistry', Delft University Press, Rotterdam, 1977. [c] F. J. McQuillin, 'Homogeneous Hydrogenation in Organic Chemistry', Reidel, Dordrecht, Holland, 1976. [d] I. S. Kolomnikov, V. P. Kukolev, and M. E. Vol'pin, *Russ. Chem. Rev.*, 1974, **43,** 399; G. Brieger and T. J. Nestrick, *Chem. Rev.*, 1974, **74,** 567. [e] Ref. 49. [f] Ref. 50. [g] Ref. 47; E. R. H. Walker, *Chem. Soc. Rev.*, 1976, **5,** 23. [h] J. S. Pizey, 'Synthetic Reagents', Ellis Horwood, Chichester, 1974, vol. 1, chapter 2; J. Málek and M. Cerny, *Synthesis*, 1972, 217. [i] E. Schenker, in 'Newer Methods of Preparative Organic Chemistry', ed. W. Foerst, Verlag Chemie, Weinheim, 1968, vol. IV, p. 196; Refs. 53–59. [j] Ref. 61. [k] Ref. 63; N. M. Yoon and H. C. Brown, *J. Amer. Chem. Soc.*, 1968, **90,** 2927. [l] H. G. Kuivila, *Synthesis*, 1970, 499. [m] Ref. 47.

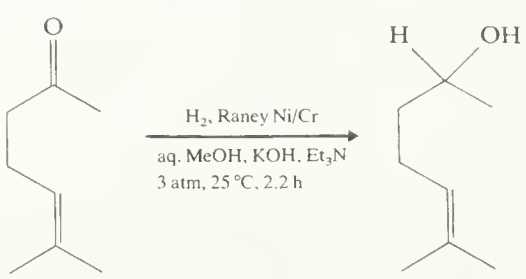
Catalytic hydrogenation of carbon monoxide over Cr–Zn or Cu-based catalysts is the major route to methanol, and the hydrogenation of aldehydes and esters features in other industrial processes (Table 1). Laboratory reductions of simple aldehydes and ketones are often clean and efficient, but applications tend to be restricted by the *generally* greater ease of hydrogenation of alkenic and alkynic multiple bonds, the need to avoid hydrogenolysis of benzylic products, and the variable stereoselectivity in the reduction of alicyclic ketones. Equations (38)–(40) show typical heterogeneous reductions, and equation (41) exemplifies the exceptional situation in which a carbonyl group has been selectively reduced in the presence of alkenic unsaturation. The newer methods of homogeneous hydrogenation, mainly based on organophosphine-containing complexes of rhodium, iridium, or ruthenium, have yet to achieve routine utility; their major impact seems to be in the area of asymmetric hydrogenation (Section 4.1.1.3, p. 616).

$$n\text{-}C_{13}H_{27}CO_2Et \xrightarrow[220\ atm,\ 250\ ^\circ C,\ 2\ h]{H_2,\ 'CuCr_2O_4'} n\text{-}C_{14}H_{29}OH \quad (98\%) \qquad (38)$$

$$Me_2C(OH)COMe \xrightarrow[EtOH,\ 20\ ^\circ C]{H_2,\ Pt} Me_2C(OH)CH(OH)Me \quad (88\%) \qquad (39)$$

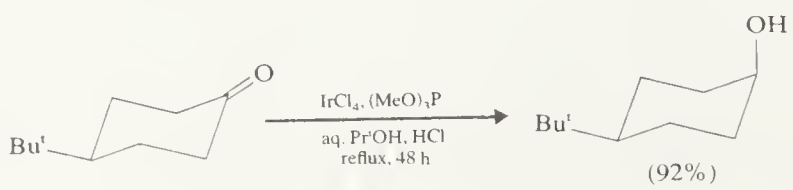


(99%) (40)



(89%) (41)

Homogeneous catalysis has also contributed to recent progress in reductions *via* hydrosilylation and by hydrogen transfer from an organic donor. The reduction of ketones by hydrogen transfer tends to be slow, but can be highly stereoselective. With Henbest's iridium-based catalyst, excellent yields of axial alcohols have been obtained in the reduction of unhindered cyclohexanones (equation 42) and 3-oxo steroids. Isopropanol is the most widely used hydrogen donor, but a miscellany of other compounds will also serve.[48] Homogeneous hydrosilylation of aldehydes and ketones is often rapid in the presence of the Wilkinson catalyst $[(Ph_3P)_3RhCl]$; overall reduction is completed by the facile hydrolysis of the silyl ether (equation 43).[49] As with homogeneous hydrogenation, the reaction is mainly being developed as a method of asymmetric synthesis.



(92%) (42)

$$Ph_2CO \xrightarrow{\text{i, ii}} Ph_2CHOH \quad (95\%) \qquad (43)$$

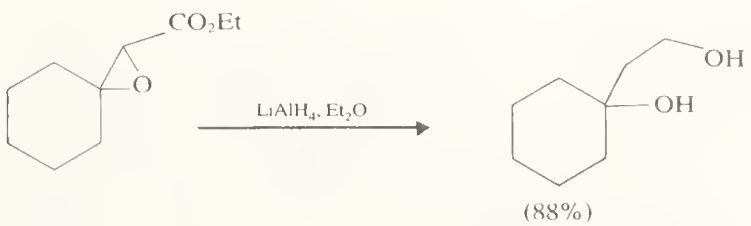
i, Et_2SiH_2, $(Ph_3P)_3RhCl$, 25 °C, 5 min; ii, MeOH, MeONa.

Hydride transfer from organosilanes to carbonyl compounds can be catalysed by other means; the term 'ionic hydrogenation' has been coined for the reactions catalysed by acids.[50] Optimum conditions for the reduction (equation 44) and its mechanistic features have been determined.[51] Pre-eminent among hydride reductants, however, are the nucleophilic reagents belonging to the hydridoaluminate and hydridoborate series, represented with distinction by $LiAlH_4$ and $NaBH_4$. Together with the electrophilic alanes and boranes they form one of the most important group of reagents available to organic chemists.

$$Bu^tCOMe \xrightarrow[MeCN,\ 28\ °C,\ 1\ h]{Et_3SiH,\ H_2SO_4,\ H_2O} Bu^tCH(OH)Me \quad (>80\%) \qquad (44)$$

Both $LiAlH_4$ and $NaBH_4$, and most other members of their respective series, readily reduce carbonyl groups in aldehydes *and* ketones, but do not usually affect isolated carbon–carbon multiple bonds. The individual reagents differ markedly in their solubilities and in their reactivities towards other functional groups. The most powerful reductant, $LiAlH_4$, is widely used for the unselective reduction of aldehydes, ketones, acids, acid chlorides, esters, and oxirans soluble in diethyl ether, THF, or dichloromethane, *e.g.* equations (45) and (46). With some oxirans, the normal regioselectivity of $LiAlH_4$

$$PhCOCO_2H \xrightarrow{LiAlH_4,\ Et_2O,\ reflux} PhCH(OH)CH_2OH \quad (80\%) \qquad (45)$$



(88%) (46)

(involving S_N2 reaction at the least hindered carbon) can be reversed by the addition of a proportion of $AlCl_3$ to form a 'mixed hydride' (equivalent to alane or a chloroalane), *e.g.* equation (47). Such modified reagents also show improved chemoselectivity. Thus, the $LiAlH_4$–$AlCl_3$ (3:1) mixture or alane is particularly useful for the preparation of allylic alcohols from α,β-unsaturated carbonyl compounds that tend to undergo conjugate reduction with $LiAlH_4$ alone (equation 48). Other important hydridoaluminates derive

(84%) (47)

(14%) (i)
(90%) (ii) (48)

i, $LiAlH_4$, THF; ii, AlH_3, THF.

their enhanced selectivities from the steric and electronic effects of alkoxy substitution in $LiAlH_4$. The reducing power of $LiAlH(OBu^t)_3$, *e.g.* equation (49), is similar to that of $NaBH_4$. Although useful stereoselectivity can be achieved with bulky reagents of this

(49)

type, *e.g.* 93% selectivity for the less-stable *cis*-alcohol in the reduction of 4-t-butylcyclohexanone with (**39**),[52] superior results can be obtained with the hydridotrialkylborates discussed below.

The major applications of the mild, hydrophilic reagent $NaBH_4$ are to the reduction of aldehydes, ketones, and some reactive esters such as (**40**), (**41**), and (**42**) [the enol ester formed by the reaction of an acid with Woodward's reagent K (**43**)]. The acid-stable cyanohydridoborates[53] are even milder reagents: the selective reduction of aldehydes can be achieved with $Bu^n_4NBH_3CN$ in acidified HMPT, and also with $NaBH_4$ treated with acetic acid (about 0.8 equiv.)[54a] or certain thiols.[54b] The range of acceptable solvents for $NaBH_4$ reductions can be extended by using a phase-transfer catalyst (a quaternary ammonium salt, crown ether, or cryptand)[43,55] in a heterogeneous reaction, *e.g.* (**44**) in

$LiAlH(OAr)_2(OR)$

(**39**) Ar = 2,6-di-t-butylphenyl
R = neopentyl

RCO_2Ar

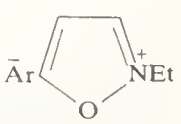
(**40**) Ar = 2,4-dinitrophenyl

$RCO_2CH_2CF_3$

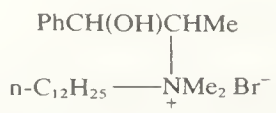
(**41**)

$RCO_2C\bar{A}r{=}CHCONHEt$

(**42**) ArH = 3-sulphophenyl

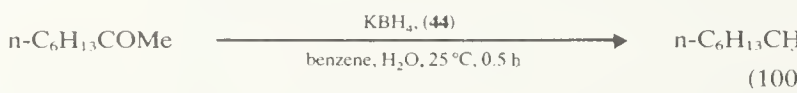


(**43**)

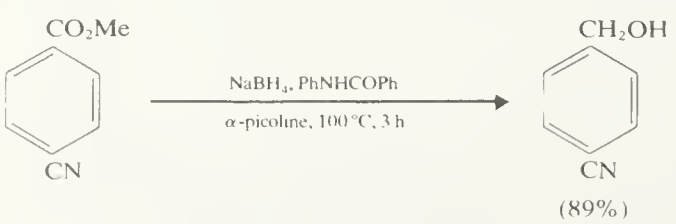


(**44**)

equation (50), or by using $Bu^n_4NBH_4$ (soluble in CH_2Cl_2)[56] in place of $NaBH_4$. Hydridoborates with enhanced organic solubility or reactivity involve other cations (*e.g.* Zn^{2+})[57a] or the modification of $NaBH_4$ in various ways: recent examples include treatments with sulphur,[57b] anilides,[57c] or ethane-1,2-dithiol.[57d] Like $LiBH_4$, the last two permit the reduction of normal esters, *e.g.* equation (51), while the first extends reduction to aromatic nitro groups.



(50)



(51)

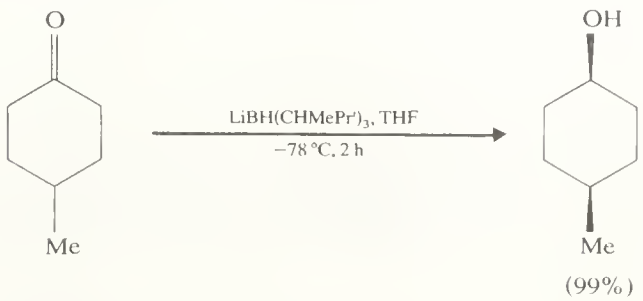
Remarkable properties are associated with alkyl- and aryl-substituted hydridoborates. Even hindered oxirans, and oxirans prone to rearrange, readily undergo normal ring-opening with the strongly nucleophilic reductant $LiBHEt_3$ (equation 52).[58] Other reagents, *e.g.* $LiBHBu^s_3$, $KBHBu^s_3$, $KBH(OPr^i)_3$, $LiBH(CHMePr^i)_3$, (**45**), and (**46**), in this

(52)

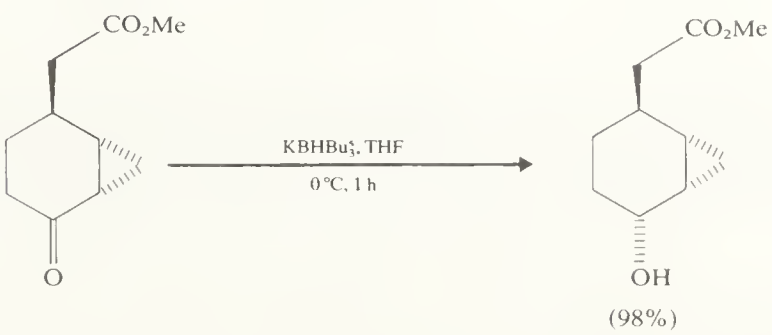
$LiBH_2Ar_2$,$(MeOCH_2CH_2OMe)_2$
(**45**) Ar=mesityl

$LiBHR_3$
(**46**) R = *trans*-2-methylcyclopentyl

group reduce ketones with exceptional stereoselectivity, *e.g.* equations (53) and (54).[59] Conjugate reduction is a problem with cyclohex-2-en-1-ones unsubstituted in the 3-position,[60] but allylic alcohols are formed preferentially from acyclic enones. Alongside

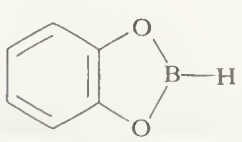


(53)

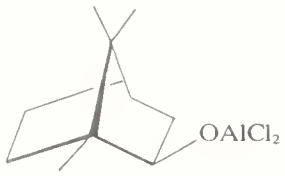


(54)

their work on hydridoborates, Brown and his colleagues have systematically evaluated the reducing characteristics of the boranes. The observed variations in chemoselectivity for diborane,[61a] thexylborane (**32**),[61b] disiamylborane (**33**),[61c] 9-BBN (**34**),[61d] and benzo[1,3,2]dioxaborole, *i.e.* catecholborane (**47**),[61e] provide considerable scope for differential reductions. Diborane is used extensively for the rapid and selective reduction of carboxyl groups, *e.g.* equation (55), and complements $LiAlH_4$ in its regioselective reduction of oxirans (equation 56). By contrast, the dialkylboranes can be used to reduce a carbonyl group in the presence of a carboxyl group, and show useful stereoselectivity in the reduction of cyclic ketones.[62] The very mild reagent 9-BBN (**34**) shows outstanding promise for the reduction of α,β-unsaturated carbonyl compounds (equation 57): even with cyclopent-2-en-1-one, conjugate reduction does not occur, *cf.* equation (48).

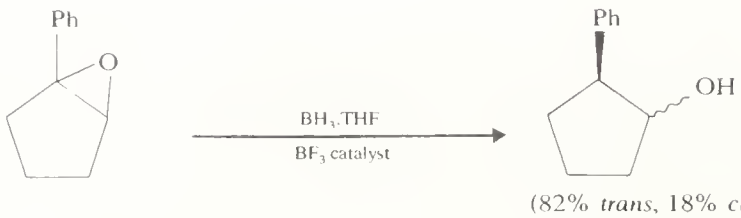


(**47**)

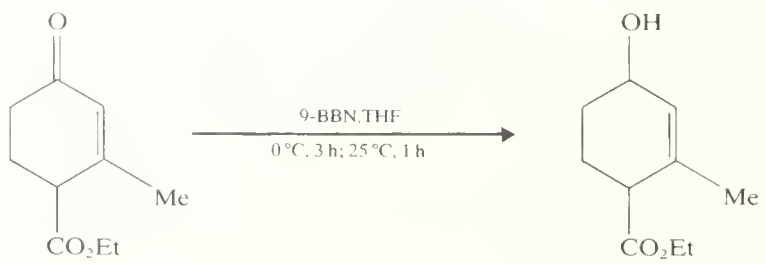


(**48**)

$$HO_2C(CH_2)_4CO_2Et \xrightarrow[-18\text{ to }25\,^\circ C,\ 16\text{ h}]{BH_3,\ THF} HOCH_2(CH_2)_4CO_2Et \quad (88\%) \qquad (55)$$

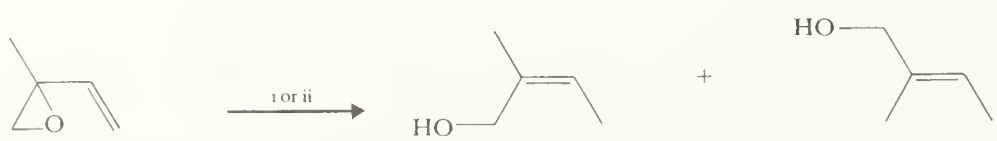


(82% *trans*, 18% *cis*) (56)



(95%) (57)

The ability of alane and its di-isobutyl derivative to obviate conjugate reduction is an established virtue of these reagents. Interestingly, however, the conjugate reduction of α,β-unsaturated oxirans can be accomplished by using Bu^i_2AlH in hexane, in place of THF, to provide a stereoselective route to allylic alcohols (equation 58). Metal–ammonia



(58)

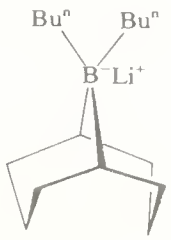
	Yield	*Product distribution*	
i	71%	95	5
ii	64%	8	92

i, Bu^i_2AlH, hexane, 68 °C; ii, Ca, NH_3, −33 °C.

reductions have the opposite selectivity. Organostannanes have found only spasmodic use for the reduction of aldehydes and ketones, but this situation may be changed by two recent developments. In one,[64a] the hydride was generated in catalytic amounts by the reaction of $(Bu^n_2AcSn)_2O$ with a polymeric hydrosiloxane, the ultimate reductant. In the other,[64b] stannane residues were incorporated in an insoluble polymeric reagent.

In addition to catalytic hydrogen transfer, various methods for carbonyl reduction involve an organic hydride donor. Most prominent is the mild Meerwein–Ponndorf–Verley reduction, usually using aluminium isopropoxide in isopropanol. An interesting variation is the small-scale, selective reduction of aldehydes by the alcohol on dehydrated alumina (equation 59).[65] Another innovation is the use of the 'ate' complex (**49**) related to 9-BBN (**34**) for chemo-, stereo-, or regio-specific reductions, *e.g.* equation (60).[66]

$$MeCO(CH_2)_8CHO \xrightarrow[25\,^\circ C,\ 2\ h]{Pr^iOH,\ Al_2O_3} MeCO(CH_2)_8CH_2OH \quad (70\%) \qquad (59)$$



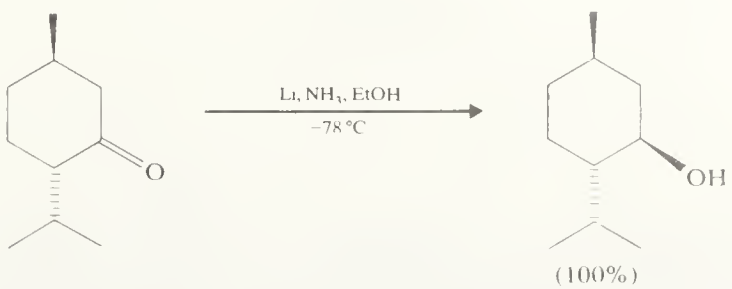
(**49**)

$$p\text{-}Pr^iCOC_6H_4CH_2CH_2COMe \xrightarrow[MeOH,\ hexane]{(49)} p\text{-}Pr^iCOC_6H_4CH_2CH_2CH(OH)Me \quad (69\%) \qquad (60)$$

Whereas the reduction of hindered ketones by Grignard reagents finds little synthetic use, the analogous reaction of ketones with aluminium alkyls, especially Bu^i_3Al, is of some importance.[63]

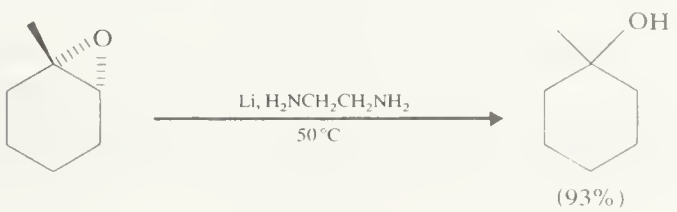
With the development of the many excellent methods and reagents described above, the importance of reductions by dissolved or dissolving metals, *e.g.* the Bouveault–Blanc reduction (equation 61), has declined. Reactions that exemplify useful features of the method are given in equations (62)–(64). Despite a growing interest in synthetic electrochemistry, the analogous reactions by cathodic reduction have not been widely exploited.

$$n\text{-}C_{11}H_{23}CO_2Et \xrightarrow{Na,\ EtOH,\ toluene} n\text{-}C_{11}H_{23}CH_2OH \quad (75\%) \qquad (61)$$



(100%) (62)

$$n\text{-}C_{11}H_{23}CONMe_2 \xrightarrow[-40\,^\circ C]{K,\ HMPT,\ Bu^tOH} n\text{-}C_{11}H_{23}CH_2OH \quad (100\%) \qquad (63)$$



(93%) (64)

(*f*) *Reactions of carbonyl compounds and cyclic ethers with organometallic reagents.* Such reactions of aldehydes, ketones, esters, oxirans, and oxetans represent the classical constructional (carbon–carbon bond forming) approach to the synthesis of alcohols. Uses

of the familiar organometallic reagents are described here, and those of organoboranes are included in the following section.

Despite the increasingly adventurous exploitation of the Periodic Table by organic chemists,[67] the inestimable Grignard reagents and the organolithiums remain pre-eminent for general-purpose syntheses of both saturated and unsaturated alcohols. The standard Grignard routes (equations 65–68) have long been known,[68] and the emphasis in recent

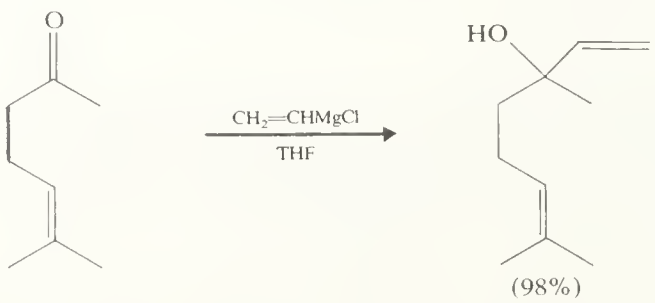
$$R^1COR^2 \xrightarrow{R^3MgX} R^1R^2R^3COH \quad (65)$$

$$\underset{n = 2 \text{ or } 3}{\text{cyclic ether } (CH_2)_n} \xrightarrow{R^1MgX} R^1(CH_2)_nOH \quad (66)$$

$$R^1CO_2R^2 \xrightarrow{R^3MgX} R^1R^3_2COH \quad (67)$$

$$CO(OR^1)_2 \xrightarrow{R^2MgX} R^2_3COH \quad (68)$$

years has been on mechanistic aspects of the reactions, particularly on the stereochemistry of addition to cycloalkanones.[69] The yields of adduct alcohols are generally good, except when competing reactions — mainly reduction and enolization — are promoted by steric hindrance to addition. Even then, the ratio of addition to reduction products can often be improved by the addition to the Grignard reagent of certain salts, *e.g.* $MgBr_2$, $LiClO_4$, Bu^n_4NCl.[70] The advent of vinylic Grignard reagents[68b] has provided a good route to allylic alcohols (equation 69), and the alkynic reagents avoid the strongly basic conditions of the



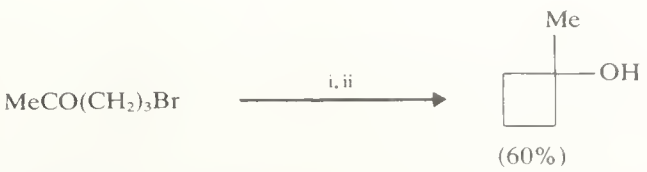
(98%) (69)

Nef and Favorskii methods for the preparation of α-alkynic alcohols. Allylic Grignard reagents are extremely reactive, but complications of alternative, mixed or even equilibrated products can arise.[71] For example, the normal preference for the formation of the *transposed* homoallylic alcohol (**50**) can be reversed if the carbonyl group is sufficiently crowded (equation 70). Similar considerations apply to the use of other allylic organometallic reagents,[72] though the reactions of allylic silanes catalysed by Lewis acids are claimed[73] to be regioselective for the formation of alcohol (**50**).

$$R^1COR^2 + R^3CH{=}CHCH_2MgBr \longrightarrow \underset{\textbf{(50)}}{R^1R^2C(OH)CHR^3CH{=}CH_2} + \underset{\textbf{(51)}}{R^3CH{=}CHCH_2C(OH)R^1R^2} \quad (70)$$

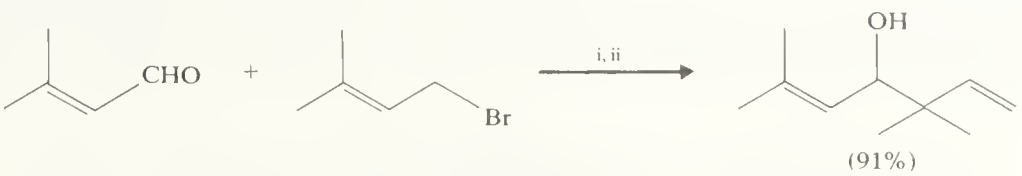
	Product ratio	
	(50)	**(51)**
$R^1 = Pr^i$, $R^2 = Et$, $R^3 = Me$	19 :	1
$R^1 = R^2 = Pr^i$, $R^3 = Bu^t$	1 :	100

Apart from special applications, *e.g.* equation (71), the synthesis of homoallylic alcohols from allylic halides has been one of the main uses of the one-step Barbier alternative to the Grignard reaction,[74] and interest in analogous one-step reactions with other metals (Li, Ca, Zn) has recently been heightened. Excellent yields can be obtained in Reformatsky-type reactions with a continuous-flow technique,[75] *e.g.* in the synthesis of racemic artemisia alcohol (equation 72), while one-step reactions with lithium often compare favourably with the corresponding Grignard syntheses.[76] The general advantages of organolithiums over organomagnesiums include a greater ability to react with hindered carbonyl compounds (equation 73), an improved ratio of addition to reduction products, and less tendency for conjugate addition to 2-enones.[77] Monolithium acetylide, often stabilized as the complex with 1,2-diaminoethane, and other lithium alkynylides often give superior yields of α- and β-alkynic alcohols, in comparison with sodium salts, in reactions with carbonyl compounds and oxirans, respectively.[78] Stabilization by an amine is unnecessary when monolithium acetylide is generated at low temperature in THF (equation 74).



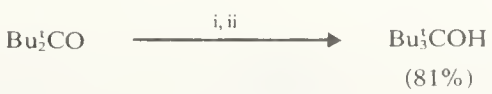
(71)

i, Mg, THF; ii, H_3O^+.



(72)

i, Zn, THF, reflux; ii, H_3O^+.



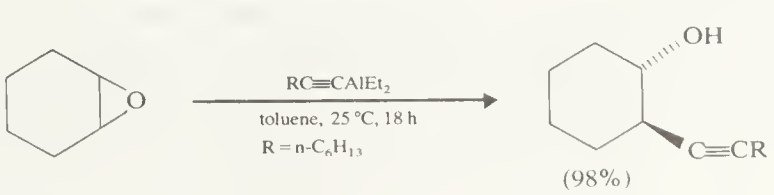
(73)

i, Bu^{t}Li, Et_2O, −70 °C; ii, H_2O.

(74)

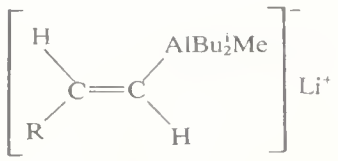
i, HC≡CLi, THF, −78 °C; ii, H_2O.

Although the reactions of aluminium alkyls — and other organometallic reagents — with carbonyl compounds[69] and oxirans[79] have been studied extensively in recent years, they have yet to secure general preferential acceptance: reduction often outweighs addition for reagents containing β-hydrogen. Recent examples of useful and distinctive applications[80] include very mild alkynylations, *e.g.* equation (75), and specific alkenylations using the readily accessible vinylic alanes (*e.g.* from hydroalumination of alkynes).



(75)

For the best results, the vinylic alanes are converted into the more nucleophilic 'ate' complexes, *e.g.* (**52**), as in equation (76). Other recent studies[81] have shown that the addition reactions of simple alanes and the derived alanates are strongly catalysed by nickel(II) compounds.

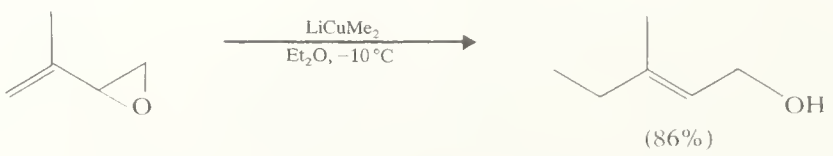


(**52**)

$$n\text{-}C_4H_9C{\equiv}CH \xrightarrow{\text{i, ii, iii}} n\text{-}C_4H_9CH{=}CHCH_2OH \quad (E)\ (73\%) \qquad (76)$$

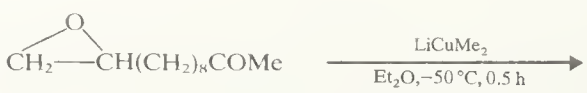
i, Bu^i_2AlH; ii, MeLi; iii, HCHO.

The copper(I) catalysed addition reactions of organometallic reagents and the analogous stoichiometric reactions of organocuprates are widely used for conjugate addition to 2-enones. The corresponding reactions of α,β-unsaturated oxirans provide a stereoselective route to allylic alcohols (equation 77),[82] and an efficient preparation of α-allenic alcohols (equation 78).[82b] Among saturated compounds, oxirans[82a] and aldehydes[83] react much more readily than ketones and esters, thus permitting chemo- and regio-selective additions (equation 79). On the other hand, the dilithium trialkylcuprates add to cyclohexanones readily and with exceptional stereoselectivity (equation 80).[84a] In contrast to these reagents, the corresponding trialkynylcuprates give 1,2-addition products with conjugated enones in the presence of HMPT.[84b]

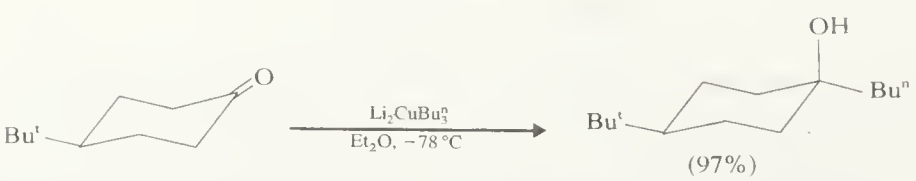


(86%) (77)

(>90%) (78)



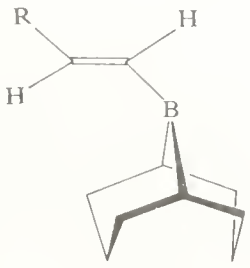
(68%) (79)



(97%) (80)

(g) *Constructional reactions of organoboron compounds.* The proliferation of synthetic applications of organoborane chemistry is a phenomenon of the last decade. Here, the account is restricted to carbon–carbon bond-forming reactions directed specifically to the synthesis of alcohols. For methods of construction and other manipulations of organoboranes, one of the excellent recent reviews[85] or monographs[38b,86] should be consulted.

As electrophiles, the organoboranes do not readily participate in nucleophilic addition reactions with carbonyl compounds or oxirans. Exceptions to this generalization are the allylic boranes, which resemble conventional organometallic reagents,[87] and the *B*-alkenyl derivatives (**53**) of 9-BBN (**34**) (see Ref. 88). The reactions of (**53**) with aldehydes are slow but occur without *cis–trans* isomerization (equation 81). The mildness of 9-BBN as a



(**53**)

$$\text{PhCHO} \xrightarrow{\text{i, ii}} \underset{(E)\ (86\%)}{\text{Bu}^{n}\text{CH=CHCHPhOH}} \qquad (81)$$

i, (**53**; R = Bu^{n}), THF; ii, NaOH, H_2O_2.

reductant means that various functional groups can be tolerated in the preparation of (**53**) by hydroboration of substituted alkynes, and therefore offers an advantage over the related hydroalumination sequence (equation 76). Like other organometallic reagents, simple trialkylboranes react with α,β-unsaturated oxirans to give allylic or α-allenic alcohols, *e.g.* equation (82), but by an oxygen-induced radical chain mechanism. Few

$$\text{Et}_3\text{B} + \text{HC}\equiv\text{CCMe}(\text{O})\text{CH}_2 \xrightarrow{\text{i, ii}} \underset{(47\%)}{\text{EtCH=C=CMeCH}_2\text{OH}} \qquad (82)$$

i, O_2 (catalytic), benzene; ii, NaOH, H_2O_2.

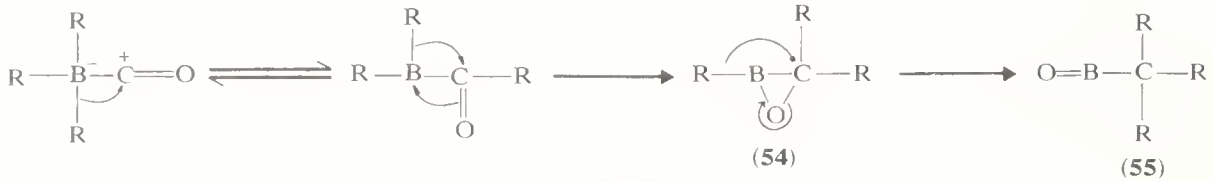
studies of the addition reaction of ketones with saturated 'ate' complexes (*e.g.* $LiBMe_4$) have been made, but such reagents seem to have no particular applications; the more complex reactions of unsaturated borates with carbonyl compounds and oxirans are discussed below and in Section 4.1.2.3.

The most distinctive and useful reactions of organoboranes and organoborates are those in which the 1,2-migration of a group from boron to carbon takes place, and is followed by oxidation or hydrolysis of the product. Several complementary methods — involving carbonylation, cyanidation, or carbenoidation — are available for the synthesis of tertiary alcohols with migration of all three groups of the original organoborane (equation 83). Carbonylation (equation 84)[89] requires fairly vigorous but neutral conditions (100–125 °C), and is often done in the presence of ethane-1,2-diol to convert (see Scheme 3) the rearranged product (**55**) into the cyclic boronate ester, thereby facilitating the final oxidation.

$$\text{R}^1\text{R}^2\text{R}^3\text{B} \xrightarrow[(84),\ (85),\ \text{or}\ (86)]{\text{as equation}} \text{R}^1\text{R}^2\text{R}^3\text{COH} \qquad (83)$$

$$\text{Bu}^{s}_2\text{Bu}^{t}\text{B} \xrightarrow{\text{i, ii}} \underset{(81\%)}{\text{Bu}^{s}_2\text{Bu}^{t}\text{COH}} \qquad (84)$$

i, CO, $HOCH_2CH_2OH$; ii, NaOH, H_2O_2.



(54) (55)

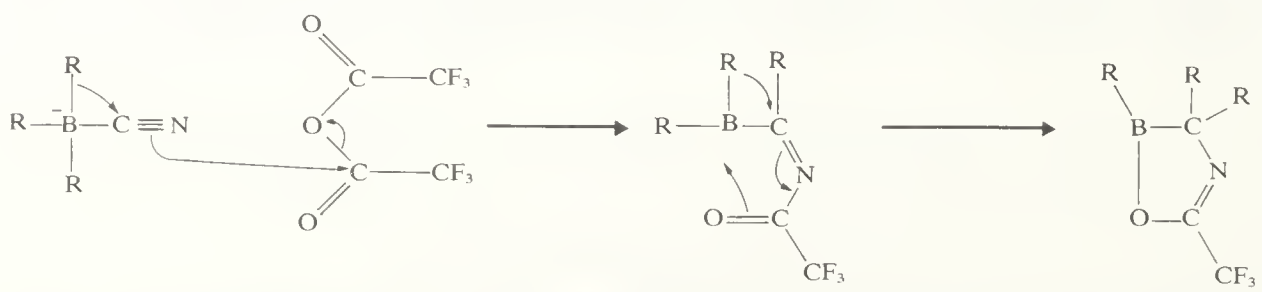
SCHEME 3

In the presence of water, hydration of (**54**) retards the final migration and allows the secondary alcohol to be obtained by alkaline hydrolysis. A further modification to the reaction[89] provides the primary alcohol corresponding to a single migration: this is useful for alcohol homologation *via B*-alkyl derivatives of 9-BBN with which the alkyl group migrates preferentially during carbonylation. In the cyanidation method (equation 85),[90]

$$(n\text{-}C_6H_{13})_3B \xrightarrow{\text{i, ii, iii}} (n\text{-}C_6H_{13})_3COH \quad (86\%) \qquad (85)$$

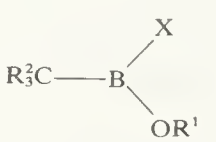
i, KCN, THF; ii, $(CF_3CO)_2CO$; iii, NaOH, H_2O_2.

migrations are induced by treating a trialkylcyanoborate with the electrophile trifluoroacetic anhydride (Scheme 4). With suitable compounds and solvents (*e.g.* tri-s-alkylcyanoborates in diethyl ether), the third migration (not shown in the scheme) can be



SCHEME 4

avoided. The third route to trialkylmethanols (*via* 'carbenoidation') involves reaction of the organoborane with either a polyhalogenomethane (notably $CHClF_2$) or dichloromethyl methyl ether, in the presence of a hindered alkoxide ($LiOCEt_3$).[91] The latter combination is the better with hindered organoboranes, as it produces the more readily oxidized intermediate, *i.e.* (**56a**) rather than (**56b**). It appears to be the method of choice for base-stable compounds (equation 86).



(**56**) a; X = Cl, R^1 = Me
b; X = F, R^1 = CEt_3

$$Bu^s_3B \xrightarrow{\text{i, ii}} Bu^s_3COH \quad (95\%) \qquad (86)$$

i, $CHCl_2OMe$, $LiOCEt_3$, THF; ii, NaOH, H_2O_2.

$$R^1_3B + Li^+ {}^-CR^2(SPh)_2 \longrightarrow [R^1_3BCR^2(SPh)_2]^- Li^+ \longrightarrow R^1_2BCR^1R^2(SPh)$$

(57)

$$\xrightarrow[(EX)]{\text{electrophile}} R^1BXCR^1_2R^2$$

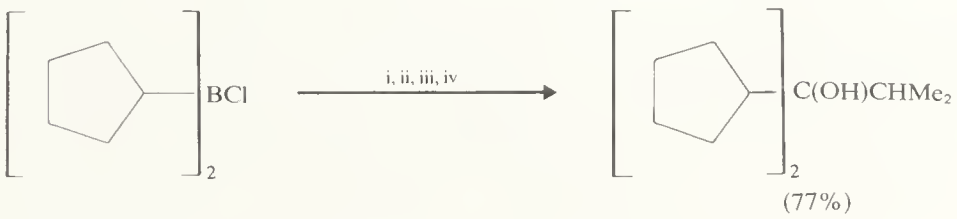
SCHEME 5

Other organoborane reactions provide wider access to constitutionally unsymmetrical trialkylmethanols. One approach[92] (Scheme 5 and equation 87) has been to react a constitutionally symmetrical trialkylborane with a 1-lithio-1,1-bis(phenylthio)alkane (**57**); the first migration accompanying loss of LiSPh is spontaneous, the second is provoked by using mercury(II) chloride as the electrophile. With (**57**; $R^2 = H$) the product is the

$$(n\text{-}C_8H_{17})_3B \xrightarrow{\text{i, ii, iii}} (n\text{-}C_8H_{17})_2Pr^nCOH \quad (90\%) \qquad (87)$$

i, (**57**; $R = Pr^n$), THF; ii, $HgCl_2$; iii, NaOH, H_2O_2.

constitutionally symmetrical secondary alcohol. A second approach, which avoids the waste of a borane alkyl, involves reaction between a dialkylchloroborane and a lithium aldimine (**58**), the adduct formed by t-butyl isocyanide and a lithium alkyl.[93] Alkyl migrations are induced by successive treatments of the product (**59**) with thioglycolic acid and alkali (equation 88).



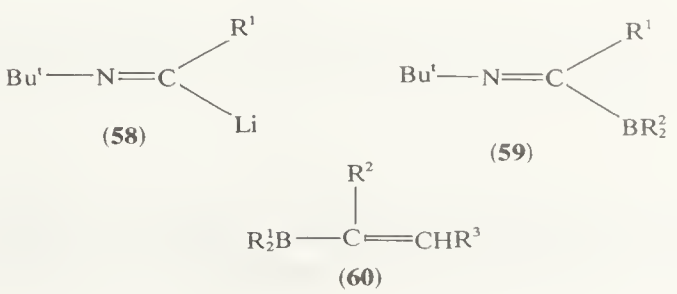
(77%) (88)

i, (**58**; $R^1 = Pr^i$); ii, $HSCH_2CO_2H$; iii, NaOH, diglyme; iv, NaOH, H_2O_2.

Single or double migrations can be achieved with α,β-unsaturated borates. The treatment of lithium trialkylalkynylborates with excess of acid, followed by the usual oxidation, leads to tertiary alcohols (equation 89).[94] Products containing three different groups can be obtained by similar treatment of a vinylic borane (**60**), analogous to the reaction

$$Bu^n_3\bar{B}C{\equiv}CH\ Li^+ \xrightarrow{\text{i, ii}} Bu^n_2MeCOH \quad (82\%) \qquad (89)$$

i, HCl, H_2O, THF; ii, NaOH, H_2O_2.



intermediate. For secondary alcohols it is necessary to convert (**60**; $R^2 = H$) into the borate to effect migration by protonation.[95] Methyl-lithium is suitable for this purpose, as methyl has a relatively low migratory amplitude (equation 90). The formation of dialkylmethylmethanols is also observed when a trialkylborane is reacted with 1-methoxyvinyllithium, followed by treatment of the products with acid, and oxidation.[96]

$$R^1_3B-\underset{\displaystyle R^2}{\underset{|}{C}}=CHR^3 \xrightarrow{\text{i, ii, iii}} R^1CH(OH)CH_2R^3 \qquad (90)$$

R^1 = cyclohexyl, $R^2 = H$, $R^3 = Bu^n$ (69%)

i, MeLi; ii, HCl, Et_2O; iii, NaOH, H_2O_2.

Trialkylalkynylborates will also undergo regio- and stereo-selective reactions with oxirans[97] to give γ-keto alcohols (by oxidative work-up) or homoallylic alcohols (by protonolysis of the rearranged adducts). The sense of stereoselectivity varies with the solvent (equation 91).

$$Bu^s_3\bar{B}C{\equiv}CMe\ Li^+ \xrightarrow{\text{i or ii, iii}} Bu^nCH{=}CMeCH_2CH_2OH \qquad (91)$$

	Total yield	*(E) : (Z) ratio*
i	62%	8 : 92
ii	72%	60 : 40

i,  in CH_2Cl_2; ii,  in THF-hexane; iii, AcOH

A further reaction sequence, α-bromination–oxidation, permits a different assembly of the groups in a trialkylborane.[98] Controlled photochemical bromination — usually with Br_2 or *N*-bromosuccinimide — in the presence of water induces rapid migration(s) of groups to the α-position(s) (Scheme 6). The sequence lends itself to the synthesis of highly branched alcohols (equation 92), and its variations include the use of dialkylborinic acids analogous to (**61**) (prepared *via* hydroborations with monochloroborane, followed by hydrolysis), and the use of mixed trialkylboranes containing a non-migrating group.

$$Et_3B \xrightarrow{Br_2,\ h\nu} Et_2BCHBrMe \xrightarrow{H_2O} EtB(OH)CHMeEt$$

(61)

$$\xrightarrow{Br_2,\ h\nu} EtB(OH)CBrMeEt \xrightarrow{H_2O} (HO)_2BCMeEt_2$$

SCHEME 6

$$Bu^sB \xrightarrow[CH_2Cl_2,\ H_2O]{Br_2,\ h\nu} CHMeEtCMeEtCMeEtOH \qquad (92)$$

(46%)

(ii) Specific methods

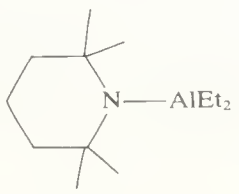
The intention here is to present a *selection* of reactions directed to the synthesis of particular *classes* of alcohols. In general, the selection is based on hydroxyl-forming reactions, rather than on the generation of other structural features.

(a) Unsaturated alcohols. Several indirect methods for allylic oxidation have recently been developed. The base-catalysed rearrangement of simple oxirans[99] involves *syn* elimination with attack at the least-substituted β-carbon and formation of the (*E*)-alkenol

(equation 93). The behaviour of various alicyclic and substituted oxirans has been established, notably by Rickborn's group.[99b] The rearrangement is usually effected with

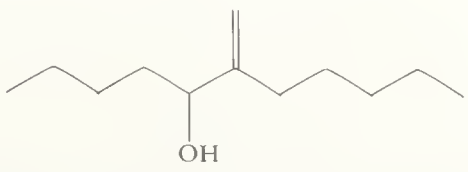
(93)

the weakly nucleophilic lithium dialkylamides, but other bases [Bu^{t}OK, $(Pr^iO)_3Al$, (**62**)] and catalysts (Al_2O_3, lithium phosphates) have been used successfully. With the bulky dialkylamide (**62**) the 'normal' product (**64**) is obtained from (*Z*)-5,6-epoxy-6-methylundecane (**63**), whereas the 'abnormal' product (**65**) is obtained from the (*E*)-isomer.[100] Other novel syntheses exploit the facile and stereoselective fragmentation of

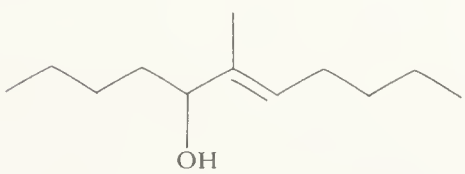


(**62**)

(**63**)

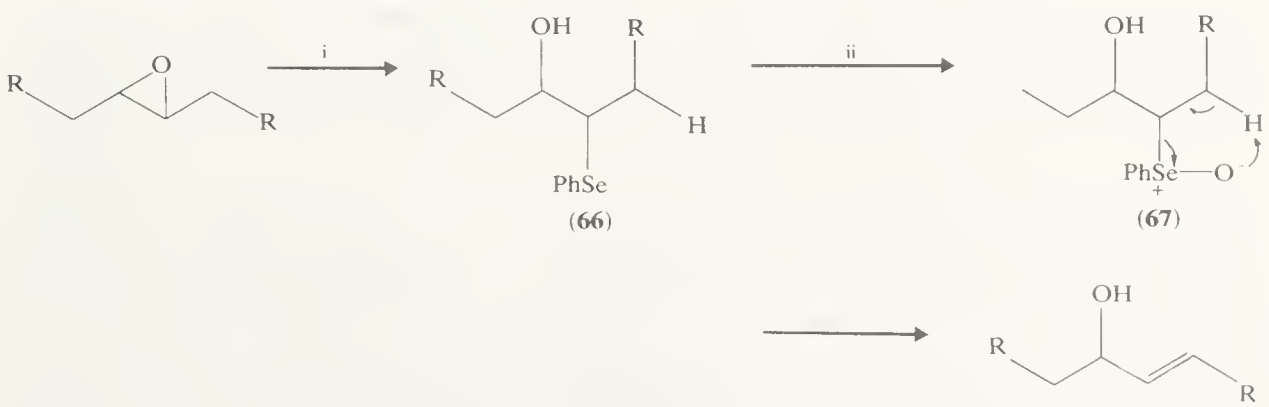


(**64**)



(**65**)

selenoxides, which also produces (*E*)-alcohols through *syn* elimination *away from* an existing β-hydroxy group. The Sharpless route[101a] from an oxiran is indicated in Scheme 7. The oxiran can be by-passed, for example by the addition of $PhSeOCOCF_3$ to the



i, PhSeNa, EtOH; ii, H_2O_2.

SCHEME 7

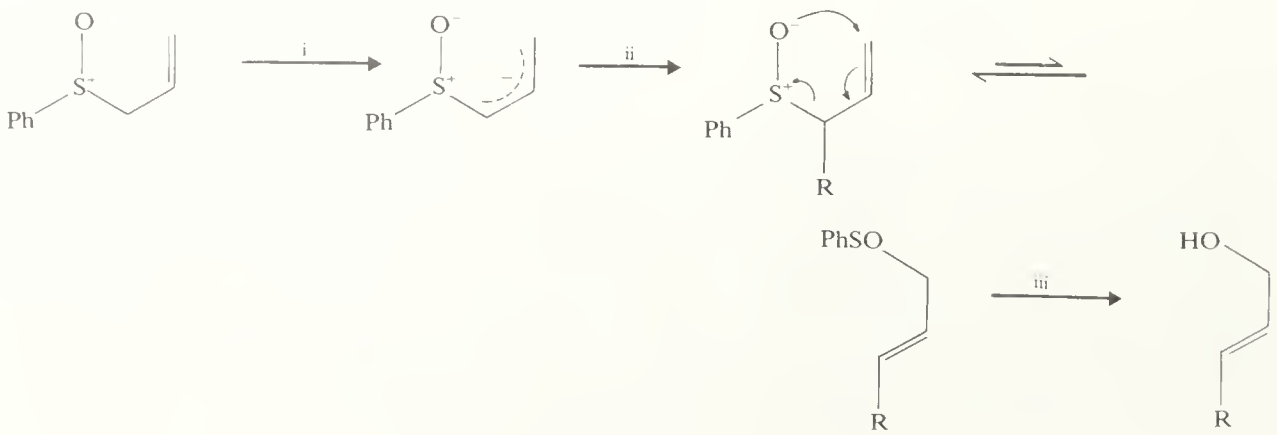
parent alkene, to give (**66**) on mild hydrolysis. Other routes[101b] to the β-hydroxyselenides (**66**) of defined structure involve the addition of an α-lithioselenide to a carbonyl compound (*e.g.* Scheme 8), or the reaction of an α-selenocarbonyl compound with

i, R^2SeH, H^+; ii, Bu^nLi; iii, R^3_2CO.

SCHEME 8

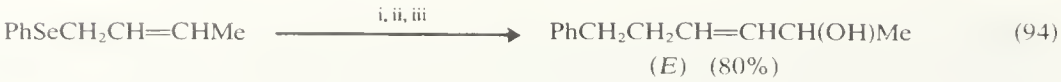
$LiAlH_4$ or a Grignard reagent. The unstable β-hydroxyselenoxides (**67**) can also be prepared[101c] by low-temperature oxidation and lithiation ($LiNPr^i_2$) of alkyl phenyl selenides, followed by the addition of a carbonyl compound.

Other stereoselective syntheses of allylic alcohols are based on [2,3]-sigmatropic rearrangements of allylic sulphoxides[102a] or selenoxides.[102b] The reaction sequence for sulphoxides which involves regioselective alkylation followed by trapping of the sulphenate with a suitable thiophile [$(MeO)_3P$ or Et_2NH] is shown in Scheme 9. The corresponding sequence for the more unstable selenoxides is indicated in equation (94). Established



i, $LiNPr^i_2$; ii, RX; iii, $(MeO)_3P$.

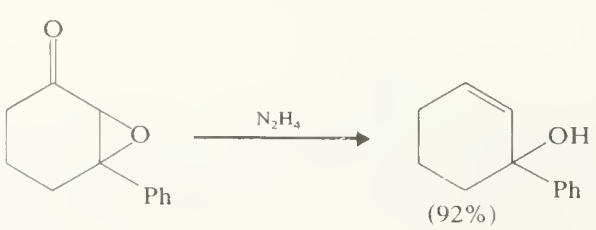
SCHEME 9



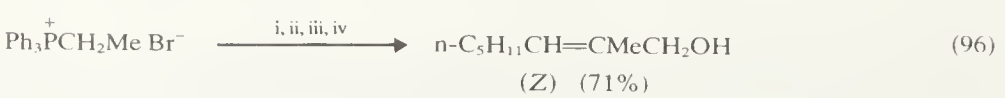
(94)

i, $LiNPr^i_2$, −78 °C; ii, $PhCH_2CH_2Br$, −78 °C; iii, H_2O_2, CH_2Cl_2, 25 °C.

routes to allylic alcohols discussed by House[47] are the hydrazine reduction of α,β-epoxy carbonyl compounds (equation 95), the 'scoopy' extension[103] of the Wittig reaction (equation 96), the forcing reduction of enolizable β-dicarbonyl compounds (equation 97),



(95)



(96)

i, Bu^nLi; ii, $n\text{-}C_5H_{11}CHO$; iii, Bu^nLi; iv, HCHO.

(83%) (97)

and the partial reduction (*e.g.* by catalytic hydrogenation or $LiAlH_4$) of α-alkynic alcohols. The latter compounds are also important as precursors of allenic alcohols; the conversions involved are described in Section 4.1.1.4 (p. 658), along with other addition and substitution reactions of unsaturated alcohols. Methods for the preparation of α-allenic alcohols have been reviewed by Huché[104], and the major methods for β-allenic alcohols have been listed.[105]

(*b*) *Halohydrins.* Methods for consideration here comprise the formal or actual addition of HOX to alkenes (Section 2.2.3.1) and of HX to oxirans (Section 4.4.4.2). Standard reagents for the preparation of chloro- and bromo-hydrins by the first method are extensively referenced by Rosowsky,[106] and are exemplified by equations (98) and (99).

$$PhCH{=}CH_2 \xrightarrow{Cl_2,\ H_2O,\ Me_2CO,\ Na_2CO_3} PhCH(OH)CH_2Cl \quad (72\%) \qquad (98)$$

$$\underset{(E)}{Bu^tCH{=}CHMe} \xrightarrow{\text{i, ii}} \underset{\textit{erythro}\ (90\%)}{Bu^tCHBrCH(OH)Me} \qquad (99)$$

i, *N*-bromosuccinimide, moist DMSO; ii, H_2O.

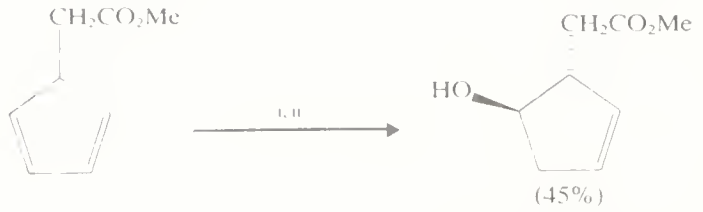
The relative neglect of iodohydrins has recently been remedied by the development of several efficient syntheses. They include the reaction of an alkene with iodine and water in the presence of a suitable oxidant (HIO_3 or O_2/HNO_2),[107a] or in tetramethylene sulphone–chloroform,[107b] or with iodine–silver(I) trifluoroacetate (Prévost addition) followed by neutral methanolysis of the iodotrifluoroacetate.[107c] The preparation of halohydrin esters is discussed further in Sections 4.1.2.3 (p. 666) and 4.1.2.4 (p. 684).

All classes of halohydrins can be prepared from oxirans by treatment with hydrogen halides or appropriate Lewis acids. The former reagents are usually preferred, although compounds such as BF_3 and $MgBr_2$ have advantages in certain cases. Iron(III) chloride in diethyl ether effectively converts some oxirans into chlorohydrins.[108]

(*iii*) *Asymmetric synthesis*

Useful reviews of this important topic range from the succinct[109a] to the expansive.[109b] Here the account is limited to the addition reactions of achiral alkenes and carbonyl compounds already described in Section 4.1.1.3 but using chiral reagents. For economy, reagents based on natural chiral compounds are the most generally useful for stoichiometric reactions, but catalysed reactions are less constrained in this way.

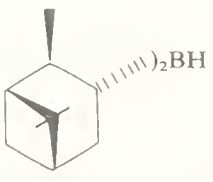
Asymmetric versions of hydroboration, oxymercuration, and hydroformylation of alkenes have all been explored, but the most impressive results come from the hydroboration of (*Z*)-alkenes with dialkylboranes derived from either enantiomer of α-pinene. Thus (−)-(*R*)-butan-2-ol can be obtained in 90% yield and 87% optical purity by the reaction of (*Z*)-but-2-ene with (−)-di-isopinocamphenylborane (**68**) in diglyme, followed by the usual oxidation. A further example involving the application of (**68**) to the synthesis of a prostaglandin intermediate is given in equation (100). By contrast, the optical purities of alcohols obtained by the hydroboration of terminal, hindered, and (*E*)-alkenes are only modest,[86] and the same applies to the products from the asymmetric oxymercuration of alkenes with mercury(II) tartrate or similar chiral salts.[110]



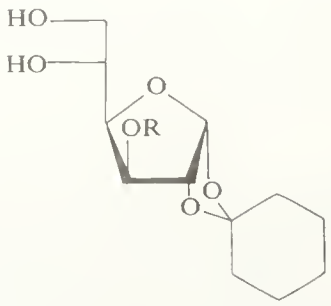
(100)

i, (**68**); ii, NaOH, H_2O_2.

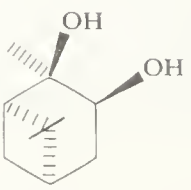
Despite much effort, the search for general-purpose reagents for the consistently efficient asymmetric reduction of carbonyl compounds has only been rewarded with partial successes. Among hydride reductants, the alkoxyhydridoaluminates prepared by treating $LiAlH_4$ with various chiral hydroxy compounds have been the most thoroughly studied. Suitable chiral compounds include the D-glucofuranose derivative (**69**), terpenoid alcohols and diols, *e.g.* (−)-menthol (**12**) or (−)-(*Z*)-pinane-2,3-diol (**70**), alkaloids, *e.g.* (−)-quinine, (−)-ephedrine, or (−)-*N*-methylephedrine (**71**), and other amino-alcohols and -diols, *e.g.* (**72**) or (**73**), and the 2-oxazoline (**74**). Reagents further modified by the



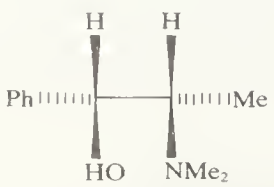
(**68**)



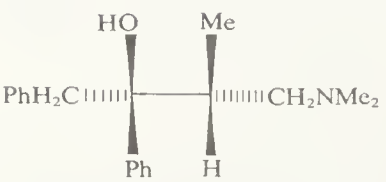
(**69**) R=$PhCH_2$



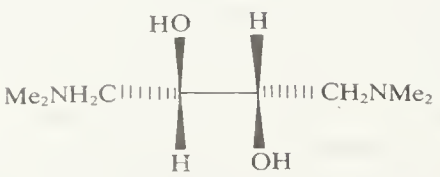
(**70**)



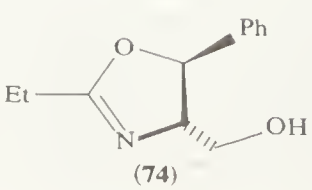
(**71**)



(**72**)



(**73**)



(**74**)

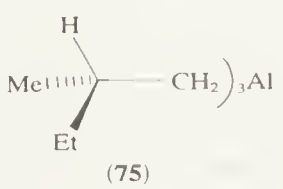
TABLE 6

Asymmetric Reduction of Simple Ketones ($PhCOR^1$ and $MeCOR^2$)

Method	*Reagent*	*Optical purity of alcohol (%)*[a] (R^1) Me	Et	(R^2) Et	Pr^i	Bu^t
Hydride reduction	$LiAlH_4$ + (**69**)[b]	34(*S*)	37(*S*)	—	—	2(*S*)
	$LiAlH_4$ + (**69**) + EtOH[c]	71(*R*)	46(*R*)	—	—	18(*R*)
	$LiAlH_4$ + (**71**) + 3,5-dimethylphenol[d]	84(R)	85(*R*)	14(*S*)	41(*S*)	21(*S*)
	$LiAlH_4$ + (**72**) (fresh)[e]	68(*R*)	—	—	—	28(*R*)
	$LiAlH_4$ + (**72**) (aged)[e]	62(*R*)	—	—	—	21(*S*)
	$LiAlH_4$ + (**73**)[f]	42(*S*)	44(*S*)	2(*S*)	—	12(*S*)
	$LiAlH_4$ + (**74**)[g]	65(*R*)	62(*R*)	—	—	—
	Reagent (**75**)[h]	6(*S*)	11(*S*)	5(*S*)	14(*S*)	17(*S*)
	Reagent (**76**)[i]	85(*S*)	—	—	—	23(*S*)
	Reagent (**48**)[j]	27(*R*)	38(*R*)	3(*R*)	15(*R*)	18(*R*)
	Reagent (**68**)[k]	14(*R*)	—	11(*R*)	17(*R*)	30(*S*)
Catalytic hydrogenation	Catalyst (**77**; L^1 = cod, L_2^2 = **78**)[l]	43(*R*)	31(*R*)	—	—	43(*R*)
Catalytic hydrosilylation	Catalyst (**81**) + (**82**); Ph_2SiH_2[m]	44(*R*)	52(*R*)	25(*R*)	31(*R*)	35(*R*)

[a] Configuration of major enantiomer in parentheses. [b] S. R. Landor, B. J. Miller, and A. R. Tatchell, *J. Chem. Soc.* (*C*), 1966, 2280. [c] S. R. Landor, B. J. Miller, and A. R. Tatchell, *J. Chem. Soc.* (*C*), 1967, 197. [d] J. P. Vigneron and I. Jacquet, *Tetrahedron*, 1976, **32**, 939. [e] S. Yamaguchi and H. S. Mosher, *J. Org. Chem.*, 1973, **38**, 1870. [f] D. Seebach and H. Daum, *Chem. Ber.*, 1974, **107**, 1748. [g] A. I. Meyers and E. D. Mihelich, *Angew. Chem. Internat. Edn.*, 1976, **15**, 270. [h] G. Giacomelli, R. Menicagli, and L. Lardicci, *J. Org. Chem.*, 1974, **39**, 1757. [i] G. M. Giongo, F. Di Grègorio, N. Palladino, and W. Marconi, *Tetrahedron Letters*, 1973, 3195. [j] D. Nasipuri, G. Sarkar, and C. K. Ghosh, *Tetrahedron Letters*, 1967, 5189. [k] H. C. Brown and D. B. Bigley, *J. Amer. Chem. Soc.*, 1961, **83**, 3166. [l] T. Hayashi, T. Mise, and M. Kumada, *Tetrahedron Letters*, 1976, 4351. [m] Ref. 117e.

introduction of achiral alkoxy or aryloxy groups (effectively causing the use of a different hydrogen in the reduction) can also be used to good effect; Table 6 gives a selection of the best results from reductions of some simple ketones. The optimization of optical purity usually requires the careful tailoring of the reagent (*e.g.* its composition, method of preparation, and method of use) and the experimental conditions (*e.g.* the choice of solvent, temperature, absolute, and relative concentrations of reactants) for the particular substrate. There are even instances of the reversal of enantioselectivity during the 'aging' of reagents (see Table 6). At present, the most promising reagents appear to be those based on *N*-methylephedrine. Derived quaternary ammonium salts have also been used[111] as phase-transfer catalysts for asymmetric reductions with $NaBH_4$, but with relatively low enantioselectivity. There is also interest in other chiral hydride reductants, including the dialkylborane (**68**), complexes of borane with chiral amines or amino-esters,[112] the organoalanes (**75**) and (**76**), Meerwein–Ponndorf–Verley-type reagents such as (**48**), and



(**75**)

(−)-PhCHMeNMeAlH$_2$

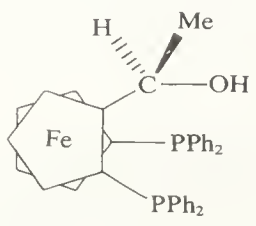
(**76**)

chiral Grignard reagents. The reactions are discussed in detail by Morrison and Mosher,[109b] and specimen results for some reagents are included in Table 6.

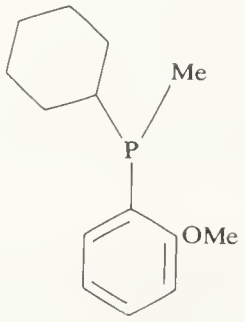
Catalysed reactions of preparative potential are the reductions effected with micro-organisms or isolated enzymes,[113] insoluble catalysts such as Raney nickel modified by various chiral additives,[114] and soluble chiral complexes of transition metals, notably rhodium.[115] The latter have attracted much attention for asymmetric hydrogenation, hydrosilylation, and also hydroformylation. Asymmetry is induced by the presence in the catalyst of a suitable phosphine, chiral at either carbon or phosphorus. For direct hydrogenation, cationic rhodium(I) complexes of the general structure (**77**) have generally been used as catalyst precursors. The complex (**77**; $L^1 = cod$, $L_2^2 = $ **78**) shows both good catalytic activity and useful enantioselectivity (Table 6), and encouraging results have also been obtained with non-cationic complexes.[116] Complexes of the latter type are particularly useful for asymmetric hydrosilylation,[117] although similar platinum(II) complexes[118] and cationic rhodium(I) complexes[117d] have also been applied. Results for individual ketones vary widely with the choice of catalyst and silane, but those (Table 6) obtained by using diphenylsilane and a non-cationic catalyst prepared from (**81**) and the diop analogue (**82**) are fairly representative. With disubstituted silanes, conjugated enones undergo 1,2-addition[119] leading to asymmetric allylic alcohols (equation 101), while the recovery of the catalyst from the reaction products is simplified by supporting it on an insoluble polymer.[117c]

$$[RhL^1L_2^2]^+ X^-$$

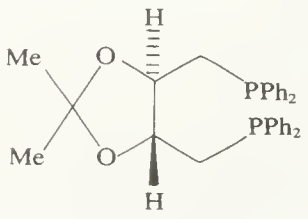
(**77**) *e.g.* L^1 = cyclo-octa-1,5-diene (cod) or norborna-2,5-diene (nbd)
$L_2^2 = [(PhCH_2)PhMeP]_2$, (**78**), $(\mathbf{79})_2$, or (**80**) (diop)
$X = ClO_4$ or BF_4



(**78**)



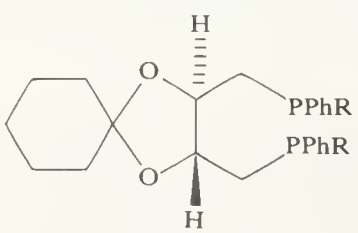
(**79**)



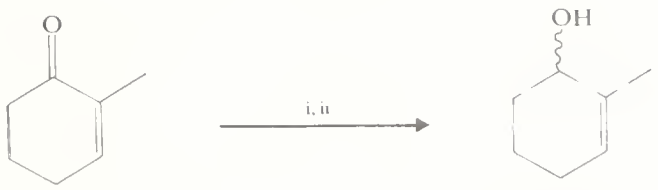
(**80**)

$[Rh(C_2H_4)_2Cl]_2$

(**81**)



(**82**) R=cyclohexyl



(82%)
(Optical purity 43%)

(101)

i, α-naphthylphenylsilane, catalyst from $[Rh(cod)Cl]_2$ and chiral $(PhCH_2)PhMeP$; ii. MeOH, K_2CO_3.

The extent of asymmetric induction in reactions between achiral carbonyl compounds and organometallic reagents in the presence of chiral solvents is generally low.[109b] Rather better results have been obtained by the use of complexing chiral additives. Examples are Grignard additions in the presence of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (optical purities of products mostly about 25%, but rising to 70%)[109a] or the 2-methyl analogue of the oxazoline (**74**) (optical purities 9–25%),[120] and alkylations using $LiAlBu^n_4$ treated with *N*-methylephedrine (optical purities 8–31%).[121]

4.1.1.4 Reactions

(*i*) *General aspects*

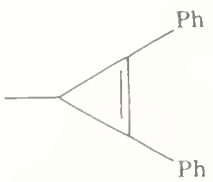
The functional group organization of these volumes and of the preparative methods described in Section 4.1.1.3 invites a similar approach to the treatment of the reactions of alcohols. The major reactions involving only the hydroxy group can be categorized according to whether the product corresponds to formal O—H or C—O bond fission (p. 619 and 629, respectively). The additional involvement of C—H bond fission brings in dehydration (β-hydrogen, p. 640), oxidation (α-hydrogen, p. 644), and oxidative cyclization (mainly δ-hydrogen, p. 653). The latter reaction leads naturally to the consideration of examples of remote functionalization in which the hydroxy group is retained (p. 655). The remaining sections are devoted to special topics.

Two of the disadvantages of this formalized 'practical' approach, with the emphasis on reaction products, are the necessary limitation of systematic coverage to major functional groups, and the dispersal of mechanistically related reactions. Some general comments on hydroxyl reactions and reactivities, and on unifying mechanistic features, are therefore appropriate at this point.

The O—H bond in an alcohol is rather strong, albeit polar and kinetically labile. The values for the homolytic bond dissociation energies ($D°$) for the C_1 to C_4 alkanols lie in the range 427–436 kJ mol^{-1}. The homolytic abstraction of hydroxyl hydrogen by radicals is unusual for primary and secondary alcohols in *solution*, attack at the α-carbon generally being preferred. On the other hand, deprotonation with the formation of an alkoxide is readily achieved by treating an alcohol with a strongly electropositive metal or a powerful base. Reactivity decreases from primary to tertiary alcohols in accord with the order of liquid-phase acidities (Table 4). Heterolysis of the O—H bond also follows electrophilic attack on hydroxyl oxygen, *e.g.* in the alkylation and acylation of alcohols. Because of the high electronegativity and low polarizability of oxygen, alcohols are only weak and relatively hard bases (Table 4) and only moderately reactive as nucleophiles. Their addition reactions with unsaturated compounds usually require catalysis or the use of activated substrates. Alcohols themselves may be activated as nucleophiles by (a) conversion to alkoxides, or (b) replacement of the hydroxyl hydrogen by an electropositive or electron-releasing group. The first approach is commonly applied, *e.g.* in nucleophilic substitutions of alkyl halides, in nucleophilic (Michael) addition to activated alkenes, and in nucleophilic addition–elimination transesterification reactions. The second, less common approach employing a covalent derivative ROX, in which X is readily lost as X^+,

avoids strongly basic reaction conditions. Examples of such derivatives applied to the synthesis of glycosides by nucleophilic substitution on acylated glycosyl halides[122] are indicated by (**83**).

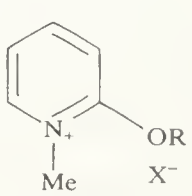
ROX
(**83**) *e.g.* X = CMe_3, CPh_3, $SiMe_3$, $SnBu^n_3$, $CH(OR)NMe_2$ or



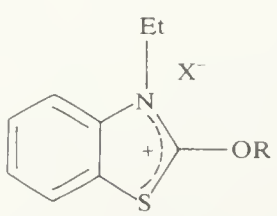
The values of $D°$(C—O) for primary, secondary, and tertiary alkanols are very similar (380–385 kJ mol^{-1}), but significantly greater than the values for alcohols giving mesomeric radicals (*e.g.* allyl, 330 kJ mol^{-1}; triphenylmethyl, 280 kJ mol^{-1}). Direct fission of these relatively weak C—O bonds is rather easy (*e.g.* deoxygenation, p. 629). However, the displacement of hydroxyl by nucleophilic attack at the α-carbon normally requires its conversion into a group with better leaving properties. Such activation, involving the weakening and further polarization of the C—O bond, can be achieved by the simple expedient of protonation (applicable when the attacking nucleophile is a weak base). More generally, classical derivatives of the type (**84**) (complementary to those (**83**) used to activate alcohols as nucleophiles) open the way to a wide range of substitution reactions comparable with those of alkyl halides (Chapter 3.3). The concept of activation is more diversely exemplified later, mainly with reaction intermediates rather than isolated derivatives. Synthetic versatility has been demonstrated for several such intermediates, including alkoxyphosphonium salts (**85**), 2-alkoxy-*N*-methylpyridinium salts (**86**), and 2-alkoxy-*N*-ethylbenzothiazolium salts (**87**). The heterocyclic intermediates, explored by Mukaiyama's

ROY
(**84**) *e.g.* Y = tosyl or mesyl

$R^1_3\overset{+}{P}OR^2\ X^-$
(**85**) a, $R^1 = Ph$
b, $R^1 = Me_2N$

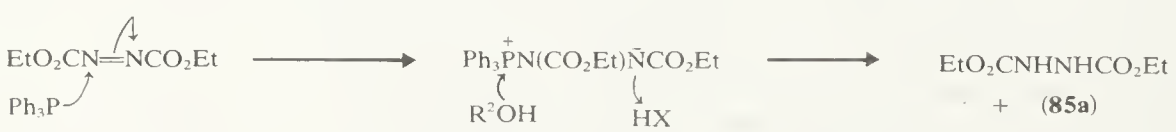


(**86**)

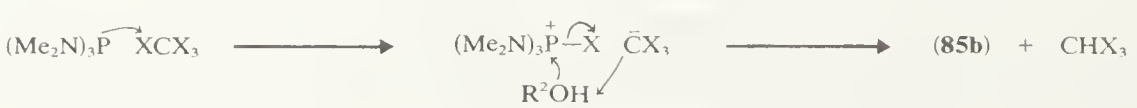


(**87**)

group,[123] are readily prepared from the corresponding 2-chloro or 2-fluoro compounds, while important examples of reactions thought to proceed *via* (**85**) are those induced by diethyl azodicarboxylate and triphenylphosphine[124] (Scheme 10), or tetrachloromethane and a similar phosphine[125] (Scheme 11).



SCHEME 10



SCHEME 11

(*ii*) *Products formally corresponding to O—H bond fission*

(*a*) *Alkoxides.* These compounds are important both as reactants (nucleophiles) and as reagents (mainly as bases). Reviews of their general chemistry[126] and of their nucleophilic reactions[127] are available. As bases, the most useful compounds are those derived from the lower alcohols and alkali metals (Li, Na, K), usually by direct reaction with the metal or its hydride. With the relatively unreactive tertiary alcohols, KH is particularly effective.[128] Tertiary alkoxides combine high basicity with relatively low nucleophilicity, which favours their use for reactions such as dehydrohalogenation. Other advantages of Bu^{t}OK include the commercial availability of the solid and its high solubility in THF.[129] For many purposes, alkoxides are used as solutions in the parent alcohols, in which there is extensive association (ion pairs, their aggregates, and solvates), with consequential impairment of basicity. This effect can be countered by the choice of a dipolar aprotic solvent, notably DMSO, or a highly hindered tri-s-alkylmethoxide.[130]

Among other metal alkoxides, $(Pr^iO)_3Al$ and $(Bu^tO)_3Al$ are the classical reagents for the Meerwein–Ponndorf–Verley reduction (Table 5, p. 597) and the Oppenauer oxidation (Table 8, p. 644). The reactions of copper(I) alkoxides have recently been studied.[131]

(*b*) *Hypohalites.* The major developments in the chemistry of alkyl hypohalites that have occurred since the appearance of general reviews[132] have been discussed for both hypofluorites[133a] and hypobromites.[133b] In general, hypohalites are unstable compounds and are usually formed and used *in situ* (tertiary hypochlorites excepted). The major reagent in the class, Bu^{t}OCl, is most safely and conveniently prepared[134] by treating Bu^{t}OH with aqueous NaOCl in the absence of direct light (equation 102). The reaction is

$$Bu^tOH \xrightarrow{NaOCl,\ AcOH,\ <10\,^\circ C} Bu^tOCl \quad (80\%) \qquad (102)$$

also applicable to primary and secondary alcohols in inert solvents (CH_2Cl_2, CCl_4, benzene, cyclohexane), and can be adapted for the preparation of hypobromites. Mercury(II) oxide–halogen reagents are convenient and effective for the conversion of alcohols to both hypobromites and hypoiodites. The simplest and most important hypofluorite, CF_3OF, is prepared by the action of fluorine in the presence of silver(II) fluoride on CO, COF_2, MeOH, or KNCO, and is commercially available.

The weak O—X bond in hypohalites readily undergoes homolysis, which makes the compounds important for the study of alkoxy radicals,[135] and for radical halogenations.[47,136] The value of Bu^{t}OCl for stereoretentive allylic chlorinations, *e.g.* equation (103), is based partly on the marked preference of Bu^{t}O·, the main chain carrier, for hydrogen abstraction rather than radical addition.

$$\underset{(E)}{Bu^tCH{=}CHMe} \xrightarrow{Bu^tOCl,\ h\nu} \underset{(E)}{Bu^tCH{=}CHCH_2Cl} + Bu^tCHClCH{=}CH_2 \qquad (103)$$

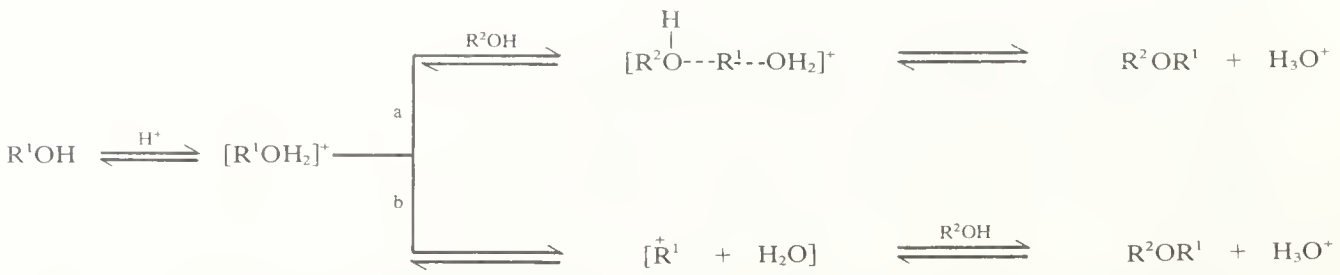
Product ratio: 93 7

In hydroxylic solvents, hypohalites can also serve as sources of 'positive halogen', giving electrophilic addition to alkenes and substitution of arenes. Such reactions[137] are usefully catalysed by BF_3 (equation 104). Electrophilic fluorinations by CF_3OF are described in Ref. 133a, and other applications of t-butyl hypohalites in Ref. 136b. The important intramolecular reactions of hypohalites are covered later (pp. 653 and 655).

$$Me_2C{=}CH_2 \xrightarrow[Pr^nOH]{Bu^tOCl,\ BF_3} Pr^nOCMe_2CH_2Cl \quad (67\%) \qquad (104)$$

(*c*) *Ethers.* Dialkyl ethers can be regarded as condensation products of alcohols, resulting from the respective C—O and O—H bond fission of two alcohol molecules. It is apparent from this concept that their synthesis can be achieved by the appropriate activation (p. 617) of either reactant or both, and most of the important routes to ethers from alcohols[24,138] reflect this rationale.

Classically, the alkylation of alcohols is realized in acid-catalysed etherification and in the Williamson synthesis. The former process is mainly suited to the synthesis of simple symmetrical primary and mixed primary–tertiary ethers. In general, the reaction conditions and pathway (S_N1 or S_N2 displacement of water from the oxonium cation, Scheme 12) depend on the ease of carbenium ion formation. Alkyl hydrogen sulphates may also



Path a, *e.g.* $R^1 = R^2$ = primary alkyl.
Path b, *e.g.* R^1 = tertiary alkyl, allyl, or benzyl, R^2 = primary or secondary alkyl.

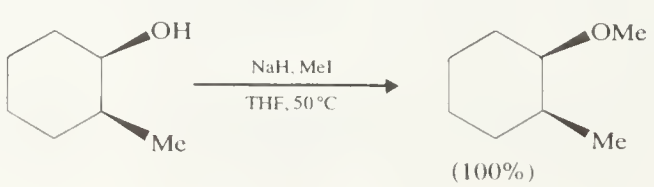
SCHEME 12

be intermediates in the self-condensation of primary alkanols catalysed by concentrated H_2SO_4 at temperatures (130–140 °C) somewhat lower than those used to effect intramolecular dehydration. Much milder conditions are possible and usually necessary to minimize dehydration and other side reactions for reactions involving the S_N1 mechanism, *e.g.* equations (105) and (106).

$$\text{Bu}^t\text{OH} + \underset{\text{(excess)}}{\text{EtOH}} \xrightarrow[70\,^\circ\text{C}]{15\%\ H_2SO_4} \underset{\text{(95\%)}}{\text{Bu}^t\text{OEt}} + H_2O \qquad (105)$$

$$\text{Ph}_3\text{COH} + \underset{\text{(excess)}}{\text{MeOH}} \xrightarrow[25\,^\circ\text{C}]{I_2} \underset{\text{(90\%)}}{\text{Ph}_3\text{COMe}} + H_2O \qquad (106)$$

The Williamson synthesis (the S_N2 reaction between an alkali metal alkoxide and an alkyl halide, sulphonate, or sulphate) and its numerous variants and relatives are of major importance. Many combinations of base, solvent, and alkylating agent have been used with success. The use of preformed alkoxide dissolved or suspended in the parent alcohol (for simple alkanols), an ether (diethyl ether, THF, or glyme), an aromatic hydrocarbon (benzene or toluene), a dipolar aprotic solvent (DMSO, DMF, or HMPT), or liquid ammonia is well-established practice. Like basicity, the nucleophilicity of alkoxides is considerably enhanced in dipolar aprotic solvents[139] (permitting the use of less reactive salts such as ROMgBr) and in the presence of cation-complexing polyethers.[140] A recent modification of the Williamson synthesis[141] employs thallium(I) alkoxides in MeCN. The *in situ* generation of a sodium alkoxide by the addition of the alcohol to NaH in the presence of a methylating agent (equation 107) avoids the partial racemization that



(100%) (107)

sometimes complicates reactions with preformed alkoxide.[142] In polysaccharide chemistry, the combination of the dimsyl reagent ($MeSOCH_2^-$ Na^+ in DMSO) with MeI has largely superseded older combinations, *e.g.* Ag_2O or BaO with MeI, and NaOH with Me_2SO_4, for permethylations.[143] Phase-transfer catalysts promote the efficient etherification of alcohols in the presence of aqueous NaOH not only with Me_2SO_4 (equation 108)[144a] but also with

$$(HC{\equiv}C)_2C(OH)Bu^n \xrightarrow[Bu^n_4NI]{Me_2SO_4,\ aq.\ NaOH} (HC{\equiv}C)_2C(OMe)Bu^n \quad (95\%) \qquad (108)$$

primary alkyl chlorides.[144b] The intramolecular Williamson reaction (base-induced cyclization of halogenoalcohols), a standard route to oxirans, oxetans, and higher cyclic ethers (Sections 4.4.4 and 4.4.5), is often carried out with aqueous alkali.

The strongly basic conditions of the Williamson synthesis preclude the use of tertiary alkyl halides and others prone to undergo dehydrohalogenation. Halides solvolysed by the S_N1 mechanism can sometimes be etherified efficiently under neutral or weakly basic conditions, as in the tritylation of primary alcohols by Ph_3CCl in pyridine. The more critical preparation of di-t-butyl ether[145] by the carbenium ion alkylation of Bu^tOH requires the use of a hindered base (equation 109). The Koenigs–Knorr synthesis of

$$Bu^tCl \xrightarrow{i,\ ii} Bu^tOBu^t \qquad (109)$$

i, SbF_5, SO_2ClF, −70 °C; ii, Bu^tOH, $EtNPr^i_2$, −80 to 0 °C.

O-glycosides involves the neutral alcoholysis of a glycosyl halide (effectively an α-halogenoether) assisted by a silver(I) or mercury(II) salt. Simple ethers can be prepared similarly from alkyl bromides by alcoholysis under mildly acidic conditions, by using the highly electrophilic mercury(II) perchlorate to compensate for the lower reactivity of the halide, *cf.* equation (31)[44].

As alkylating agents, the alkyl bromides represent an acceptable compromise between accessibility and reactivity. Highly reactive reagents are represented by the unstable triflate esters (CF_3SO_2OR) and the trialkyloxonium fluoroborates (R_3O^+ BF_4^-), which can be used to etherify weakly nucleophilic and hindered alcohols under neutral conditions. Reactions with trialkyloxonium salts in the presence of a hindered base avoid rearrangement and racemization of labile alcohols caused by the acid liberated (equation 110).[146]

$$\underset{(S)}{EtMeCHCH_2OH} \xrightarrow[EtNPr^i_2]{Et_3O^+\ BF_4^-,\ CH_2Cl_2} \underset{(S)\ (89\%)}{EtMeCHCH_2OEt} \qquad (110)$$

Less reactive alkylating agents formed *in situ* from alcohols are the alkoxyphosphonium salts (**85**), which can be converted only into alkyl aryl ethers (products of alkyl C—O bond fission) by nucleophilic displacement. The very mild azodicarboxylate–triphenylphosphine route (Scheme 10 and equation 111) gives good results with primary and secondary alcohols; success with tertiary alcohols and nitrophenols appears to depend on the choice of conditions or other reactant.[147] In the alternative route (Scheme 11), the initial product (**85b**; X = Cl) is converted into the stable hexafluorophosphate, which is then heated with the potassium phenate in DMF.[148] Phenols can also be condensed with primary (and some secondary) alcohols by heating with dicyclohexylcarbodi-imide (DCC) (equation 112); the reactive intermediate is an

$$ArOH + ROH \xrightarrow[0\text{–}25\ °C]{Ph_3P,\ EtO_2CN{=}NCO_2Et} ArOR \qquad (111)$$

$$PhOH + PhCH_2OH \xrightarrow[100\ °C]{DCC} \underset{(96\%)}{PhOCH_2Ph} \qquad (112)$$

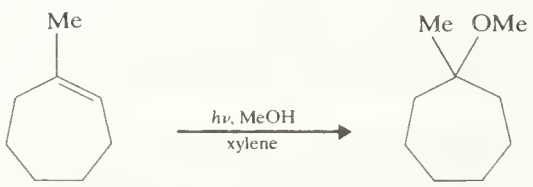
O-alkylisourea.[149] The preparation of alkyl aryl ethers by nucleophilic substitution of aryl halides is mainly confined to activated halides (Section 4.5.1.1), but the S_N1 displacement reaction of alcohols with arenediazonium salts is rather more general. Methylation of alcohols with diazomethane in the presence of HBF_4 or BF_3 is a simple method that often gives good yields with unhindered but otherwise 'difficult' compounds (Section 4.3.5.1).

Alcohols add to carbon–carbon multiple bonds to form ethers in various ways. The mechanism and orientation of electrophilic addition to alkenes, with general acid catalysis, are analogous to those of hydration.[150] Also as in the hydration of alkenes, the limitations of acid-catalysed reactions can be overcome by the use of indirect methods. By using mercury(II) trifluoroacetate in the solvomercuration–demercuration reaction,[151] excellent yields of the Markownikov adducts can generally be obtained, even with a labile alkene and a tertiary alcohol (equation 113). A similar method[152] — treatment of the alkene with the alcohol and *N*-bromosuccinimide, followed by reduction of the *β*-bromoether — has the disadvantage of only modest yields (50–60%) in the first step.

$$Bu^tCH{=}CH_2 + Bu^tOH \xrightarrow{\text{i, ii}} Bu^tCHMeOBu^t \quad (83\%) \qquad (113)$$

i, $(CF_3CO_2)Hg$; ii, NaOH, $NaBH_4$.

Surprisingly, simple alkanols also give Markownikov ethers with medium-ring (C_6–C_8) cycloalkenes by photosensitized[153] or direct[154] irradiation. In favourable cases, *e.g.* equation (114), no additional proton source is necessary. With certain exceptions[155] (*e.g.*



(62%) (114)

polarized conjugated compounds that undergo Michael-type additions) acyclic and exocyclic alkenes, and cyclohalkenes of other ring sizes, do not add alcohols by an ionic photochemical pathway. (They can react with primary and secondary alcohols by a radical pathway, involving the direct or ketone-sensitized photoaddition of $R^1R^2\dot{C}OH$, and the formation of an alcohol adduct in place of an ether.) The atypical photoprotonation of the medium-ring cycloalkenes is attributed to the relief of the high strain in *trans*-cycloalkenes formed by initial photoisomerization. The formation of ethers from activated alkenes (equation 115) and from alkynes (equation 116) by the base-catalysed nucleophilic addition of alcohols is standard chemistry.[24,127] Several methods are available[24] for the etherification of alcohols *via* acetals. The direct reductive coupling of alcohols and carbonyl compounds by 'ionic hydrogenation'[50] (equation 117) provides an attractive alternative, particularly for the preparation of di-primary ethers.

$$n\text{-}C_9H_{19}CH{=}CHCO_2Me \xrightarrow[\text{MeONa, 40 °C}]{\text{MeOH}} n\text{-}C_9H_{19}CH(OMe)CH_2CO_2Me \quad (90\%) \qquad (115)$$

$$Bu^tC{\equiv}CH \xrightarrow[\text{ROK, 200 °C}]{\text{ROH}} ROCBu^t{=}CH_2 + Bu^tCH{=}CHOR \quad (Z) \qquad (116)$$

	Product ratio
R = Me	78 : 22
R = Bu^t	5 : 95

$$PhCHO + EtOH \xrightarrow[CF_3CO_2H]{Et_3SiH} PhCH_2OEt \quad (90\%) \qquad (117)$$

(*d*) *Acetals and orthoesters.* Summaries of the major preparative routes from alcohols to acetals [$R^1CH(OR^2)_2$ and $R^1R^2C(OR^3)_2$] are given by Buehler and Pearson,[24] and to orthocarboxylates [$R^1C(OR^2)_3$] and orthocarbonates [$C(OR^1)_4$] by Sandler and Karo.[156] As the structural resemblance of the compounds (the presence of *gem*-alkoxy groups) indicates, they can be prepared by similar methods.

The routes indicated by equations (118)–(120) are formally extensions of the Williamson ether synthesis, although the reactions are mechanistically distinct. The highly reactive α-halogenoethers tend to undergo S_N1 displacement of halogen, while carbenes are intermediates in the reactions of *gem*-polyhalides. Such reactions are mainly of interest for the preparation of orthoesters, although α-halogenoethers are important in glycoside synthesis (the Koenigs–Knorr reaction) and can be used as reagents (*e.g.* chloromethyl methyl ether, 2-chlorotetrahydrofuran) in hydroxyl protection (see p. 660).

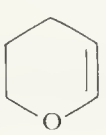
$$R^1OCH_2Cl + R^2OH \xrightarrow{R^3_3N} R^1OCH_2OR^2 \qquad (118)$$

$$CHCl_3 + 3RONa \longrightarrow CH(OR)_3 \qquad (119)$$

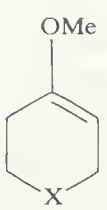
$$CCl_3NO_2 + 4RONa \longrightarrow C(OR)_4 \qquad (120)$$

$$R^1CH{=}CHOR^2 + R^3OH \xrightarrow{H^+} R^1CH_2CH(OR^2)(OR^3) \qquad (121)$$

An extension of another ether synthesis that has more important applications in hydroxyl protection is the acid-catalysed addition of an alcohol to a vinylic ether (equation 121). Examples of reagents used in this way for the protection of hydroxy groups are 2,3-dihydro-4*H*-pyran (**88**), 4-methoxy-5,6-dihydro-2*H*-pyran (**89a**), methyl vinyl ether (**90**), and 2-methoxypropene (**91**). Typical catalysts are TsOH, HCl, $POCl_3$, and BF_3. Similar additions to 1-alkoxyalkynes and keten acetals, catalysed by Lewis acids (BF_3, $ZnCl_2$) or alkoxides, produce orthocarboxylate esters.



(**88**)

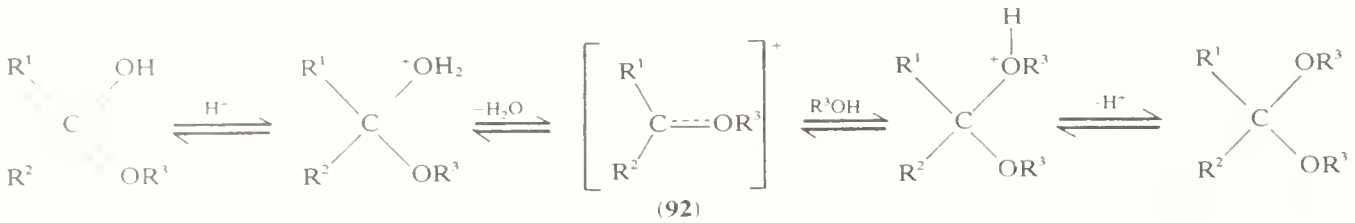


(**89**) a; X = O
b; X = S
c; X = SO_2

$CH_2{=}CHOMe$
(**90**)

$CH_2{=}CMeOMe$
(**91**)

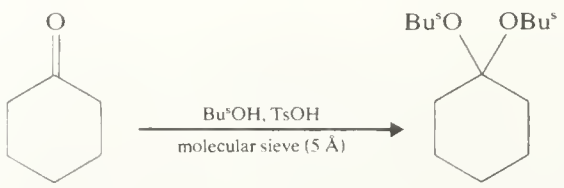
The best-known and most direct method for the preparation of simple acetals is the acid-catalysed reaction between the appropriate alcohol and carbonyl compound. This reversible reaction involves etherification of the intermediate hemi-acetal *via* an alkoxy-carbenium ion (**92**; Scheme 13).[157] The electrophilic attack of (**92**) on the alcohol is



(**92**)

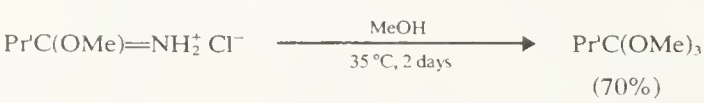
SCHEME 13

common to this reaction and the vinylic ether reaction described above. As the formation of (**92**) indicates, the rate of reaction depends on the electronic influence of groups R^1 to R^3. The relatively high rate coefficients for ketones compared to aldehydes, and the low reactivity of chloral hemiacetals, reflect the inductive influences of the relevant groups. From the practical viewpoint, however, structural influences on the position of equilibrium are more important. The forward reaction is disfavoured by an increase in number, size, or branching of the alkyl groups, through a combination of steric and electronic effects. Thus aldehydes react more efficiently than ketones, and primary alcohols more than tertiary (the latter will not form acetals). The usual devices are employed to displace the equilibria. For the protection of carbonyl groups, alcohols are used in excess, and the converse applies to the protection of diols by acetalation (Section 4.1.2.4, p. 676). Conversions are further improved by removal of the water produced, either physically, *e.g.* by azeotropic distillation or by adsorption with a molecular sieve or other desiccant[158] (equation 122), or chemically, *e.g.* by reaction with triethyl orthoformate or 2,2-dimethoxypropane (acetone dimethyl acetal). Among the wide variety of catalysts,[24] HCl, TsOH, and sulphonated polystyrene resins are used extensively.



(80%) (122)

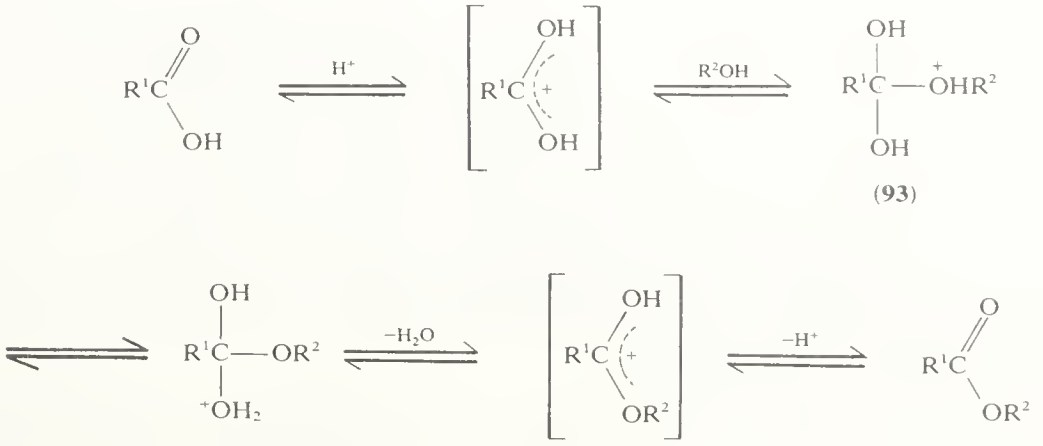
The synthesis of orthoesters that is the nearest equivalent to the carbonyl addition route to acetals is the Pinner reaction (equation 123). The imido-ester hydrochlorides are readily available from the corresponding nitrile by acid-catalysed addition of the alcohol. Thus, constitutionally symmetrical orthoesters can be prepared from the nitrile in a one-step reaction. Such derivatives of higher alcohols are conveniently prepared by catalysed alcoholysis of lower orthoesters and orthothioesters, with continuous removal of the more volatile alcohol or thiol displaced. The reversibility of acetalation lends itself to similar exploitation.



(70%) (123)

(*e*) *Esters.* This section deals mainly with preparation of monocarboxylate esters, and that from the alcohol viewpoint. Other accounts of esterification (Volume 2, Chapter 9.8) provide the complementary emphasis on the acylating agent, and extend the coverage of polyfunctional carboxylic acids, carbonates, and carbamates. The specialized preparations of the esters of various inorganic oxo acids, notably those of phosphorus and sulphur, are also considered in later chapters.

In the acid-catalysed reaction of a primary or secondary alcohol with a carboxylic acid, the function of the catalyst is to activate the carboxylic acid to nucleophilic attack.[159] In the common $A_{AC}2$ mechanism, the bimolecular rate-determining step (Scheme 14) is formation of the tetrahedral adduct (**93**). In the $A_{AC}1$ mechanism, applicable to hindered carboxylic acids in concentrated H_2SO_4, the unimolecular rate-determining step is the formation of an acylium ion (R^1CO^+) from the protonated carboxylic acid.



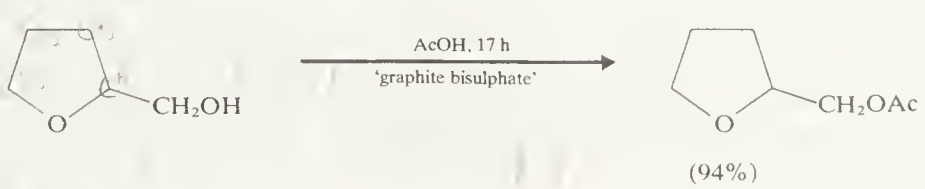
(**93**)

SCHEME 14

Because the slow step in the $A_{AC}2$ process involves the formation of the protonated adduct (**93**) from a planar cation, reactions of this type are subject to steric retardation. Therefore tertiary alcohols, that form carbenium ions with *relative* ease, react by the alternative $A_{AL}1$ pathway (Scheme 15), in which the function of the catalyst is to activate the alcohol. Allylic and benzylic alcohols react similarly, but acid-catalysed esterification is generally unsatisfactory for alcohols prone to rearrange or dehydrate.

SCHEME 15

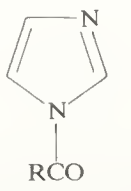
The efficient realization of these reversible reactions is based on techniques similar to those described for acetalation. Reactions may be driven by using the alcohol in excess, with dry HCl (Fischer–Speier), concentrated H_2SO_4, $ArSO_3H$, or BF_3 as the catalyst, or drawn by the removal of water produced. Recent examples of insoluble reagents that combine the roles of catalyst and dehydrating agent are an aluminium(III) chloride–polystyrene complex[160a] and 'graphite bisulphate.'[160b] The latter, an electrolytic lamellar compound containing intercalated H_2SO_4 and formulated as $C_{24}^{+}HSO_4^{-}\cdot 2H_2SO_4$, produces efficient esterification of primary, secondary, and benzylic alcohols in stoichiometric reactions at room temperature (equation 124).



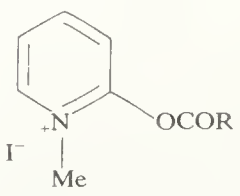
(94%)

(124)

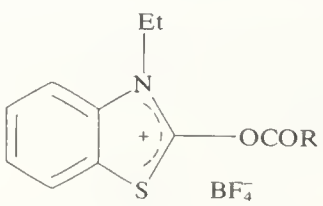
Problems caused either by the reversibility or by the strongly acidic conditions of direct esterifications are usually solved by the conversion of the carboxylic acid to a derivative (RCOX) suitably activated towards nucleophilic attack. Conventional, general-purpose acylating agents are epitomized by acid chlorides and anhydrides (the former being more reactive, accessible, and economical in the utilization of acyl groups). More unusual acylating agents with specialized applications are represented by the *N*-acylimidazoles (**94**),[161] 2-acyloxypyridinium salts (**95**),[162] 2-acyloxybenzothiazolium salts (**96**),[163] *S*-t-butyl thiocarboxylates (**97**),[164] and the heterocyclic thiol esters (**98**)[165] and (**99**).[166] If required, acylating agents can be further activated by a Brønsted or Lewis acid catalyst, which may enhance the electrophilicity of RCOX or facilitate heterolysis of the C—X bond. Bases used as catalysts may function by activating the alcohol by deprotonation before or during nucleophilic attack (*e.g.* NaOH, in Schotten–Baumann acylations), by providing the actual nucleophile (*e.g.* RO^-, in alkoxide-catalysed transesterifications), or by nucleophilic catalysis (*e.g.* R^1_3N, reacting with R^2COX to give the acylating intermediate $R^1_3NCOR^2$). Depending on the reactants and conditions, esterification may proceed *via* (i) an acylium ion, (ii) a tetrahedral intermediate, *e.g.* (**100**), in a carbonyl addition–elimination pathway, or (iii) nucleophilically assisted displacement of X without the formation of a discrete intermediate.



(**94**) a; R = n-pentyl

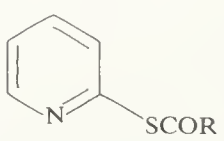


(**95**)

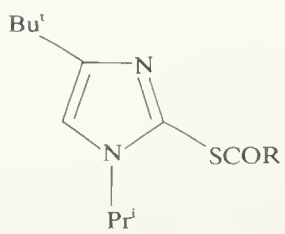


(**96**)

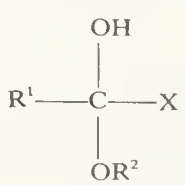
(**97**) a; R = cyclohexyl



(**98**) a; R = $(CH_2)_nOH$



(**99**)



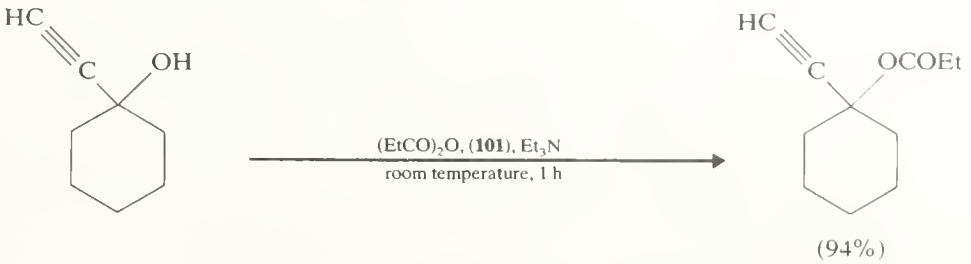
(**100**)

In esterifications with acid chlorides, the presence of an adequate amount of base (*e.g.* pyridine, $PhNMe_2$) is often necessary to ensure irreversibility and to protect tertiary and other acid labile alcohols. A mild alternative[167] is to use silver(I) cyanide, which allows highly hindered esters to be prepared in excellent yield (equation 125). Good results can also be obtained from reactions of lithium alkoxides with base-tolerant acid chlorides (equation 126).[168]

$$Me_3CCOCl + Bu^tOH \xrightarrow[80\,^\circ C,\ 10\ min]{AgCN,\ HMPT} Me_3CCOOBu^t \quad (94\%) \qquad (125)$$

$$PhCOCl + Et_3COLi \xrightarrow[reflux,\ 1\ h]{THF,\ hexane} PhCOOCEt_3 \quad (94\%) \qquad (126)$$

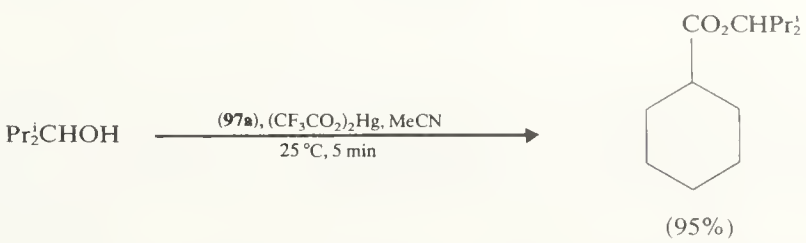
With the less reactive acid anhydrides, catalysis by acids (*e.g.* H_2SO_4, $HClO_4$, TsOH, $ZnCl_2$) or bases (*e.g.* pyridine, Et_3N, RCO_2Na) is often necessary. 4-*N*,*N*-Dimethylaminopyridine (**101**), used stoichiometrically or catalytically with Et_3N (equation 127), is exceptionally efficient.[169] The reactivities of the novel acylating agents (**94**), (**97**),



(94%) (127)

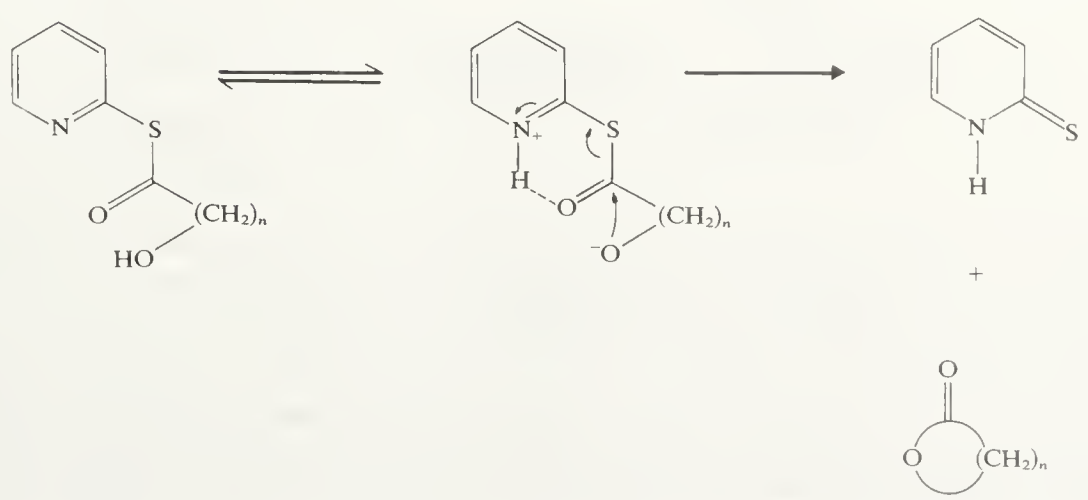
and (**98**) can be increased by coordination with bromine (from NBS),[170] Hg^{II},[164] and Ag^I,[165] respectively. Equations (128) and (129) show representative reactions. The major

$$Bu^sOH \xrightarrow[room\ temperature,\ 1\ h]{(94a),\ NBS,\ CH_2Cl_2} n\text{-}C_5H_{11}CO_2Bu^s \quad (80\%) \qquad (128)$$



(95%) (129)

applications of the thiol esters (**97**), (**98**), and (**99**) are to intramolecular reactions, and recent triumphs in the synthesis of complex macrocyclic lactones have been described by Nicolaou.[171] The design of (**98a**) as a molecule producing simultaneous activation of the hydroxyl and acyl components through an internal proton transfer is indicated in Scheme 16.

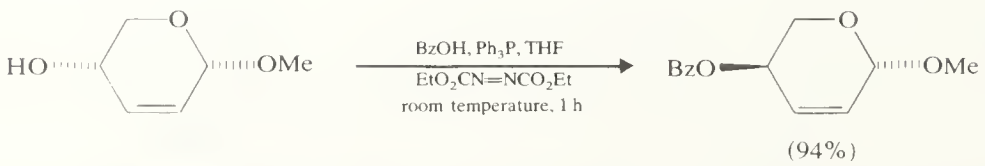


SCHEME 16

The generation of acylating derivatives of carboxylic acids *in situ* has obvious advantages. The conversions to reactive mixed anhydrides by treatment with TsCl–pyridine[172a] or $(CF_3CO)_2O$[172b] are well-established examples. Reagents (**95**) and (**96**), formed by nucleophilic displacements *in situ*, *e.g.* on 2-bromo-*N*-methylpyridinium iodide (**102**) and 2-chloro-*N*-ethylbenzothiazolium fluoroborate (**103**), show promise for stoichiometric reactions under mild conditions (equations 130 and 131). Another very mild procedure for the *in situ* activation and condensation of the reactants that is finding diverse applications is the Ph_3P–azodicarboxylate method introduced by Mitsunobu.[173] Here, of course, the sense of activation is reversed, the α-carbon of the alcohol residue in (**85a**) being susceptible to nucleophilic attack by the carboxylate anion. Unhindered primary and secondary alcohols react by the S_N2 mechanism with inversion of configuration and without allylic rearrangement (equations 132 and 133).[174] With 1,3-di-*O*-acylglycerols,[175] isomeric products attributable to neighbouring group participation cannot be detected (equation 134). Reagent (**103**) and its fluoro analogue can also be used to esterify chiral secondary alcohols with inversion of configuration;[45,163] initial reaction with the alcohol produces the alkoxy derivative (**87**), which undergoes S_N2 displacement on treatment with a salt of the acid. Other recent papers on the interactions of alcohols with organophosphine–azodicarboxylate combinations suggest their use for transesterifications under neutral conditions[176] and for the synthesis of carbonate esters.[177]

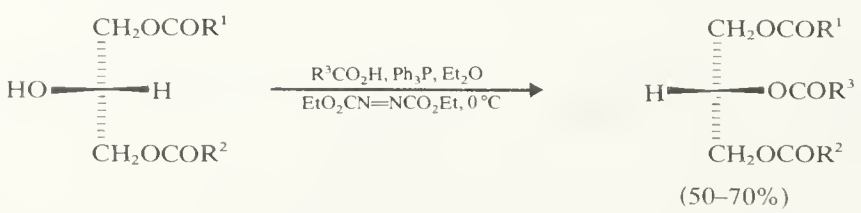
$$PhCH{=}CHCH_2OH + AcOH \xrightarrow[CH_2Cl_2,\ reflux]{(\mathbf{102}),\ Bu^n_3N} PhCH{=}CHCH_2OAc \quad (80\%) \qquad (130)$$

$$PhCH_2CO_2H + PhCH(OH)Me \xrightarrow[CH_2Cl_2,\ 0\,^\circ C]{(\mathbf{103}),\ Bu^n_3N} PhCH_2COOCHMePh \quad (92\%) \qquad (131)$$



(94%) (132)

$$CH_2{=}CHCHDOH \xrightarrow[EtO_2CN{=}NCO_2Et,\ room\ temperature,\ 1\ h]{BzOH,\ Ph_3P,\ THF} CH_2{=}CHCHDOBz \quad (92\%) \qquad (133)$$



(50–70%) (134)

Partly because the emphasis in preparative applications of sulphonate esters has been on the protection or replacement of hydroxyl groups, acylating agents and methods in common use are rather limited. Normal practice is to react the sulphonyl halide with the alcohol in the presence of base (*e.g.* pyridine, Et_3N), with special conditions for hindered alcohols and highly reactive sulphonates. For example, the unstable benzylic tosylates can be prepared by low-temperature reaction of tosyl chloride with the alkoxides, while the activation of mesyl chloride by Et_3N (through elimination to the sulphene, CH_2SO_2) provides a general route to mesylates,[178] including those of hindered and weakly nucleophilic alcohols (equations 135 and 136).

$$Me_3CCH(OH)C{\equiv}CH \xrightarrow{MsCl,\ Et_3N,\ CH_2Cl_2} Me_3CCH(OMs)C{\equiv}CH \quad (92\%) \qquad (135)$$

$$(CF_3)_2CHOH \xrightarrow{MsCl,\ Et_3N,\ CH_2Cl_2} (CF_3)_2CHOMs \quad (85\%) \qquad (136)$$

Quaternary methylsulphonylammonium salts[179] are also highly active reagents for the preparation of base-sensitive mesylates. An indirect route to unstable tosylates involves the preparation and oxidation (with *m*-chloroperbenzoic acid) of the corresponding *p*-toluenesulphinates.[180] In general, preparatively useful sulphonylations are limited to primary and secondary alcohols, and these often differ sufficiently in reactivity to permit selective esterifications with aromatic sulphonyl chlorides.

Methods for the preparation of carbamates (NH_2CO_2R) and their *N*-substituted derivatives (urethanes) have been summarized,[181] and the acylating characteristics of isocyanates ($RN{=}C{=}O$) compared with those of ketens ($R_2C{=}C{=}O$).[182] A compound like acetyl isocyanate reacts readily with all classes of alcohols, giving derivatives (**17**) useful for spectroscopic characterization (Section 4.1.1.2, p. 585), but simple isocyanates only esterify primary and secondary alcohols readily (in the absence of a catalyst). Catalysis can be provided by a base, a Lewis or carboxylic acid, or — most effectively — by various organometallic compounds including iron(III) acetylacetonate and di-n-butyltin dilaurate.[181a,183] High yields of tertiary urethanes have been obtained in reactions catalysed by organotin compounds[184] or by light.[185]

(*iii*) *Products formally corresponding to C—O bond fission*

(*a*) *Hydrocarbons* via *deoxygenation.* In synthetic chemistry, useful methods for the replacement of a hydroxy group by hydrogen are less drastic and more selective than those, *e.g.* treatment of a compound with red P and HI, employed in classical degradative chemistry. Direct and relatively specific methods are available for activated alcohols (tertiary, allylic, benzylic), but more general methods necessitate the formation of a reactive derivative.

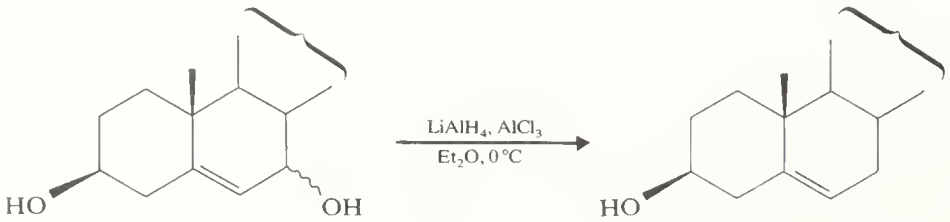
The Pd-catalysed hydrogenolysis of benzylic C—O bonds, including those of alcohols, is well known; the fission of C—O bonds in homobenzylic alcohols (*via* benzylidene intermediates)[186] and allylic alcohols (preferably containing hindered double bonds) under similar conditions (protic solvent, often with a trace of a strong mineral acid) has less preparative importance. The stereochemistry of hydrogenolysis can vary with the substrate, catalyst, and reaction conditions,[187] but inversion of configuration usually predominates in reactions over Pd, whereas configuration is largely retained in reactions of benzylic alcohols over Raney Ni. Tertiary aliphatic alcohols undergo slow hydrogenolysis in the presence of a soluble or an insoluble Pt catalyst and CF_3CO_2H.[188] Under the conventional conditions of 'ionic hydrogenation' with an organosilane as the hydride source,[50] alcohols forming stable carbenium ions are readily deoxygenated (equation 137). By using BF_3 in place of a protic acid, even labile and less reactive alcohols can be reduced.[189]

$$Et_3COH \xrightarrow[25\,^\circ C,\ 24\ h]{CF_3CO_2H,\ Ph_3SiH,\ CH_2Cl_2} Et_3CH \quad (78\%) \qquad (137)$$

The major complex metal hydrides (Table 5, p. 597) are only of limited use for direct deoxygenations. Although powerful reductants such as $LiAlH_4$ will sometimes reduce activated alcohols under rather vigorous conditions, *e.g.* equation (138), more attention has been paid to electrophilic reductants of the 'mixed hydride' type. Most widely

$$CH_2{=}CPhCH(OH)Bu^t \xrightarrow[\text{reflux}]{LiAlH_4,\ THF} MePhC{=}CHBu^t \quad (100\%) \qquad (138)$$

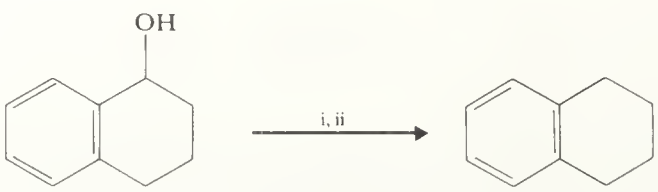
studied[190] are mixtures of $LiAlH_4$ with $AlCl_3$, particularly that equivalent to $AlHCl_2$; a similar reagent based on $TiCl_4$ has also been used.[191] Good results have been obtained with secondary and reactive primary benzylic alcohols, and with steroidal allylic alcohols (equation 139), but variable migration of the double bond and the occurrence of side reactions mar the preparative applications to acyclic alcohols.



(139)

(**14**) (75–90%)

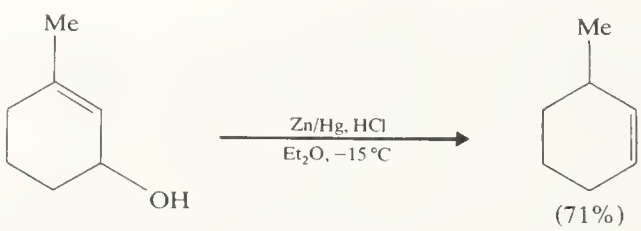
The reductive fission of C—O bonds in allylic and benzylic alcohols can also be achieved by dissolving-metal reagents or by electrochemical methods. Applications of the Birch ($Na–NH_3–ROH$) and Benkeser ($Li–RNH_2$) reagents have been reviewed,[192] and an improved variant of the former (equation 140) has recently been described.[193] A complementary method (equation 141) that produces mainly the least-stable alkene from an



(140)

(100%)

i, Li, NH_3, THF; ii, NH_4Cl.



(141)

(71%)

allylic alcohol is another innovation.[194] Although cathodic deoxygenation has been applied successfully to several benzylic and benzylic-allylic alcohols, the problem of activating the hydroxy group sufficiently without incurring concurrent reduction of carbon–carbon multiple bonds during reaction appears to limit the choice of suitable substrates.[195] Another novel reaction of uncertain potential is the deoxygenation of allylic alcohols by *reducing* Grignard reagents activated by the complex $(Ph_3P)_2NiCl_2$ (equation 142).[196]

Standard procedures for the indirect deoxygenation of alcohols are (i) dehydration, followed by hydrogenation of the alkene (best for tertiary alcohols), and (ii) conversion to a halide or sulphonate ester, followed by hydride reduction (mainly applicable to primary

$$PhCH{=}CHCH_2OH \xrightarrow{Pr^nMgBr,(Ph_3P)_2NiCl_2} PhCH{=}CHMe \qquad (142)$$

(*E*) (*E*) (68%)

and unhindered secondary alcohols). For normal purposes $LiAlH_4$ is the preferred reductant, though competing elimination can be a major problem. In such cases the highly nucleophilic reagent $LiBHEt_3$ is a useful alternative;[197] the efficiency of the reagent with a neopentylic tosylate is indicated by equation (143). Various other hydride reductants[198]

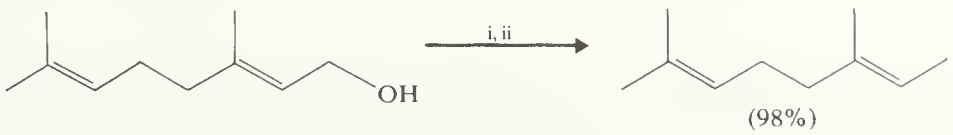
$$Bu^nCMe_2CH_2OTs \xrightarrow[\text{reflux, 3 h}]{LiBHEt_3,\ THF} Bu^nCMe_3 \quad (81\%) \qquad (143)$$

permit more selective reductions to be carried out: examples are $NaBH_4$ in DMSO or another polar aprotic solvent, the borate complex (**49**) (specific for tertiary, allylic, and benzylic halides), $LiCuHBu^n$ (applicable to all classes of halides and sulphonates), and cyanohydridoborates in HMPT (exceptionally selective for halides and sulphonates). Other useful techniques are the formation and reduction *in situ* of iodides, starting from primary alcohols (equation 144)[198] and from primary or secondary sulphonates (equation 145),[199] and of sulphates from benzylic or allylic alcohols (equation 146).[200] The many other established methods for the reduction of alkyl halides are described in Section 3.3.4 and elsewhere.[24,47]

$$PhCH{=}CHCH_2OH \xrightarrow{i,\ ii} PhCH{=}CHMe \quad (68\%) \qquad (144)$$

i, $(PhO)_3\overset{+}{P}Me\ I^-$, HMPT, 25 °C; ii, $NaBH_3CN$, 70 °C.

$$n\text{-}C_{18}H_{37}OTs \xrightarrow[\text{reflux}]{NaI,\ Zn,\ glyme} n\text{-}C_{18}H_{38} \quad (90\%) \qquad (145)$$



(98%) (146)

i, SO_3, pyridine; ii, $LiAlH_4$.

Another distinctive feature of recent work on methods of indirect deoxygenation is the exploration of alternative intermediates. Table 7 lists a number of these for which efficient methods of preparation and reduction have been devised.

(*b*) *Hydrocarbons* via C—C *bond formation.* Compared with their reactive derivatives, alcohols find only limited use as alkylating agents. The most familiar C—C bond-forming reactions are the electrophilic alkylations of the Friedel–Crafts type, involving activation of the alcohol by protonation or coordination to a Lewis acid. Such carbenium ion reactions, *e.g.* the formation of polyalkenes in strong acid[201a] and aromatic substitutions,[201b] will not be discussed here, nor will reactions involving the alkylation of carbanions.[201c]

Both thermal[202] and photochemical[203] reactions between alcohols and trialkylaluminiums have been reported. Thermal *C*-methylation with Me_3Al is apparently an ionic reaction applicable to tertiary and benzylic alcohols. The photochemical process, probably following a radical mechanism, is restricted to benzylic alcohols, but succeeds with a wider range of reagents (Me_3Al, Et_3Al, Bu^i_3Al).

Whereas allylic alcohols undergo deoxygenation on treatment with a reducing Grignard reagent in the presence of $(Ph_3P)_2NiCl_2$ (equation 142), the use of a non-reducing reagent produces substituted alkenes, possible *via* a π-allylnickel intermediate.[196] In favourable

TABLE 7

Indirect Methods for the Deoxygenation of an Alcohol

Derivative of R^1OH	*Preparation of the derivative*	*Reduction of the derivative*
O-Alkylisourea $[R^2NHC(OR^1)=NR^2]$[a]	$R^2N=C=NR^2$, CuCl	$Pd-H_2$
Sulphide (R^1SPh)[b]	i, $(CF_3SO_2)_2O$; ii, PhSNa	$Na-NH_3$
O-Alkyl thio benzoate ($PhCSOR^1$)[c]	i, $PhCCl=\overset{+}{N}Me_2Cl^-$; ii, H_2S	Bu^n_3SnH
O-Alkyl *S*-methyl dithiocarbonate ($MeSCSOR^1$)[c]	i, NaH, CS_2; ii, MeI	Bu^n_3SnH
Carboxylate ester (R^2COOR^1)[d]	Standard methods	$h\nu$, HMPT–H_2O
Chloroformate ester ($ClCOOR^1$)[e]	$COCl_2$	Pr^n_3SiH, $(Bu^tO)_2$
N^1,N^1,N^2,N^2-Tetramethyl-phosphorodiamidate esters $[(Me_2N)_2POOR^1)]$[f]	Bu^nLi, $(Me_2N)_2POCl$	$Li-EtNH_2-Bu^tOH$

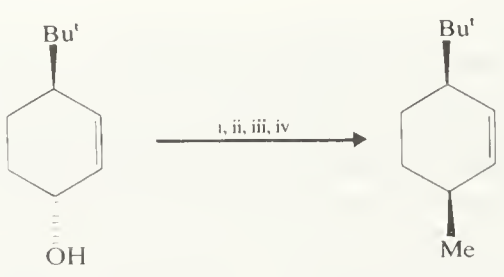
[a] E. Vowinkel and I. Büthe, *Chem. Ber.*, 1974, **107,** 1353. [b] T. H. Haskell, P. W. K. Woo, and D. R. Watson, *J. Org. Chem.*, 1977, **42,** 1302. [c] D. H. R. Barton and S. W. McCombie, *J.C.S. Perkin I*, 1975, 1574. [d] H. Deshayes, J.-P. Pete, C. Portella, and D. Scholler, *J.C.S. Chem. Comm.*, 1975, 439. [e] N. C. Billingham, R. A. Jackson, and F. Malek, *J.C.S. Chem. Comm.*, 1977, 344. [f] R. E. Ireland, D. C. Muchmore, and U. Hengartner, *J. Amer. Chem. Soc.*, 1972, **94,** 5098.

cases — equation (147) is a simple example — the predominance of one isomer can make this a useful synthesis.

$$\underset{(Z)}{MeCH=CHCH_2OH} \xrightarrow{MeMgBr,\ (Ph_3P)_2NiCl_2} \underset{(72\%)}{Me_2CHCH=CH_2} + \underset{(8\%)}{Isomers} \qquad (147)$$

A very promising method[204] for the regio- and stereo-selective replacement of the hydroxy group in allylic (and other) alcohols is the formation of an alkoxyalkylcuprate [provisionally formulated as $Li_3Cu(OR^1)R^2_3$] from the alcohol, followed by reaction with the aminophosphonium salt (**104**) (equation 148). The reaction can be rationalized as involving characteristic S_N2 attack on an alkoxyphosphonium cation by an R^2 group of the counter-anion of an intermediate salt (**105**).

$(Ph_3PNMePh)^+\ I^-$ (**104**) $\qquad$ $(Ph_3POR^1)^+\ (R^2_3CuNMePhLi_2)^-$ (**105**)



(75%) (148)

i, MeLi; ii, CuI; iii, MeLi; iv, (**104**).

The thermal fragmentation of titanium(II) alkoxides has been developed by van Tamelen's group as a method for the reductive coupling of allylic and benzylic alcohols. The most efficient procedure[205] seems to be the treatment of the alcohol with a reagent prepared from $TiCl_3$ and $LiAlH_4$ (equation 149). The reductive coupling of benzhydrols

$$PhC(OH)Me_2 \xrightarrow[\text{glyme, reflux}]{TiCl_3,\ LiAlH_4} PhCMe_2CMe_2Ph \quad (95\%) \qquad (149)$$

on heating with the hydrogen-transfer catalyst $(Ph_3P)_3RuCl_2$ has recently been announced.[206]

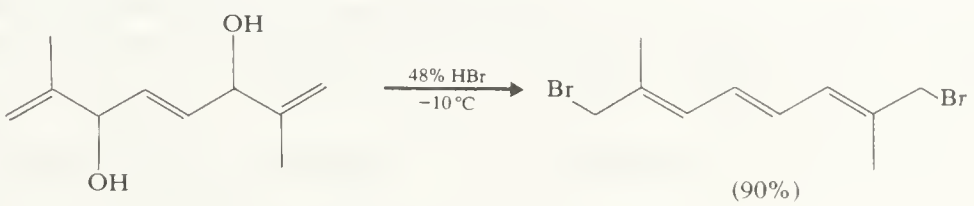
(*c*) *Halides.* The numerous reagents and methods[24,207] for the replacement of a hydroxy group by a halogen reflect the importance of the conversion and the varied problems encountered. Only the generally useful and certain novel reactions can be considered here.

The synthetic value of the elementary reaction (equation 150) between an alcohol and a hydrogen halide (HCl, HBr, HI) is mainly restricted to simple, primary and tertiary

$$ROH + HX \longrightarrow RX + H_2O \qquad (150)$$

alcohols. Reactivities follow the familiar trends: tertiary > secondary > primary alcohols, and HI > HBr > HCl. Thus, with conditions favouring ionization, tertiary alcohols react rapidly with cold, concentrated aqueous acids by the S_N1 mechanism. The more difficult S_N2 displacement of water from primary alkyloxonium ions — particularly by chloride ions — usually requires heat and additional assistance, *e.g.* anhydrous HCl alone or in HMPT,[208] concentrated HCl with $ZnCl_2$ or a phase-transfer catalyst,[209] $HBr–H_2SO_4$, $HI–H_3PO_4$. With many secondary alcohols, *e.g.* equation (151), β-branched primary alcohols, and β,γ-unsaturated alcohols, partial or complete rearrangement occurs. Such rearrangements can, in fact, have synthetic value, *e.g.* equations (152) and (153). However, the reaction is not suited to the conversion of chiral alcohols into halides, either

$$Me_2CHCH(OH)Me \xrightarrow[\text{room temperature}]{\text{dry HCl}} Me_2CBrCH_2Me \quad (64\%) \qquad (151)$$



(90%) (152)

$$MeEtC(OH)C{\equiv}CH \xrightarrow{48\%\ HBr,\ CuBr} MeEtC{=}C{=}CHBr \quad (90\%) \qquad (153)$$

because of carbenium ion participation or because of racemization by halogen exchange.[210] Until recently, HF was seldom used for the preparation of fluorides from alcohols, but as a 70% (w/w) solution in pyridine it gives good to excellent yields with simple secondary and tertiary alcohols.[211]

Thionyl halides ($SOCl_2$, and to a lesser extent $SOBr_2$) are popular reagents for the preparation of halides (SO_2Cl_2 is occasionally used and has important applications in carbohydrate chemistry[212]). The reactions (equation 154) proceed *via* the decomposition of intermediate halogenosulphites. The mechanism, and its structural and stereochemical consequences,[213] depend on the presence or choice of solvent (especially participating

$$ROH + SOX_2 \longrightarrow RX + SO_2 + HX \qquad (154)$$

solvents such as dioxan, DMF, or HMPT) and catalyst (normally pyridine, $ZnCl_2$ is a new option[214]). The S_N2 displacement (*e.g.* Scheme 17) is favoured and (at least for alkanols) rearrangements minimized or abolished by using a stoichiometric amount of pyridine, or by using DMF or HMPT as the solvent. In the absence of these the predominant retention of configuration is observed in reactions of chiral arylmethanols (attributed to ion-pair S_Ni decomposition) or other alcohols in dioxan (attributed to a double inversion, involving first the solvent and then the halide ion).

SCHEME 17

The reactions of metal halides[207] with tosylates or mesylates are important for the indirect conversion of primary and secondary alcohols to halides under mild conditions with inversion of configuration. With proper precautions to minimize racemization (usually extensive for iodides), chiral secondary halides are obtainable in good yield and with high optical purity. Recent prescriptions for preparing all the 2-octyl halides are (i) reaction of the mesylate with aqueous KX in the presence of a phase-transfer catalyst,[215a] and (ii) reaction of the tosylate with LiX or KX in tri- or tetra-ethylene glycol.[215b] Conditions have also been found for the more critical conversion of branched primary allylic alcohols into chlorides without rearrangement.[216] The similar approaches of Stork and Meyers are indicated by equation (155) for preparations of geranyl chloride. Simpler

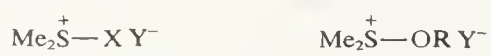
(i, 85%; ii, 100%) (155)

i, (a) MeLi, HMPT, Et_2O, (b) TsCl, (c) LiCl;
ii, MsCl, DMF, 2,4,6-trimethylpyridine, LiCl.

procedures[216c,d] rely on pyridinium chloride for the displacement step. The Meyers method is superior to the use of $SOCl_2$–Bu^n_3N with secondary allylic alcohols, but rearrangement is not prevented (equation 156).[217] Further comments on the use of halogenating agents in DMF are offered later in this section.

	Product ratio		
R = Me	73	2	7
R = Bu^t	6	9	4

The dimethylhalogenosulphonium salts (**106**), formed from dimethyl sulphide and the halogen or *N*-halogenosuccinimide, react with alcohols to give unstable alkoxysulphonium salts (**107**). Attack by the halide ion at carbon with the expulsion of DMSO, analogous to



(**106**) a; X = Y = Cl
b; X = Y = Br
c; X = succinimido, Y = Cl
d; X = succinimido, Y = Br

(**107**)

the similar reactions of alkoxyphosphonium salts, completes the conversion of the alcohol to the halide.[218] Carried out at low temperature, the reaction is specific[218a] to allylic and benzylic alcohols, *e.g.* equation (157). In contrast to phosphorus-based reagents, simple

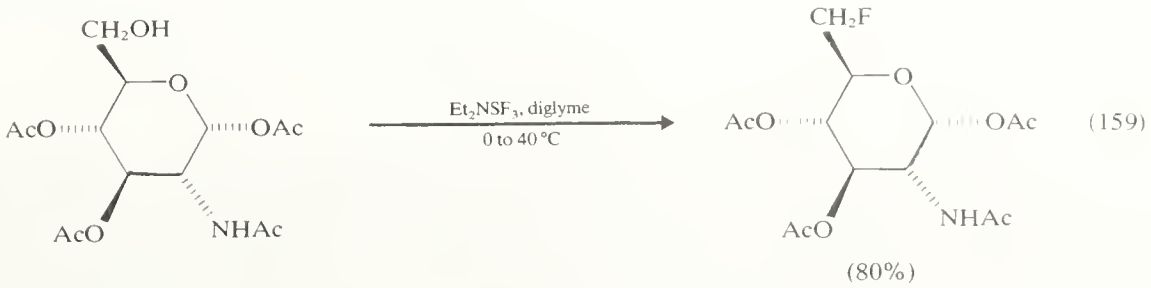
$$HOCH_2CH_2CMe{=}CHCH_2OH \xrightarrow[-20\text{ to }0\,^\circ C]{(\mathbf{106c}),\ CH_2Cl_2} HOCH_2CH_2CMe{=}CHCH_2Cl \quad (157)$$

(Z) (Z) (87%)

sulphur halides are rarely used to transform alcohols. Potential exceptions in the specialized area of fluorine chemistry[133a] are SF_4 in liquid HF (equation 158)[219a] and Et_2NSF_3 (equation 159).[219b] The 1:1 complex of SeF_4 with pyridine can also be used to prepare fluorides from alcohols.[220]

$$MeCH(OH)CH(NH_2)CO_2H \xrightarrow[-78\,^\circ C]{SF_4,\ HF} MeCHFCH(NH_2)CO_2H \quad (158)$$

(85%)



(159)

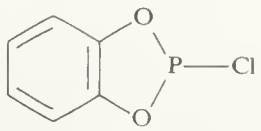
(80%)

Phosphorus-based reagents have long been prominent in the preparation of alkyl halides, and a formidable range of them has been developed.[24,207] Few comments are necessary on the common usage of simple reagents like PCl_5, PBr_3, and red P–I_2, particularly with primary and secondary alcohols. The familiar problems of rearrangements, *e.g.* with β-branched alcohols,[221] and of the preparation of chiral halides[210,222] have been discussed. Provided that the dealkylation of the intermediate phosphite esters is completed at room temperature or below, good yields of the inverted halides are obtained from the reactions of secondary alcohols with PCl_3 and PBr_3. Interestingly, retention of configuration occurs when tertiary alcohols are treated briefly with PCl_5 at 0 °C in the presence of $CaCO_3$.[223]

In recent years, much use has been made of the adducts (quasiphosphonium salts) formed by phosphite esters or organosphosphines with alkyl halides, halogens, tetrahalogenomethanes, or *N*-halogenosuccinimides. Such reagents are noted for selective halogenations under mild conditions, with minimum rearrangement and (usually) high inversion of configuration (for chlorides and bromides). Alkyltriphenoxyphosphonium salts (**108**) react with all classes of alcohols, and are used particularly for preparing iodides. One application of the Rydon–Landaeur reagent (**108b**)[224] is shown in equation (144) and another in equation (160).

$(PhO)_3\overset{+}{P}—R\ X^-$

(**108**) a; R = benzyl, X = Cl or Br
b; R = methyl, X = I



(**109**)

$$Me_3CCH_2OH \xrightarrow{(\mathbf{108b})} Me_3CCH_2I \quad (160)$$

(75%)

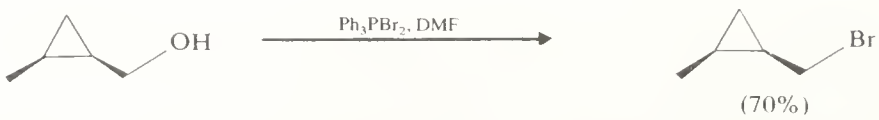
The action of iodine at room temperature on phosphite triesters prepared by using the phosphorochloridite (**109**) provides an alternative mild route to iodides. Equation (161) illustrates the synthetic use of phosphite–halogen adducts analogous to that of the alkyltriphenoxyphosphonium reagents (**108**). The corresponding adducts of triphenylphosphine

$$CH_2{=}C{=}CHCH_2OH \xrightarrow[\text{pyridine, 0 to 20 °C}]{(PhO)_3PBr_2} CH_2{=}C{=}CHCH_2Br \quad (70\%) \qquad (161)$$

(particularly the chloride and bromide) also find useful applications, exemplified by equations (162)–(164). Separation of the alkyl halide from phosphine oxide by-product

$$Me_3CCH_2OH \xrightarrow{Ph_3PCl_2,\ DMF} Me_3CCH_2Cl \quad (92\%) \qquad (162)$$

$$HOCH_2C{\equiv}CCH_2OH \xrightarrow{Ph_3PBr_2,\ MeCN} BrCH_2C{\equiv}CCH_2Br \quad (92\%) \qquad (163)$$



(70%) (164)

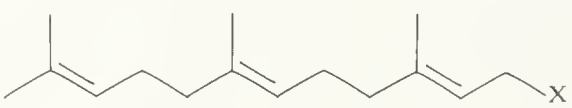
can be simplified by using an insoluble polymer-supported reagent.[225a] This increasingly popular device has also been applied[225b] to the related reactions based on Ph_3P–CX_4 combinations. The latter, and similar combinations incorporating other phosphines, are much used in general and natural product chemistry.[125,212,226] A comparison of equations (156) and (165) demonstrates the suitability of the reagents for the preparation of allylic halides; equation (166) and the conversion of farnesol (**110a**) into the bromide (**110b**) in

$$MeCH(OH)CH{=}CH_2 \xrightarrow{\text{i or ii}} MeCHClCH{=}CH_2 + MeCH{=}CHCH_2Cl \qquad (165)$$

	Production ratio		
i	89	1	1
ii	98		2

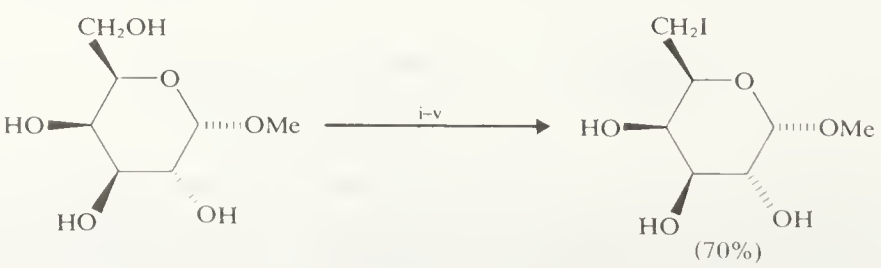
i, Ph_3P, CCl_4, room temperature; ii, $(Me_2N)_3P$, CCl_4, Et_2O, −70 °C to room temperature.

$$MeCOCH_2COMe \xrightarrow{Ph_3P,\ CCl_4} MeCOCH{=}CClMe \quad (75\%) \qquad (166)$$



(**110**) a; X = OH
b; X = Br

90% yield further illustrate the reaction. The distinctive features of the $(Me_2N)_3P$-based reactions exploited extensively by Castro's group[227] include the milder conditions possible with the more nucleophilic phosphine, the formation of relatively stable alkoxyphosphonium chlorides (and particularly fluorophosphates) that can be diverted to form bromides, iodides, and other derivatives by the addition of the appropriate nucleophiles, the ability to convert selectively primary hydroxy groups in the presence of secondary (equation 167), and the ready separation of the water-soluble oxide by-product (HMPT).



(70%) (167)

i, $(Me_2N)_3P$, CCl_4, pyridine, −40 °C; ii, Ac_2O; iii, KPF_6; iv, KI, DMF; v, MeONa.

Although the above reactions are usually represented as proceeding *via* nucleophilic attack by a halide ion on the alkoxyphosphonium cation of (**85**) (formed as indicated by the simplified Scheme 11), evidence for a pericyclic fragmentation of an un-ionized alkoxyhalogenophosphorane [$R^1_3PX(OR^2)$] and other reaction pathways has been obtained.[228] Finally, among this group of reactions should be mentioned the use of phosphines in combination with *N*-halogeno compounds. Good results, with selectivity for primary hydroxy groups, have been recorded for steroids and carbohydrates[229] in reactions with Ph_3P and an *N*-halogenosuccinimide (X = Cl, Br, or I). Conversions of secondary alcohols to halides can be facilitated by using the combination of $(Me_2N)_3P$ with *N*-chlorodi-isopropylamine.[230]

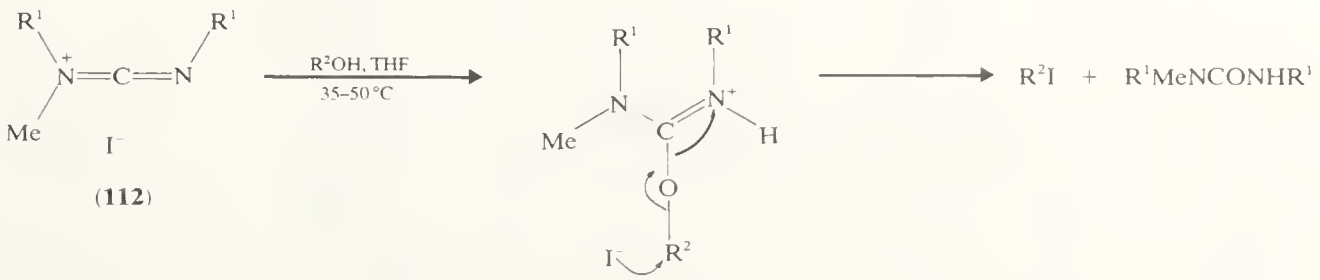
SCHEME 18

When DMF is used as the solvent in halogenations, alternative reaction pathways are conceivable and have been implicated for several reagents, *e.g.* $SOCl_2$, Ph_3PBr_2, MsCl. Thus reaction of DMF with the nominal reagent can provide the highly electrophilic Vilsmeier species (**111**), and formation of the halide *via* an alkoxymethyleneammonium salt (Scheme 18). Specific applications of pre-formed Vilsmeier reagents (**111**; X = Y = Cl

$$CCl_3C(OR)=\overset{+}{N}H_2\ Cl^- \xrightarrow{\text{heat}} RCl + CCl_3CONH_2 \qquad (168)$$

$$ArOC(OR)=\overset{+}{N}H_2\ Cl^- \xrightarrow{\text{heat}} RCl + ArOCONH_2 \qquad (169)$$

or Br) have recently been described.[231] Closely related methods for activating alcohols to S_N2 displacement by halide ions are represented by the use of Pinner-type derivatives (equations 168 and 169), the Mukaiyama intermediates (**86**) and (**87**),[232] and N^1-methyl-N^1,N^2-dicyclohexylcarbodi-imidium iodide (**112**) (Scheme 19).[233]



SCHEME 19

Until recently the only major reagent for the direct replacement of a hydroxy group by fluorine was the Yarovenko reagent, Et_2NCF_2CHClF (**113**). Yields are best with primary alcohols (equation 170), and the reagent has been used extensively with steroids.[133a] In addition to Ph_3PF_2, other fluorophenylphosphoranes (*e.g.* $PhPF_4$) can also be used to convert alcohols, directly or *via* the trimethylsilyl ethers.[133a,234] The same options are available for the preparation of iodides with the novel reagent Me_3SiI. By the direct method,[235] cyclohexanol gave the iodide in 81% yield after reaction at 25 °C for 24 h. New preparative methods awaiting exploitation include the phase-transfer catalysed

$$MeCHBrCH_2CH_2OH \xrightarrow[\text{room temperature}]{\text{(113)},\ Et_2O} \underset{(73\%)}{MeCHBrCH_2CH_2F} \qquad (170)$$

reaction of an alcohol with dichlorocarbene,[236a] the oxidation of alkyl carbazates,[236b] the homolysis of alkyl t-butylperoxyglyoxalates in CCl_4 or CBr_4,[236c] the reaction of PCl_5 with alkyl salicylates,[236d] and the reactions of halogens and various derivatives with esters containing a thiocarbonyl group.[236e]

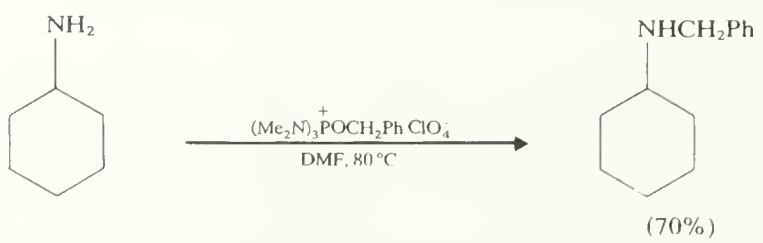
(*d*) *Amines.* Few general methods exist for the reciprocal conversions of alcohols and amines *via* the direct interchange of C—O and C—N bonds. Although alcohols are used industrially for the alkylation of ammonia and amines, the sulphonate esters of primary and secondary alcohols are more appropriate for laboratory reactions. For the preparation of primary amines, the indirect route (equation 171) using an azide for the S_N2 displacement — avoiding the problems of overalkylation and elimination with ammonia — is commonly taken. Azides can be prepared similarly by using the alkoxyphosphonium salts (**85a**)[124,237] and (**85b**).[227] Reagent (**85a**) can also be used to alkylate phthalimide in a mild alternative to the Gabriel synthesis of primary amines (equation 172),[238] while (**85b**; $X = ClO_4$) has been used for the monoalkylation of primary and secondary amines (equation 173).[239] In a related reaction the aminophosphonium salt (**104**) can be employed for the preparation of all classes of aliphatic amines in excellent yield (equation 174).[240]

$$MeC(CH_2OH)_3 \xrightarrow{\text{i, ii, iii}} MeC(CH_2NH_2)_3 \quad (76\%) \qquad (171)$$

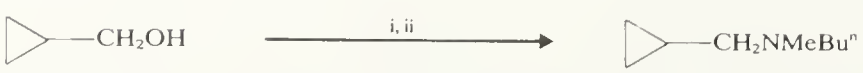
i, $PhSO_2Cl$, pyridine; ii, NaN_3; iii, $LiAlH_4$.

$$n\text{-}C_6H_{13}CH(OH)Me\ (S) \xrightarrow{\text{i, ii}} n\text{-}C_6H_{13}CH(NH_2)Me\ (R)\ (48\%) \qquad (172)$$

i, Ph_3P, $EtO_2CN{=}NCO_2Et$, phthalimide, THF; ii, N_2H_4.



(70%) (173)



(92%) (174)

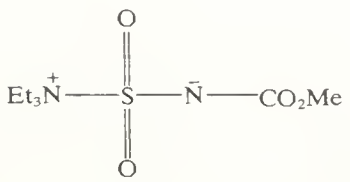
i, NaH, DMF; ii, (**104**), Bu^nMeNH, DMF, 80 °C.

Several reactions involving sulphamyl intermediates have been described. The thermal rearrangement of sulphamate esters of alcohols giving relatively stable carbenium ions[241] seems mainly to be of interest for the preparation of benzylic tertiary amines (equation 175). The formation of urethanes by the reaction of (**114**) [the inner salt of methyl (carboxysulphamyl)triethylammonium hydroxide, obtained by consecutive treatments of (**115**) with MeOH and Et_3N] with a primary alcohol (others dehydrate, see Section 4.1.1.4, p. 643) can be used in a two-step synthesis of primary amines (equation 176).[242] By contrast, the thermal decomposition of *N*-chlorosulphonylurethanes [$ROCONHSO_2Cl$, prepared from (**115**)] to *N*-alkylsulphamyl chlorides ($RNHSO_2Cl$), followed by

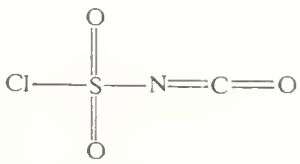
$$PhCH(OH)Me \xrightarrow{\text{i, ii, iii}} PhCH(NMe_2)Me \quad (60\%) \qquad (175)$$

i, NaH, glyme; ii, Me_2NSO_2Cl; iii, thermolysis (60 °C).

$$n\text{-}C_6H_{13}OH \xrightarrow{\text{(114), 95 °C, 1 h}} n\text{-}C_6H_{13}NHCO_2Me \quad (52\%) \qquad (176)$$

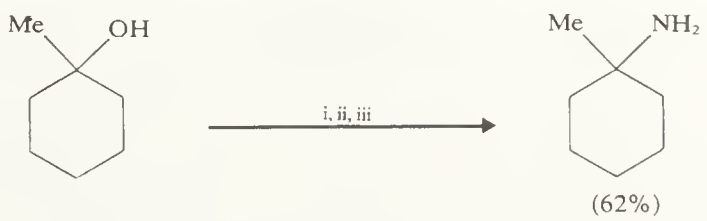


(**114**)



(**115**)

conversion to and oxidation of the t-butyloxycarbonylhydrazides (equation 177) is specific for the preparation of primary amines from tertiary alcohols.[243] The standard method for carrying out the latter transformation is the Ritter reaction,[244] followed by hydrolysis of the amide product. The scope of the Ritter reaction is determined by the strongly acidic conditions and the carbenium ion mechanism; good yields can be obtained with tertiary alcohols (equation 178), but rearrangements are common with secondary alicyclic alcohols. A formally similar reaction[245a] occurs when an alcohol is treated with chlorodiphenylmethylium hexachloroantimonate [$Ph_2\overset{+}{C}Cl\ SbCl_6^-$ (**116**)] in the presence of a nitrile, followed by aqueous work-up of the reaction mixture (equation 179). The mechanism proposed is shown in Scheme 20. A closer analogue of the Ritter reaction, also avoiding strongly acidic conditions, is the amide-forming reaction between an alcohol, MeCN, and SO_2Cl_2.[245b]



(62%) (177)

i, (**115**), hexane, warm; ii, $H_2NNHCO_2Bu^t$; iii, $Pb(OAc)_4$.

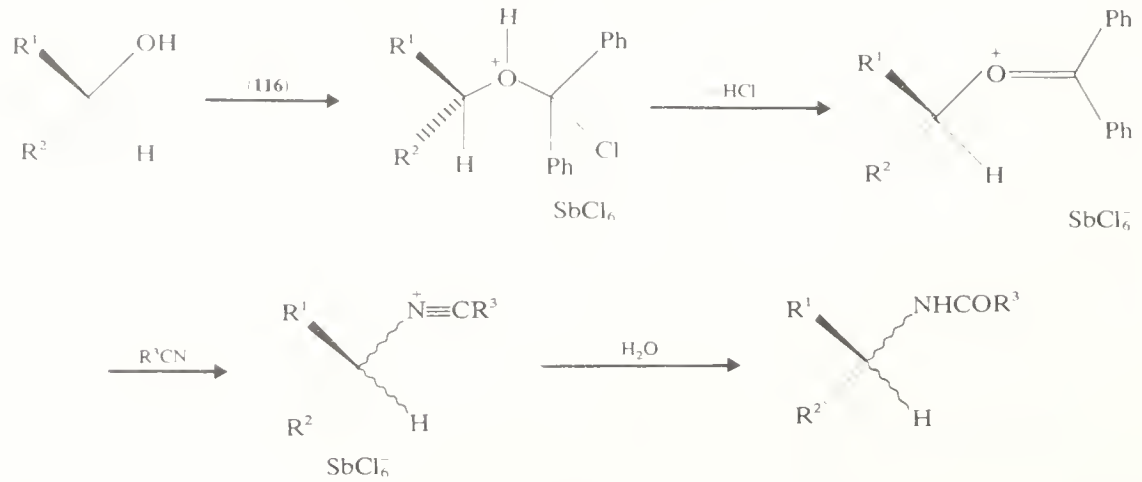
$$EtCMe_2OH \xrightarrow{\text{i, ii}} EtCMe_2NH_2 \quad (80\%) \qquad (178)$$

i, HCN, H_2SO_4, Bu^n_2O; ii, hydrolysis.

$$n\text{-}C_6H_{13}CH(OH)Me \xrightarrow{\text{i, ii}} n\text{-}C_6H_{13}CH(NHAc)Me \quad (86\%) \qquad (179)$$

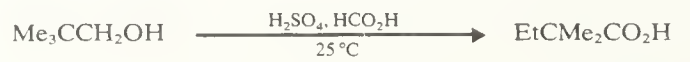
i, (**116**), MeCN; ii, H_2O.

(*e*) *Carboxylic acids* via *carbonylation.* Outside industrial circles the carbonylation reactions of alcohols are little known. The major products are formates (from base-catalysed reactions), acetates and carbonates (from reactions catalysed by Pd^{II}, Cu^{II}, Hg^{II} or RONa–Se), or carboxylic acids (from reactions catalysed by acid or Group VIII metal

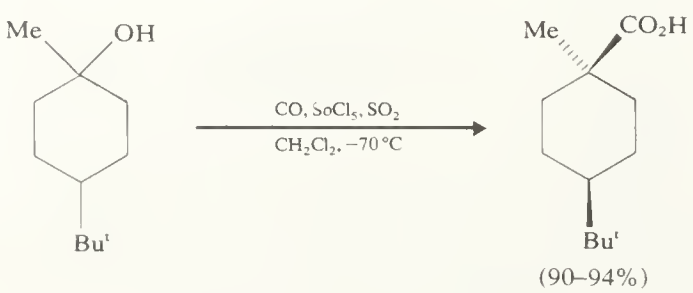


SCHEME 20

carbonyls).[246] Carbonylations in concentrated H_2SO_4 are carried out at low temperature (ambient or below) with CO under modest pressure, or generated *in situ* from HCO_2H (the Koch–Haaf reaction). Higher temperatures and pressures are needed for reactions catalysed by H_3PO_4 or BF_3 alone; the supplementary use of a copper(I) or silver(I) carbonyl catalyst produces rapid reactions at ambient temperature and atmospheric pressure in all cases.[247] Other mild and novel systems are low-temperature carbonylations in $SbCl_5$–SO_2, alone[248a] or with HCl,[248b] and in SbF_5–HF.[248c] Examples of these carbenium-ion-mediated reactions are given in equations (180) and (181). Industrially, the carbonylation of MeOH is an important process for the manufacture of $MeCO_2H$. The iodine-promoted, cobalt-catalysed process employs high operating pressures that are avoided in the more recent and highly selective (99%) process[249] based on a soluble rhodium catalyst.



(180)

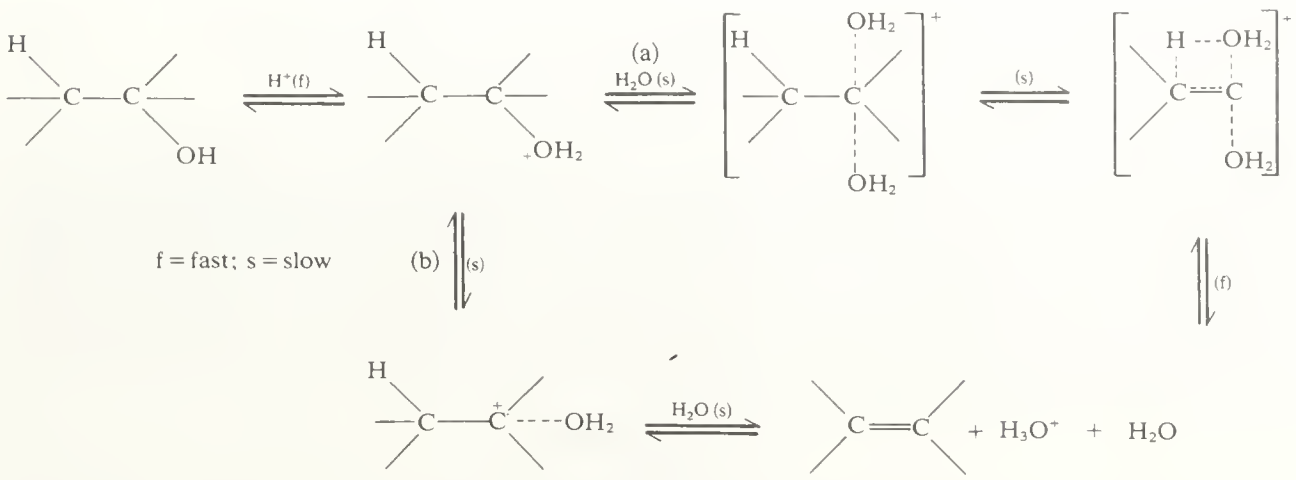


(181)

(iv) Dehydration to alkenes

Competition from elimination, involving the loss of a β-proton, is a normal expectation when the hydroxy group of an alcohol is activated towards nucleophilic displacement, and is promoted by the absence of a powerful nucleophile or the presence of base. Dehydration is most simply realized by heating the alcohol with a strong acid, commonly H_2SO_4, $KHSO_4$, TsOH, or H_3PO_4, although many other Brønsted and Lewis acids have been used as catalysts.[24,250] The vigour necessary decreases from primary alcohols (*e.g.* concentrated H_2SO_4, 170–180 °C) to tertiary alcohols (*e.g.* 20% H_2SO_4, 80–90 °C; heating with oxalic acid or I_2). This order of reactivity, together with the frequent occurrence of rearrangements and the predominant formation of Saytzeff alkenes, has often been taken to indicate a simple *E*1 mechanism for acid-catalysed dehydration, with the

rate-determining formation of the carbenium ion. A more complex picture has emerged from kinetic studies[251] which show, for example, that exchange of the hydroxy group with the aqueous reaction medium occurs more rapidly than alkene formation. Plausible mechanisms must therefore also incorporate a relatively slow deprotonation step. Scheme 21 shows recently favoured[251b] examples of such mechanisms for primary alcohols (route a, indicating a concerted process) and tertiary alcohols (route b, indicating the formation of an encumbered carbenium ion). Other conceivably significant pathways could include the formation of ethers or inorganic esters as intermediates, with the latter undergoing thermolytic elimination in the manner of acetates, xanthates, and similar derivatives.



SCHEME 21

Another classical method for converting an alcohol to an alkene is gas-phase dehydration over a metal oxide catalyst.[251a] Reactions over alumina, the most widely used and studied catalyst, are usually regioselective for Saytzeff alkenes and stereoselective for (*Z*)-isomers, although these selectivities are subject to inductive and steric influences, respectively[252] (equation 182). At moderate temperature (below 250 °C), such reactions are believed to resemble *E*2 eliminations, involving antiperiplanar abstraction of OH^- and H^+ by acidic and basic sites on the catalyst. At higher temperatures (more usual for preparative work), a carbenium ion mechanism is favoured for tertiary alcohols.[251a,253] A very distinctive application of thoria catalysts[254a] is to the preparation of terminal alkenes from secondary alkan-2-ols (equation 183). This selectivity is apparently associated with *syn* elimination and possibly an *E*1cB mechanism.[254b]

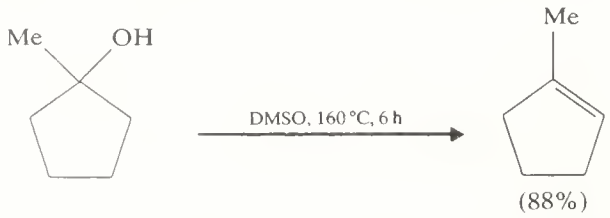
$$MeCH(OH)CH_2R \xrightarrow[210\,^\circ C]{Al_2O_3} \underset{\textbf{(117)}}{CH_2{=}CHCH_2R} + \underset{\textbf{(118}, Z\textbf{)}}{MeCH{=}CHR} + \underset{\textbf{(118}, E\textbf{)}}{MeCH{=}CHR} \quad (182)$$

Product ratios

R	(**118**):(**117**)	(**118**, *Z*):(**118**, *E*)
Me	2.4	5.9
Et	1.5	5.5
Pr^n	1.3	5.2
Pr^i	0.96	4.7
Bu^t	0.64	2.1

$$Me_2CHCH_2CH(OH)Me \xrightarrow[400\,^\circ C]{ThO_2} \underset{(85\%)}{Me_2CHCH_2CH{=}CH_2} + \underset{(2\%)}{Me_2CHCH{=}CHMe} \quad (183)$$

In suitable cases, dehydration can also be effected by heating the alcohol in DMSO (equation 184) or HMPT (equation 185) at or near reflux. The first is actually a reaction catalysed by acid generated *in situ* from the solvent,[255] whereas the second apparently involves phosphorodiamidate intermediates [$ROPO(NMe_2)_2$] that undergo $E2$ elimination



(88%) (184)

$$Bu^t_2MeCOH \xrightarrow{HMPT,\ 240\,^\circ C} Bu^t_2C{=}CH_2 + Bu^tCMe_2CMe{=}CH_2 \qquad (185)$$

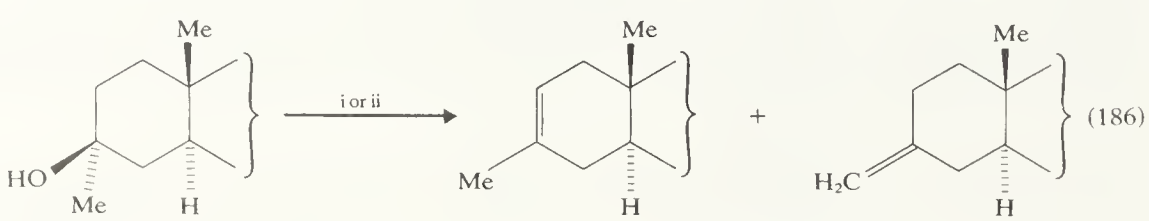
Product ratio 97 : 3

(typical primary and secondary alcohols) or $E1$ elimination (tertiary alcohols and secondary alcohols lacking a β-hydrogen).[256] In reactions proceeding *via* carbenium ions, rearrangements are less extensive with HMPT than with DMSO. Alkoxysulphuranes, *e.g.* (**119**), produce rapid elimination from secondary and tertiary alcohols under very mild conditions.[257] The alcohols are activated by an alkoxy-exchange reaction with (**119**), with subsequent elimination showing the usual divergence of mechanism ($E1$ or $E2$) according to the class of alcohol. The reagent has been used successfully for the dehydration of acid-labile tricyclopropylmethanol (yield 32%).

$PhC(CF_3)_2OSPh_2OCPh(CF_3)_2$

(**119**)

Several of the activation procedures (in addition to protonation) discussed in Section 4.1.1.4 (p. 618) can be adapted or extended to produce overall elimination. Obvious examples, which are discussed elsewhere in this work, are the elimination reactions of halides and sulphonates. Well-established one-step procedures are represented by the applications (particularly to tertiary and secondary steroidal alcohols) of $POCl_3$–pyridine and $SOCl_2$–pyridine. The latter reagent is the more powerful and has a greater tendency to induce $E1$ elimination by forming a better leaving group (OSOCl), as indicated by the product ratios for equation (186). Newer procedures are the selective dehydration of secondary alcohols by the Rydon–Landauer reagent (**108b**) in HMPT (equation 187)[258] or by Ph_3P–CCl_4 in MeCN.[259]



(186)

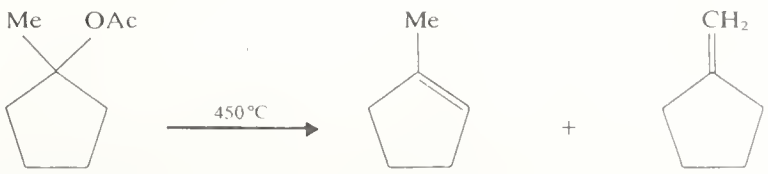
Product ratios

i	93	7
ii	48	52

i, $SOCl_2$, pyridine, 25 °C, 30 min; ii, $POCl_3$, pyridine, 100 °C, 2 h.

(53%) (187)

Thermolytic eliminations of alcohol derivatives, which well maintain their preparative value and mechanistic fascination,[251c,260] will only be considered briefly here. For preparative purposes, acetates and *S*-methyl xanthates (in the Chugaev reaction)[261] are more widely used than alternatives such as carbonates, carbamates, *p*-nitrobenzoates, and borates. The typical (but not constant) virtues of the reactions (equations 188 and 189),

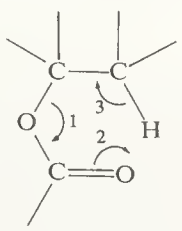


(188)

Product ratio 84 : 16

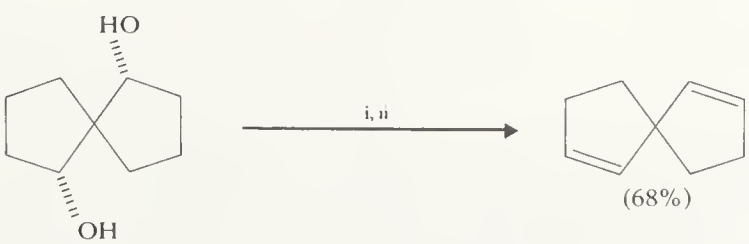
$$Bu^tCH(OCSSMe)Me \xrightarrow{170\,^\circ C} Bu^tCH{=}CH_2 \quad (71\%) \qquad (189)$$

the avoidance of acidic conditions and rearrangement, are usually attributed to *syn* elimination *via* a polarized, six-centered, cyclic transition state (**120**). The advantage of



(**120**) 1>2>3

lower temperatures (100–250 °C) for the Chugaev reaction (*vs.* 300–600 °C for acetates) must be set against the greater difficulty in preparing the xanthates and in purifying the products. Derivatives that can apparently decompose by different mechanisms include thiocarbonate *O*-esters (equation 190)[262] and the *N*-methoxycarbonylsulphamate esters of secondary and tertiary alcohols (equation 191)[263] (although specific *syn* elimination



(190)

i, *p*-MeC_6H_4OCSCl, pyridine; ii, 160 °C.

(191)

i, (**114**), benzene; ii, 60 °C.

occurs in the reaction shown, *anti* elimination has been found for some steroidal esters). Other derivatives susceptible to thermal elimination are *N*-methyl-4-alkoxypyridinium iodides[264a] and the *O*-alkylisoureas prepared by reaction of the alcohol with the tetrafluoroborate or fluorosulphonate analogues of reagent (**112**) (Scheme 19, p. 637).[264b]

The photolysis of thiobenzoate *O*-esters (equation 192) is a useful method for the dehydration of homoallylic alcohols.[265]

$$PhCH_2CH_2OCSPh \xrightarrow[CH_2Cl_2]{h\nu,\ Et_3N} PhCH{=}CH_2 \quad (90\%) \qquad (192)$$

(*v*) *Oxidation to carbonyl compounds*

The conversion of primary and secondary alcohols to aldehydes and ketones, respectively, is one of the major functional transformations and a popular system for mechanistic studies and the evaluation of new reagents. Extensive accounts of the oxidation[47,266] and of particular reagents (Table 8) are available, which may justify a selective treatment oriented towards preparative aspects and novel developments. Although indirect methods of oxidation are relatively unusual, uses of derivatives of type (**83**)—activated towards hydride abstraction from the α-carbon — will be exemplified.

TABLE 8

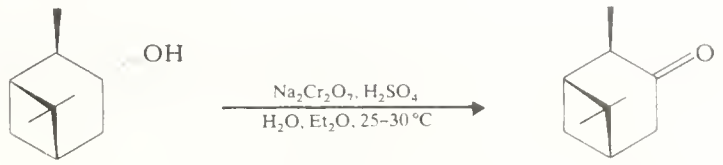
Major Methods and Reagents for the Oxidation of Primary and Secondary Alcohols

Method	*Representative reagents*
Oxidation by metal-ion-based reagents	$Na_2Cr_2O_7$, H_2CrO_4, $Bu^t_2CrO_4$, $CrO_3 \cdot 2C_5H_5N$, (**121**), (**122**), $KMnO_4$, K_2FeO_4,[a] Na_2RuO_4,[b] MnO_2, RuO_4, Ag_2CO_3/Celite, silver(II) picolinate,[c] $(NH_4)_2Ce(NO_3)_6$, $K_3Fe(CN)_6$, $Pb(OAc)_4$, nickel peroxide
Oxidation by halogen-based reagents	Br_2, NaOCl, INO_3/pyridine,[d] *N*-bromosuccinimide, $Ph_2C{=}NBr$,[e] (**124**),[f] (**125**),[g] $PhICl_2$, Me_2SCl_2
Oxidation by DMSO–electrophile reagents	Electrophiles; $RN{=}C{=}NR/H_3PO_4$, P_4O_{10}, Ac_2O, SO_3/pyridine, TsCl,[h] cyanuric chloride,[h] $(CF_3CO)_2O$,[i] $(CF_3SO_2)_2O$[j]
Oxidation and related reactions	Me_2CO/cyclohexanone/$(RO)_3Al$ (R = Bu^t, Pr^i), Al_2O_3/CCl_3CHO,[k] (**130**), (**131**)[l]
Catalytic dehydrogenation	Catalysts: Gas phase Cu, Ag, Cr, Ni, ZnO; Solution Rh, Ru, and Os complexes
Catalytic oxidation	Pt/O_2, CuO,[m] $(Ph_3P)_3RuCl_2$/(**132**)

[a] R. J. Audette, J. W. Quail, and P. J. Smith, *Tetrahedron Letters*, 1971, 279. [b] D. G. Lee, D. T. Hall, and J. H. Cleland, *Canad. J. Chem.*, 1972, **50,** 3741. [c] T. G. Clarke, N. A. Hampson, J. B. Lee, J. R. Morley, and B. Scanlon, *Canad. J. Chem.*, 1969, **47,** 1649. [d] U. E. Diner, *J. Chem. Soc.* (*C*), 1970, 676. [e] C. G. McCarty and C. G. Leeper, *J. Org. Chem.*, 1970, **35,** 4245. [f] C. W. Rees and R. C. Storr, *J. Chem. Soc.* (*C*), 1969, 1474. [g] J. J. Kaminski and N. Bodor, *Tetrahedron*, 1976, **32,** 1097, [h] J. D. Albright, *J. Org. Chem.*, 1974, **39,** 1977. [i] S. L. Huang, K. Omura, and D. Swern, *J. Org. Chem.*, 1976, **41,** 3329. [j] J. B. Hendrickson and S. M. Schwartzman, *Tetrahedron Letters*, 1975, 273. [k] G. H. Posner, R. B. Perfetti, and A. W. Runquist, *Tetrahedron Letters*, 1976, 3499. [l] R. C. Cookson, I. D. R. Stevens, and C. T. Watts, *Chem. Comm.*, 1966, 744. [m] M. Y. Sheikh and G. Eadon, *Tetrahedron Letters*, 1972, 257.

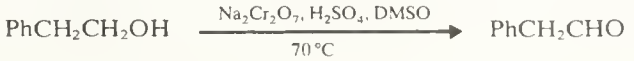
Among oxidants generally, and transition-metal oxidants in particular, chromium(VI) reagents are the most widely used. The most familar reagent, chromic acid, is normally used in water, aqueous acetic acid, or aqueous acetone (the Jones reagent); the use of a solution in DMSO has also been described.[267] In the absence of structural complications, ketones are readily obtained in high yield from secondary alcohols. Over-oxidation and — where relevant — epimerization can be minimized by using the calculated amount

of chromic acid and by providing a protective environment for the product (*e.g.* acetone in the Jones method, or diethyl ether in Brown's two-phase method) (equation 193). A further problem with some secondary alcohols is competing cleavage of the C_α—C_β bond. It is most pronounced when homolysis produces a relatively stable radical (*e.g.* up to 60% in the oxidation of t-butylphenylmethanol) or relieves molecular strain (*e.g.* at least 33% in the oxidation of cyclobutanol).



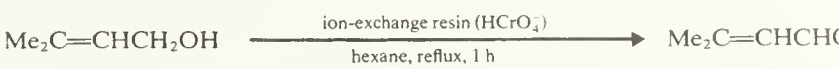
(94%) (193)

The efficient production of aldehydes from primary alcohols requires even greater care to avoid over-oxidation directly to the carboxylic acid or indirectly (*via* a hemiacetal) to the ester thereof. Procedures adopted are the distillation of the aldehyde as formed, and the use of the Jones reagent[268] or chromic acid in DMSO (equation 194). The milder



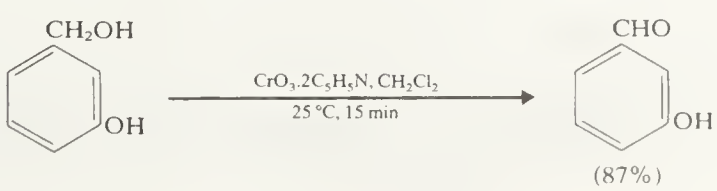
(82%) (194)

methods also permit the oxidation of unsaturated alcohols without excessive oxidation, migration, or isomerization of the multiple bonds. The goal of chemoselectivity has also encouraged the development of other mild reagents and convenient procedures. Insoluble oxidants that simplify the experimental work-up are an anion-exchange resin in the $HCrO_4^-$ form,[269] and a CrO_3–graphite reagent.[270a] The latter — its description as an intercalation complex has been disputed[270b] — shows useful selectivity for primary alcohols, whereas the former has given good results with all classes, *e.g.* equation (195),

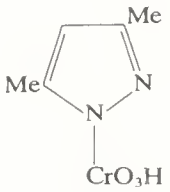


(91%) (195)

except unsaturated alcohols prone to *cis–trans* isomerization. The mild general oxidants di-t-butyl chromate (Oppenauer) and potassium dichromate (in acetic acid) appear to be mainly useful for the oxidation of primary and secondary alcohols, respectively, while neutral aqueous sodium dichromate is effective with benzylic alcohols.[271] Activated alcohols can also be readily oxidized by solutions of CrO_3 in DMF, DMSO, or HMPT.[272] However, the oxide is most commonly used as a solution of its dipyridine complex in dichloromethane. The complex is most safely and conveniently prepared *in situ*[273] (*cf.* the Collins reagent), giving a reagent more reliable than that originally described by Sarett (a suspension of the complex in pyridine). It is frequently the reagent of choice for the oxidation of acid-labile alcohols under mild conditions (room temperature or below), giving high yields of both aldehydes and ketones, *e.g.* equation (196). One disadvantage — the need to use a large excess (six- to ten-fold)[274] of oxidant — has led to the introduction of related reagents, the most notable being the CrO_3–3,5-dimethylpyrazole complex (**121**),[275a] pyridinium chlorochromate (**122**),[275b] and chromyl chloride in CH_2Cl_2–pyridine (with or without Bu^{t}OH).[275c] Examples of their use are given in equations (197)–(199).



(87%) (196)

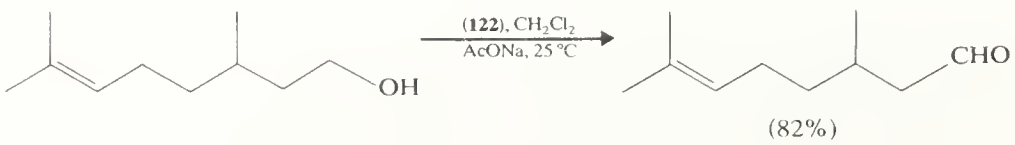


(**121**)

$C_5H_5N.HCrO_3Cl$

(**122**)

$$n\text{-}C_5H_{11}CH(OH)C{\equiv}CH \xrightarrow[0\,^\circ C]{(\mathbf{121}),\ CH_2Cl_2} n\text{-}C_5H_{11}COC{\equiv}CH \quad (78\%) \qquad (197)$$

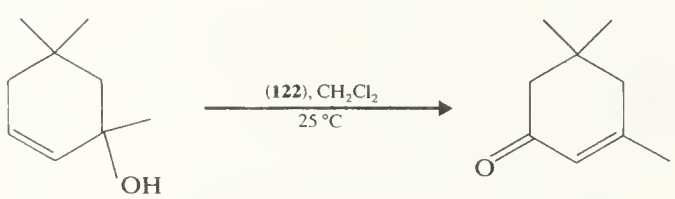


(198)

(82%)

$$n\text{-}C_{12}H_{25}OH \xrightarrow[CH_2Cl_2,\ 25\,^\circ C]{CrO_2Cl_2,\ Bu^tOH,\ pyridine} n\text{-}C_{11}H_{23}CHO \quad (99\%) \qquad (199)$$

Pyridinium chlorochromate, a stable, commercially-available solid, has found a number of interesting applications, including the formation of transposed ketones on the oxidation of tertiary allylic alcohols (equation 200).[276]



(200)

(94%)

The mechanism of chromium(VI) oxidation of alcohols has provided one of the durable problems of physical organic chemistry. The likely steps are outlined in Scheme 22. The initial steps (1 and 2) leading to chromium(IV) seem to be firmly established, with step 2 (decomposition of a chromate ester) being rate-determining except for highly hindered alcohols. Recent studies, mainly by the groups of Roček and Wiberg, indicate that the subsequent steps — which lead to chromium(III) and account for two-thirds of the carbonyl products — include radical reactions.[277] It has further been shown that the

Step 1 $R_2CHOH + HCrO_4^- + H^+ \longrightarrow R_2CHOCrO_3H + H_2O$

Step 2 $R_2CHOCrO_3H \longrightarrow R_2CO + Cr^{IV}$

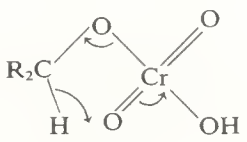
Step 3 $R_2CHOH + Cr^{IV} \longrightarrow R_2\dot{C}OH + Cr^{III}$

Step 4 $R_2\dot{C}OH + Cr^{VI} \longrightarrow R_2CO + Cr^{V}$

Step 5 $R_2CHOH + Cr^{V} \longrightarrow R_2CO + Cr^{III}$

SCHEME 22

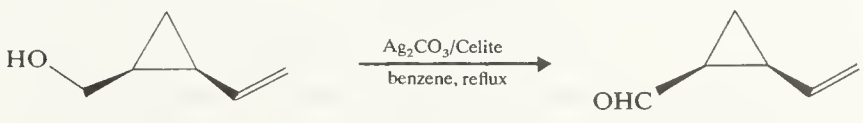
one-electron oxidant chromium (IV) [the amount of which can be increased by disproportionation of chromium(V)] is responsible for the competing C—C bond cleavage described above.[278] The mechanistic details of step 2 sustain a lively controversy,[279] and strenuous efforts are still being made (i) to characterize stereoelectronic effects on the reaction rate, (ii) to determine the direction of electron flow, (iii) to define the nature and geometry of the transition state, and (iv) to locate it along the reaction coordinate. Steric acceleration of the decomposition (*e.g.* axial esters > equatorial esters) and the negative values of the reaction constants ρ and ρ^* are often taken to indicate a product-like transition state with electron deficiency at the α-carbon resulting from hydride transfer by an electrocyclic process (**123**). Alternative schemes include proton rather than hydride transfer, proton



(**123**)

tunnelling (for highly hindered esters), and acyclic mechanisms. A mechanistic curiosity explored by Roček's group is the accelerated oxidation of Pr^iOH in the presence of oxalic acid — or various other bifunctional compounds — apparently involving a synchronous *three-electron* process. The oxidation can also be catalysed by picolinic acid (pyridine-2-carboxylic acid).[280]

Relatively few of the many other transition-metal compounds known to oxidize alcohols[266,281] have been developed as synthetically useful reagents. Manganese(VII) finds occasional use for the conversion of primary alcohols to acids and secondary alcohols to ketones, while the lanthanide cerium(IV) is recommended[282] as a convenient oxidant for benzylic alcohols. A major limitation with cerium(IV) and various other one-electron oxidants (*e.g.* Mn^{III}, V^V) is the significant competition from cleavage reactions analogous to those caused by chromium(IV). On the other hand, silver(I) carbonate on Celite (the Fétizon reagent[283]) has rapidly become established as an excellent reagent for clean oxidations under mild conditions. The reaction and its selectivity are illustrated by equations (201) and (202), while other distinctive reactions of diols are considered in Section 4.1.2.4. Specially-prepared ('active') MnO_2 is another excellent, mild oxidant.[284]



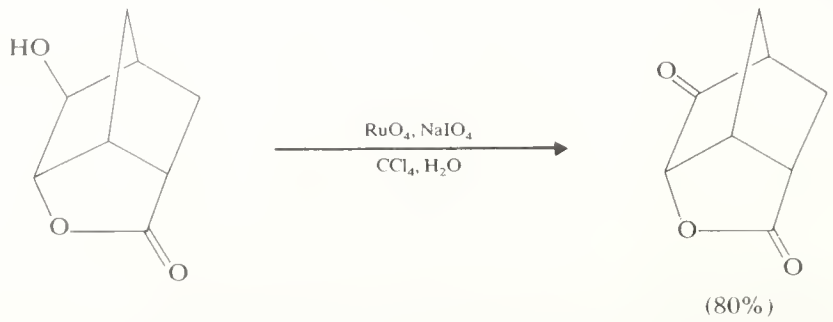
(80%) (201)

(70%) (202)

Although all classes of alcohols can be oxidized, the reagent is mainly used for the selective oxidation of activated (allylic, α-alkynic, benzylic) hydroxy groups. The ability to oxidize highly unsaturated alcohols without rearrangement or isomerization, *e.g.* equation (203), is especially attractive, and has been much exploited in the synthesis of natural products, *e.g.* 80% yield of the aldehyde from retinol (**13**).

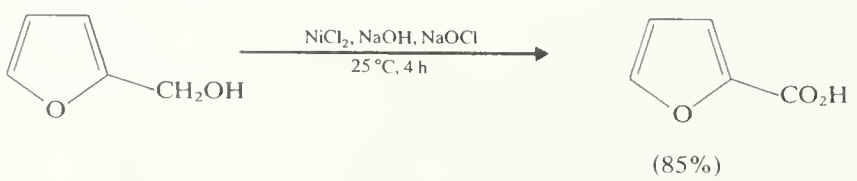
$$\underset{(Z)}{n\text{-}C_3H_7C{\equiv}CC{\equiv}CCH{=}CHCH_2OH} \xrightarrow[CH_2Cl_2,\ 25\,^{\circ}C]{MnO_2} \underset{(Z)\quad(90\%)}{n\text{-}C_3H_7C{\equiv}CC{\equiv}CCH{=}CHCHO} \qquad (203)$$

Two very powerful oxidants that also react under mild conditions are ruthenium tetroxide[285] and nickel peroxide (the Nakagawa reagent).[286] The former reagent, generated stoichiometrically or catalytically (with $NaIO_4$ or NaOCl as the co-oxidant) from RuO_2 or $RuCl_3$, has found a number of useful applications in alicyclic, steroid, and carbohydrate chemistry, particularly for 'difficult' oxidations, *e.g.* equation (204). Its low



(80%) (204)

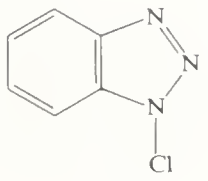
chemoselectivity (*e.g.* aldehydes, C—C multiple bonds, and ethers are oxidized) limits the range of suitable substrates. Used as a suspension in benzene or light petroleum, nickel peroxide serves as a more reactive substitute for MnO_2. In aqueous alkali, it is a good reagent for the oxidation of primary alcohols to acids, and can be used catalytically for this purpose with NaOCl as the co-oxidant (equation 205).[287] The sheer versatility of



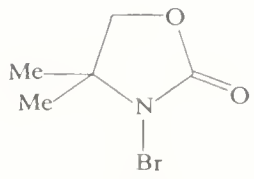
(85%) (205)

$Pb(OAc)_4$ as an oxidant[288] and the several reaction pathways available to the alkoxy derivative formed by interaction with a hydroxy group militate against its general use as a preferred reagent. In a non-polar solvent such as benzene, oxidative cyclization is often the preferred reaction for alcohols containing a δ-hydrogen (Section 4.1.1.4, p. 653). Simple oxidation is promoted at the expense of cyclization, esterification, and fragmentation by carrying out the reaction in pyridine at ambient temperature.

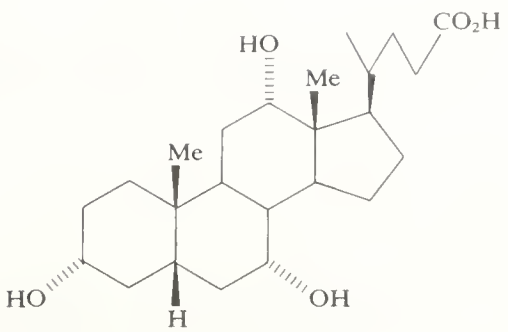
The use of a halogen in alkaline solution for the specific (haloform) oxidation of alcohols of the type, RCH(OH)Me to acids (RCO_2H) is well known. Recent work[289] indicates that aqueous NaOCl, used in the presence of a phase-transfer catalyst, may have a future as a cheap *general* oxidant for benzylic and some secondary alcohols (aliphatic aldehydes readily give the acids). Until recently, studies of oxidations in neutral or weakly acidic solutions were mainly concerned with the mechanism of the reaction with bromine. For preparative purposes, various 'positive halogen' reagents are preferred. In addition to the familiar *N*-chloro and *N*-bromo derivatives of succinimide and acetamide,[290] the group includes relatively untried reagents such as NH_2Cl, chloramine T, *N*-bromo-*o*-sulphobenzoic imide, and others (Table 7, p. 644). In polar media, such reagents and Br_2 are believed to function as electrophiles, abstracting an α-hydrogen of the alcohol as a hydride ion in the rate-determining step. Reagents such as $Ph_2C{=}NBr$ and (**124**) used under non-polar conditions with thermal or photochemical activation oxidize by radical chain mechanisms. The advantages of the *N*-halogeno reagents used under mild conditions (*e.g.* aqueous acetone or dioxan) include the ability to discriminate between different hydroxy groups. Thus, *N*-bromosuccinimide oxidizes secondary but not primary aliphatic alcohols — in contrast to the chloro analogue — and can selectively oxidize axial hydroxy



(**124**)

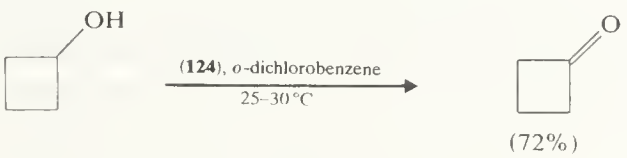


(**125**)



(**126**)

groups in the presence of equatorial, *e.g.* the 7α-group, but not the 3α- or 12α-group in cholic acid (**126**). Equation (206) shows a useful application of reagent (**124**). The selective oxidation of secondary alcohols can also be achieved (equation 207) by using a halogen (Cl_2 or Br_2) in HMPT,[291] or by the combined use[292a] of Br_2 and hexa-n-butyldistannoxane (equation 208). Primary allylic and benzylic alcohols can be oxidized by



(206)

(72%)

$$n\text{-}C_3H_7CH(OH)CHEtCH_2OH \xrightarrow[CH_2Cl_2,\ NaHCO_3,\ 0\text{–}5\ ^\circ C,\ 1\ h]{Br_2,\ HMPT} n\text{-}C_3H_7COCHEtCH_2OH \quad (207)$$

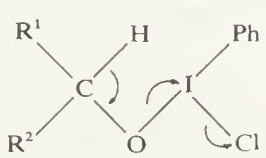
(91%)

$$PhCH(OH)CH_2CH_2OH \xrightarrow[CH_2Cl_2,\ 25\ ^\circ C]{Br_2,\ (Bu^n_3Sn)_2O} PhCOCH_2CH_2OH \quad (208)$$

(86%)

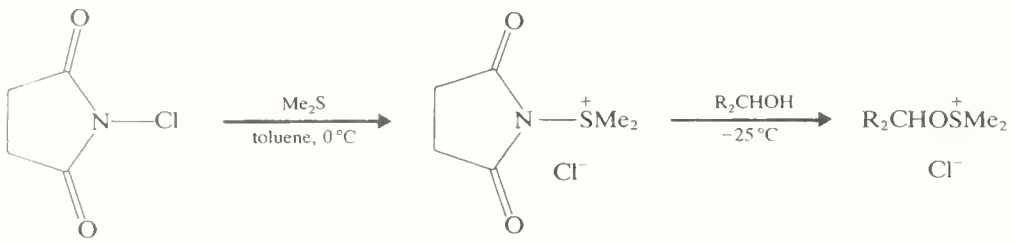
either Br_2 or *N*-bromosuccinimide by prior stannylation;[292b,c] no over-oxidation, isomerization, or bromination was detected in the case of geraniol (**11**). *N*-Chlorosuccinimide in the presence of Bu^tOLi has also been used to oxidize alcohols activated as the alkoxymagnesium bromides.[293]

Complexes formed between Cl_2 or *N*-chlorosuccinimide and various nucleophiles have emerged as valuable additions to the range of mild oxidants. In the presence of pyridine, secondary alkanols are cleanly oxidized by $PhICl_2$, probably *via* the intermediate (**127**).[294]



(**127**)

The even simpler reagent Cl_2–pyridine will oxidize both primary and secondary hydroxy groups, but the difference in reactivity is sufficient to permit selective conversion of the latter.[295] The sulphonium complexes (**106a**) and (**106c**) react readily with both primary and secondary alcohols to give alkoxysulphonium salts, which undergo elimination *via* the ylide (**128**) on treatment with base (Scheme 23).[296] The reaction has already proved its

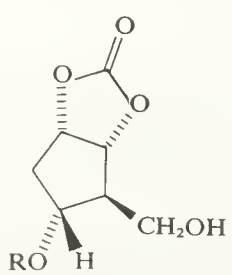


(**106c**)

(**128**)

SCHEME 23

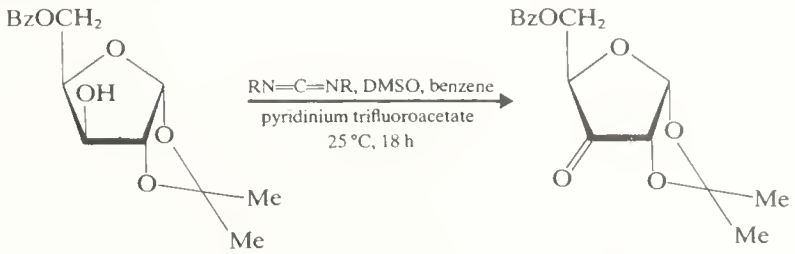
worth in a number of difficult situations, including the oxidation of the prostaglandin intermediate (**129**) to the aldehyde in 93% yield. One restriction is that alcohols that form stable carbenium ions are not oxidized but are converted to chlorides (equation 157). This problem is avoided in the related reaction[297] employing the DMSO–Cl_2 adduct, although this reagent (like $PhICl_2$) causes addition to C—C double bonds.



(**129**) R = *p*-PhC_6H_4

Alkoxysulphonium salts, the reactive intermediates in Scheme 23, are also readily accessible[298] through the nucleophilic displacement reactions of electrophilically-activated DMSO (equation 209). Subsequent decomposition of the cation follows the intramolecular pathway shown in Scheme 23. The original Pfitzer–Moffatt activation procedure, employing dicyclohexylcarbodi-imide and a proton source, has been supplemented by many others, mostly using an acid anhydride or chloride as the electrophile. As expected from equation (209), equatorial hydroxy groups are oxidized more readily than axial ones (*cf.* chromic acid). The choice of reagent is often determined by the ease of work-up, though the carbodi-imide and SO_3 methods seem best for the oxidation of primary

alcohols to aldehydes. The low-temperature $(CF_3CO)_2O$ method is particularly recommended for highly hindered alcohols. Equations (210) and (211) show typical reactions. Variations on the general method include the use of a polymer-based carbodi-imide,[299] and use of a chloroformate ester in place of the free alcohol.[300]



(62%) (210)

$$Pr^i_2CHOH \xrightarrow{\text{i, ii}} Pr^i_2CO \qquad (211)$$

i, DMSO, CH_2Cl_2, $(CF_3CO)_2O$, −65 °C; ii, Et_3N, 25 °C.

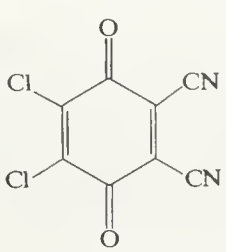
The Oppenauer oxidation[301] is a classical method for effecting hydride transfer from an alkoxide to a carbonyl acceptor. Its major applications have been to the oxidation of secondary steroidal alcohols, with the preferential reaction of equatorial hydroxy groups. Unsaturated alcohols are oxidized smoothly (equation 212), although β,γ-double bonds tend to migrate into conjugation with the carbonyl group under the basic reaction conditions. The mild Posner variant, using dehydrated Al_2O_3 as the promoter and CCl_3CHO or PhCHO as the acceptor, can be used to prepare even hindered ketones with minimal epimerization or condensation, and also to oxidize secondary alcohols and equatorial hydroxy groups selectively, *e.g.* equation (213). The high-potential quinone (**130**) is a well-known dehydrogenating agent[302] and has been widely used to effect uncatalysed hydrogen transfer from allylic steroidal alcohols, usually in dioxan at room temperature. The triazolinedione (**131**) can be used similarly to oxidize secondary and

$$MeCH(OH)CH{=}CHCH{=}CMeCH{=}CH_2 \xrightarrow[Me_2CO,\ benzene,\ reflux]{(Bu^tO)_3Al} MeCOCH{=}CHCH{=}CMeCH{=}CH_2 \qquad (212)$$

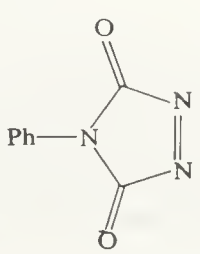
(80%)

$$MeCH(OH)(CH_2)_8CH_2OH \xrightarrow[25\ °C,\ 24\ h]{Al_2O_3,\ PhCHO} MeCO(CH_2)_8CH_2OH \qquad (213)$$

(65%)



(**130**)

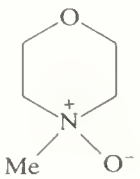


(**131**)

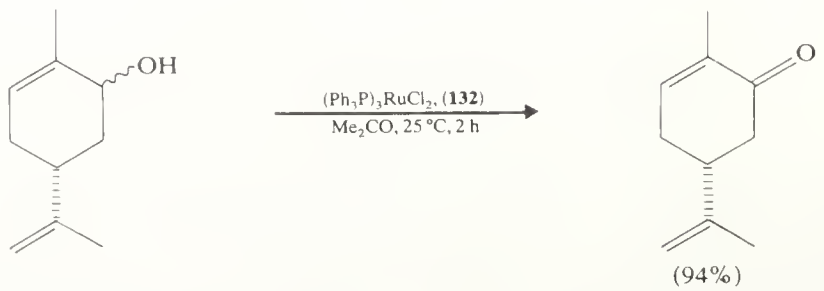
benzylic alcohols. The catalytic dehydrogenation of alcohols is mainly an industrial reaction, applied to simple alcohols in the gas phase over various metal and metal oxide catalysts (processes often combine dehydrogenation with oxidation). Soluble Ru and Os catalysts effective for dehydrogenation have been described[303] and others (Table 5, p. 597) have been used[304] to transfer hydrogen from various alcohols to a variety of organic

acceptors. However, the emphasis in the latter reactions is on the use of alcohols as reductants, rather than on the conversion to carbonyl compounds.

Of greater practical significance is the finding that soluble Ru compounds catalyse the oxidation of primary and secondary alcohols — homoallylic excepted — by *N*-methylmorpholine *N*-oxide (**132**) (equation 214).[305] There is also the prospect that t-alkyl



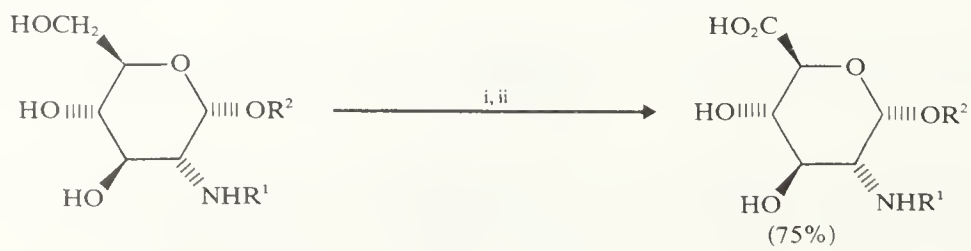
(**132**)



(214)

(94%)

hydroperoxides with $MoCl_5$ as catalyst may prove to be useful oxidants.[306] Already fully proven is the value of catalytic oxidation with Pt and O_2.[307] The general order of reactivity (primary > axial secondary > equatorial secondary hydroxyl), combined with inhibition of further oxidation by the primary product, make the method exceptionally selective for the oxidation of polyhydroxy compounds such as sugars and inositols. Furthermore, the oxidation of primary hydroxy groups stops at the aldehyde stage in neutral or slightly acidic solution, but gives the carboxylic acid under alkaline conditions. The reaction is exemplified by equation (215).

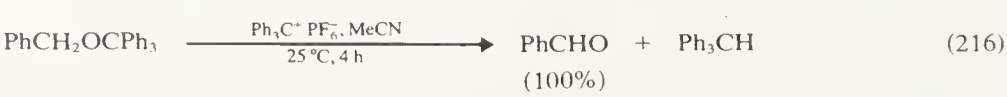


(215)

(75%)

i, Pt, O_2, H_2O, pH 7–8, 80 °C; ii, HCl.

The inventiveness in methodology that is so characteristic of the last decade of organic chemistry has produced a crop of new reagents and approaches to oxidation too plentiful to be harvested in the remaining space available, but a few pickings will be presented. Both carbenium ions[245a,308] and nitrosonium ions[300,309] can be employed as hydride-abstraction reagents for the oxidation of free reactive alcohols or activated derivatives. Such reactions are illustrated by equations (216), (217), and (218). Both primary and



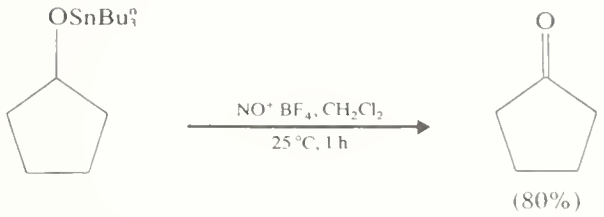
(216)

(100%)

(217)

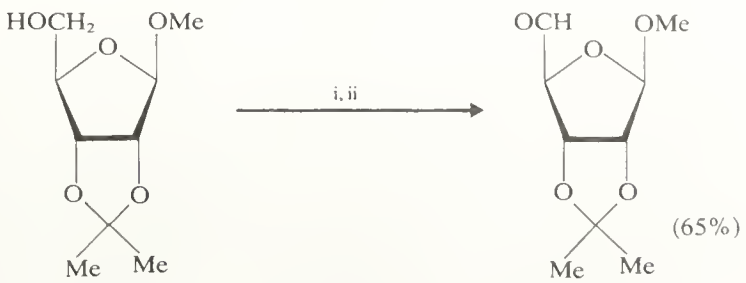
(98%)

i, Me_3SiCl, $(Me_3Si)_2NH$, pyridine; ii, $Ph_3C^+ BF_4^-$, CH_2Cl_2, 25 °C.



(218)

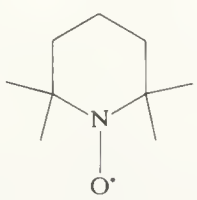
secondary alcohols are readily oxidized *via* photo-fragmentation of their pyruvate esters.[310] The clean oxidation of menthol (**12**) to menthone (yield 88%) and of a ribose derivative (equation 219) attest to the mildness of the reaction conditions. In view of the



(219)

i, MeCOCOCl, pyridine, benzene, 25 °C; ii, $h\nu$.

speed, simplicity, and efficiency with which the necessary derivatives can be prepared (often *in situ*), the 'indirectness' of these methods of oxidation need be no deterrent. Finally, the common oxidant *m*-chloroperbenzoic acid can be used to oxidize secondary alcohols in the presence of HCl or the nitroxide radical (**133**) as catalyst.[311]



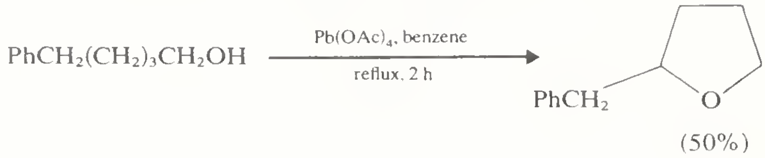
(133)

Among the notable casualties of the selection process are anodic oxidation,[312a] and biological oxidations using either whole organisms[26] or isolated enzymes,[312b] but the impact of these 'specialized' methods on preparative organic chemistry will undoubtedly grow.

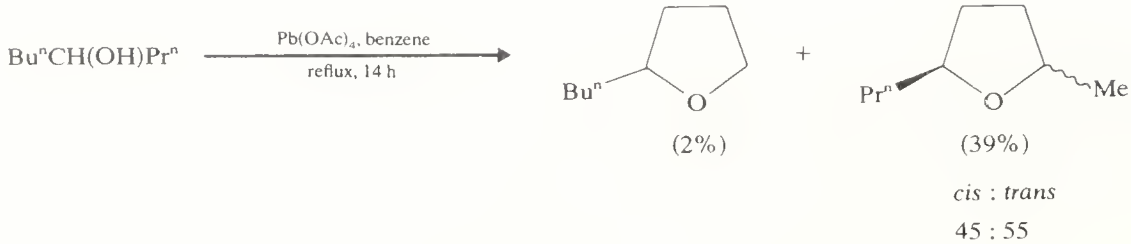
(*vi*) *Oxidative cyclization*

The formation of cyclic ethers, characteristically tetrahydrofurans, by the oxidation of alcohols is strictly a type of remote functionalization (Section 4.1.1.4, p. 655). The present section deals with those reactions that lead directly to cyclic products: oxidation with lead(IV) acetate,[288] and reactions proceeding *via* hypohalite intermediates (mainly hypobromites[133b] and hypoiodites[313]). Similar cyclizations[314] of alkanols with cerium(IV) have not yet achieved comparable importance.

The oxidative cyclization of an alcohol containing an accessible δ-hydrogen with $Pb(OAc)_4$, usually in benzene, can be carried out thermally (under reflux) or photochemically (u.v. photolysis). The yields of tetrahydrofurans from unbranched primary and secondary alkanols are typically 35–55%, *e.g.* equation (220), but are less for tertiary and hindered secondary alcohols, and are adversely affected by branching in the β-position. Equation (221) illustrates the marked preference for reaction at methylene rather than



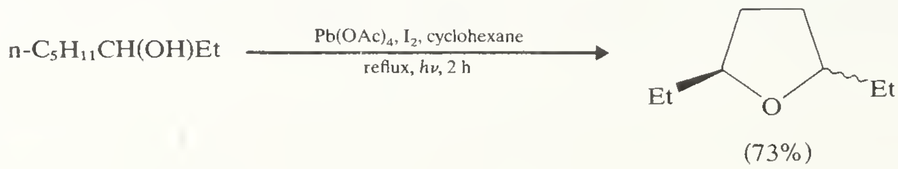
(220)



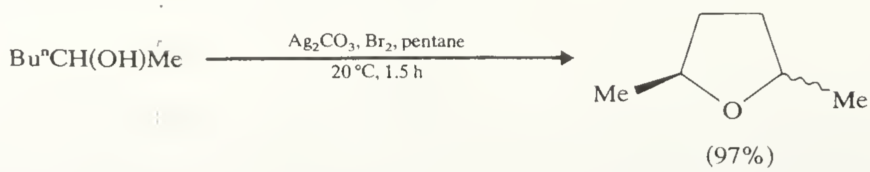
(221)

methyl, in addition to ring closure at the δ-position, and also the formation of the *trans*-isomer in slight excess.

In many cases, significantly better yields of tetrahydrofurans can be obtained by the photolysis or thermolysis of hypohalites, most conveniently prepared *in situ*. Reagents commonly used for this purpose are $Pb(OAc)_4$–I_2, HgO–X_2, and Ag_2O–X_2, in which a function of the metal is to assist in cyclization of the δ-halogenoalcohols formed initially from the hypohalites. Recent improvements include the use of silver(I) carbonate or acetate in place of the oxide, to suppress the formation of carbonyl by-products, and the inclusion of a nucleophilic ether in the reaction mixture. Typical conditions are indicated in equations (222) and (223).

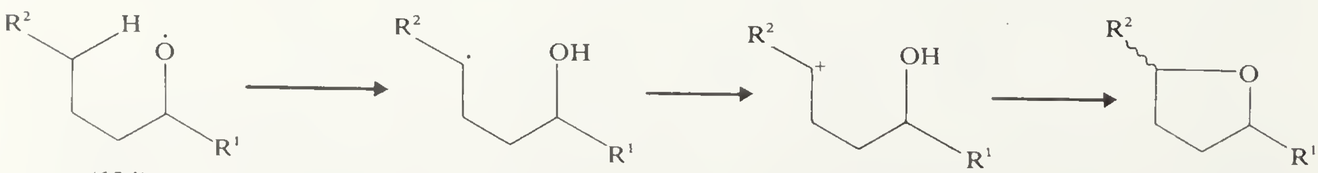


(222)



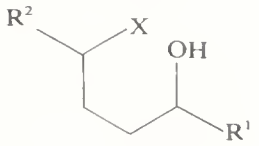
(223)

Although the precise mechanism of oxidative cyclization may vary with the structure of the alcohol and the reaction conditions (*e.g.* rigid alicyclic *vs.* conformationally flexible alcohols and silver(I)–Br_2 in the dark *vs.* the light), a generally accepted common feature is the intramolecular 1,5-abstraction of a hydrogen atom by an alkoxy radical (**134**) formed on homolysis of the hypohalite or alkoxylead triacetate. The mechanism for the oxidative cyclization of alkanols with $Pb(OAc)_4$ is shown in Scheme 24. According to the unified mechanism,[315] the radical (**135**) produced in hypohalite reactions leads to the δ-halogenoalcohol (**137**) rather than the carbenium ion (**136**). In conformationally rigid molecules where the reacting centres in (**134**) are separated by 250–270 pm (the optimum



(**134**) (**135**) (**136**)

SCHEME 24



(**137**)

for cyclization), alternative transition states seem likely, and in such circumstances the hypohalite and $Pb(OAc)_4$ reactions can be complementary rather than equivalent.[316] No attempt can be made here to review the synthetic splendours of oxidative cyclizations in steroidal and other polycyclic systems.

(*vii*) *Remote functionalization*

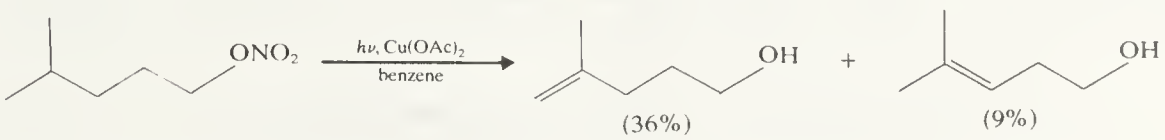
The relative stability of δ-chloroalcohols permits these compounds to be prepared by the photolysis of hypochlorites (equation 224). In the case of unbranched primary alkyl hypochlorites, the regioselectivity for the 1,5-abstraction of hydrogen in preference to 1,6 [the only other significant intramolecular alternative] is about 10:1. Side reactions emanating from radical attack at the α-position in primary and secondary hypochlorites can be suppressed by using a di- or tri-chloroethylene as a trap for chlorine atoms:[317] yields of the δ-chloroalcohols are then in the range 50–90%.

$$Bu^nCMe_2OCl \xrightarrow{h\nu,\ CCl_4,\ 0\,^\circ C} \underset{(80\%)}{MeCHClCH_2CH_2CMe_2OH} \qquad (224)$$

Other readily accessible derivatives that can be used for the remote functionalization of alcohols in analogous photolytic reactions are alkyl nitrites (in the Barton reaction[318]) and hydroperoxides.[319] As with oxidative cyclization, much of the synthetic potential of the Barton reaction has been realized in the steroid field, although its validity for acyclic and flexible alicyclic compounds in which the conformation favours the six-membered cyclic transition state for the conversion (**134**)→(**135**) has been demonstrated. This is exemplified by the photolysis of *trans*-2-ethylcyclohexyl nitrite in which the 1,5-hydrogen transfer [indicated by (**138**)], followed by capture of nitric oxide by the carbon radical,

(**138**)

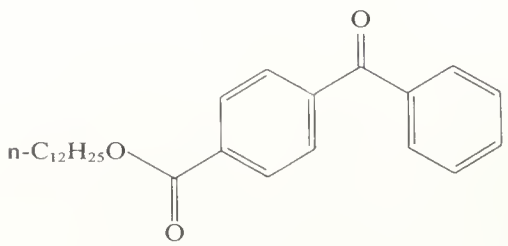
gives the nitroso dimer in about 30% yield, despite the unfavourable involvement of a primary hydrogen. By means of standard transformations, the δ-nitrosoalcohols produced by the Barton reaction can be converted into a variety of other derivatives. A recent variant[320] leading to remote unsaturation (equation 225) involves intercepting the carbon



(36%) (9%) (225)

radical (**135**) with copper(II) acetate. As shown, the *least* substituted alkenol is the major product. The same results can be obtained from the reactions of alkyl hydroperoxides with $FeSO_4$ and $Cu(OAc)_2$ in acetic acid. Here the process is initiated by reduction of the hydroperoxide with iron(II), giving the alkoxy radical (**134**).

A novel form of remote functionalization by steric engineering has been developed by Breslow's group.[321] The basic strategy is to tether the functionalizing agent — covalently or by complexation — to the substrate by means of an appropriate spacer or template, the geometric requirements of which largely determine the position(s) of attack. Using ester-linked reagents, a variety of radical reactions has been explored: chlorination by chloroiodophenyl radicals, nitrosation by the Barton reaction, and hydrogen abstraction by triplet benzophenone, leading to unsaturation or ring closure to a hydroxy-lactone. In the case of (**139**), photocyclization was largely restricted to C-11 (65%) and C-10 (28%) in the alcohol residue. For obvious reasons, such interesting reactions have most potential with steroidal alcohols.



(**139**)

The unfettered chlorination of simple alcohols in 70% H_2SO_4 (to protect the hydroxy group against oxidation) has been studied by Deno's group.[322] Photochlorination with Cl_2 shows only moderate selectivity for remote substitution, but the corresponding reaction with Pr^i_2NCl (involving attack by the cation radical $Pr^i_2NH^+\cdot$) is highly selective both for monochlorination and attack at the $\omega-1$ position ($\geq 90\%$ for hexan-1-ol and octan-1-ol). This polar effect, encouraging attack at a distal methylene group, is also evident in electrophilic oxidations with trifluoroperacetic acid[30d] and with ozone in superacids.[323].

(*viii*) *Special properties of unsaturated alcohols*

Collected under this heading are a number of reactions in most of which the hydroxy group is an active participant. It has not been the intention to include all such reactions, nor to encroach upon areas of hydrocarbon chemistry in which the influence of the hydroxy group is essentially that of a polar substituent.

(*a*) *Molecular rearrangements.* Several reactions in this category are prominent in organic synthesis, particularly of polyunsaturated natural products. The anionotropic rearrangement of allylic alcohols under catalysis by a Brønsted or Lewis acid has been reviewed[324] and will not be discussed in detail. The electronic effects of substituents on the ease of reaction are as expected for a carbenium ion type of mechanism, and the position of equilibrium is naturally sensitive to conjugative displacement (equation 226). The analogous rearrangement of an α-allenic alcohol[325] produces a 2-enone, and is particularly clean and facile for tertiary, terminal allenic alcohols (equation 227). The acid-catalysed rearrangements of α-alkynic alcohols, the Rupe and Meyer–Schuster rearrangements,[325b,326] require more vigorous conditions — as suggested by equation (226) — and tend to give more complex products. Both rearrangements lead to 2-enones,

$$MeCH{=}CHCH(OH)C{\equiv}CH \xrightarrow{H^+,\ 35\,^\circ C} MeCH(OH)CH{=}CHC{\equiv}CH \quad (226)$$

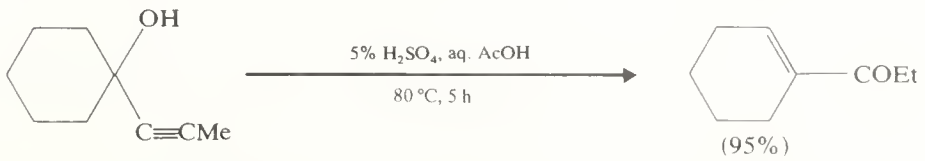
$(E):(Z) \approx 3:1$

$$MeC(OH)CH{=}C{=}CH_2 \xrightarrow[40\,^\circ C,\ 2\ min]{5\%\ H_2SO_4,\ aq.\ AcOH} MeC{=}CHCOMe \quad (227)$$

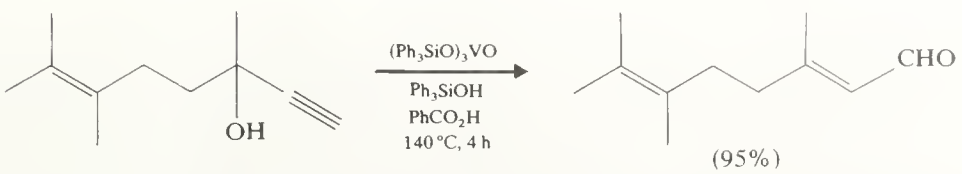
(95%)

apparently *via* a 1,3-anionotropic migration [Meyer–Schuster (equation 228)] or consecutive dehydration–hydration steps [Rupe (equation 229)] and both are mainly applicable to tertiary alcohols. The preferred reaction, where both are possible (alcohols containing a β-hydrogen), seems to depend on structural factors. Important additions[327] to the range of catalysts — commonly mineral or formic acid — are silyl vanadate esters. The formation of a Meyer–Schuster product by such a reaction is exemplified by equation (230).

$$Me_2C(OH)C{\equiv}CMe \xrightarrow[80\,^\circ C,\ 10\ h]{5\%\ H_2SO_4,\ aq.\ AcOH} Me_2C{=}CHCOMe \quad (75\%) \qquad (228)$$



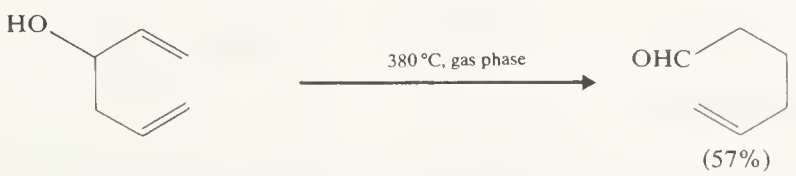
(229)



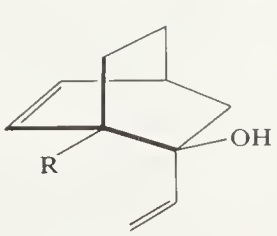
(230)

A process that competes with anionotropic rearrangement under acid catalysis is prototropic isomerization, which can also lead to carbonyl products as a result of double-bond migration followed by enol–keto tautomerism. With allylic and α-allenic alcohols, this alternative pathway is promoted by alkyl substitution at the vinylic β-carbon. Prototropic rearrangements are also promoted by a variety of other reagents:[328] bases, certain metals (*e.g.* Pd, Cu), metal oxides, and metal carbonyls [*e.g.* $Fe(CO)_5$]. The rearrangement of allylic alcohols to carbonyl compounds is also catalysed by certain soluble complexes of Ru and Rh, apparently by intramolecular hydrogen transfer[329] rather than by migration of the double bond (equation 231). Another rearrangement relevant to this section is the [3,3]-sigmatropic oxy-Cope rearrangement (equation 232).[330] Both concerted and diradical mechanisms are possible, depending on the substituents and the geometrical constraints. It appears[331] that the high temperatures employed in gas- and liquid-phase rearrangements of the free alcohols can be avoided, in suitable cases, by using the alkoxides in THF. Thus (**141b**) was obtained in at least 98% yield from the potassium salt of (**140b**) after a brief reflux and aqueous work-up. In the gas-phase reaction at 320 °C, (**141a**) was obtained in 45% yield from (**140a**).

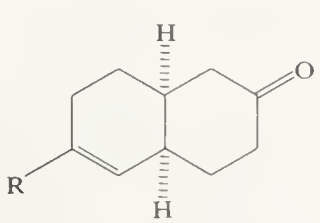
$$Pr^nCH(OH)CH{=}CH_2 \xrightarrow[110\,^\circ C,\ 1\ h]{(Ph_3P)_3RuHCl} Pr^nCOEt \quad (92\%) \qquad (231)$$



(232)

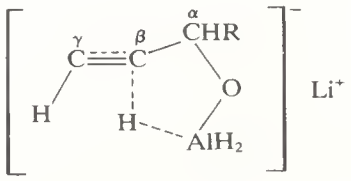


(**140**) a; R = H
b; R = OMe



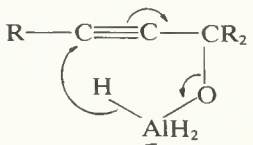
(**141**) a; R = H
b; R = OMe

(*b*) *Addition and addition–elimination reactions.* The presence of a proximate hydroxy group has a pronounced effect on the ease of reduction of C—C multiple bonds by $LiAlH_4$. The reduction, which involves intramolecular hydride delivery by the alkoxyhydridoaluminate, is well known for α-alkynic alcohols and cinnamyl alcohols. In the former case the normal expectation is formation of the (*E*)-alkenol *via* hydride attack at the β-carbon (**142**), although recent studies[332] have demonstrated that both the regio- and stereo-selectivities are sensitive to structural and environmental influences. For



(**142**)

example, the reduction of $Bu^nCH(OH)CH{\equiv}CH$ by $LiAlH_4$ in dioxan or THF occurs exclusively by *anti* addition, whereas in the less basic solvent Et_2O the *anti* : *syn* ratio is 3 : 2. In other (exceptional) cases, attack by the hydride at the γ-carbon can lead to deoxygenation as indicated by (**143**) and equation (233); an allylic example has been given earlier (equation 138). Of greater synthetic interest are the related reactions in which the attack of hydride at the β-carbon produces conjugate displacement of an appropriate δ-substituent. Equations (234) and (235) illustrate the use of such reactions for the



(**143**)

$$Bu^tMeC(OH)C{\equiv}CMe \xrightarrow[160\,^\circ C,\ 3\ h]{LiAlH_4,\ diglyme} Bu^tMeC{=}C{=}CHMe + Bu^tMeC(OH)CH{=}CHMe \quad (233)$$

(*R*) (*S*) (*S*),(*E*)

Product ratio ~2 : ~1

$$Pr^nCH(OBu^t)CH{=}CHCH_2OH \xrightarrow[reflux,\ 2\ h]{LiAlH_4,\ dioxan} Pr^nCH{=}CHCH_2CH_2OH \quad (234)$$

(68%)(97% *E*)

$$MeEtC(OTHP)C{\equiv}CCH_2OH \xrightarrow[reflux,\ 4\ h]{LiAlH_4,\ Et_2O} MeEtC{=}C{=}CHCH_2OH \quad (235)$$

(73%)

(THP = tetrahydropyran-2-yl)

preparation of homoallylic alcohols[333] and α-allenic alcohols.[334] The same approach can even be used for reductive eliminations of the corresponding derivatives of homoallylic and β-alkynic alcohols.[105,335] β-Allenic alcohols (formed in the latter reaction) can also be prepared by the controlled reduction of 2-en-4-yn-1-ols; under more vigorous conditions, allenic alcohols are reduced further to dienes and/or alkenols.[336]

A neighbouring hydroxy group also facilitates attack by organometallic reagents on multiple bonds, giving rise to a family of addition and addition–elimination reactions paralleling those described for $LiAlH_4$. Grignard additions, mostly requiring allylic reagents, *e.g.* equation (236), have been described for allylic, homoallylic, alkynic, and allenic alcohols.[337] Preliminary work[338] indicates that reactions with other Grignard

$$MeC{\equiv}CCH_2OH \xrightarrow[\text{reflux, 4 h}]{CH_2{=}CHCH_2MgCl,\ THF} MeCH{=}C(CH_2OH)CH_2CH{=}CH_2 \quad (236)$$
(75%)(*E*)

reagents can usefully be promoted by CuI. The general utility of organolithiums as reagents seems to be limited by the influence of steric and other structural features on the course of the reaction; equations (237) and (238) show useful reactions that have been reported.[339]

$$CH_2{=}CHCH_2OH \xrightarrow[25\ ^\circ C]{Bu^nLi,\ (Me_2NCH_2)_2,\ pentane} Bu^nMeCHCH_2OH \quad (237)$$
(74%)

$$n\text{-}C_5H_{11}CMe(OMe)C{\equiv}CCH_2OH \xrightarrow[Et_2O,\ -30\ to\ 25\ ^\circ C]{PhLi,\ (Me_2NCH_2)_2} n\text{-}C_5H_{11}CMeC{=}C{=}CPhCH_2OH \quad (238)$$
(85%)

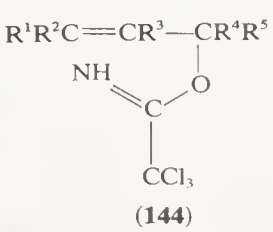
(*c*) *Miscellaneous allylic transpositions.* A number of reactions occurring with allylic transposition have been described above and in earlier sections, and more could be added. Instead, three topics of synthetic interest are briefly illustrated here.

A solution to the problem of efficient 1,3-transposition of an allylic hydroxy group is provided by conversion to the β,γ-epoxy mesylate ester followed by reductive elimination.[340] The sequence is exemplified by the conversion of geraniol to linalool (equation 239), which exploits the ability of an allylic hydroxy group to induce

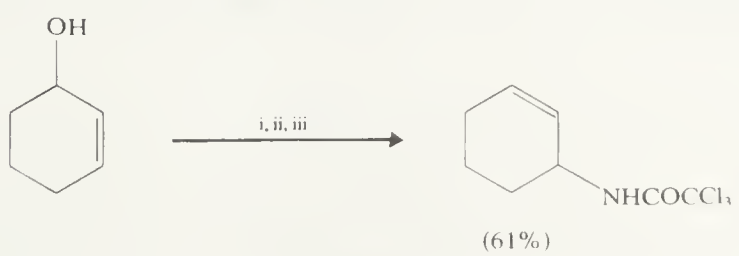
(88%) (239)

i, Bu^{t}OOH, VO(acac)$_2$, benzene, reflux; ii, MsCl, Et$_3$N; iii, Na, NH$_3$.

regioselective epoxidation by Bu^{t}OOH in the presence of vanadium(V) or molybdenum(VI) complexes. A new and general method for preparing transposed primary amines[341] is based on the thermal or mercury(II) catalysed [3,3]-sigmatropic rearrangement of allylic trichloroacetimidates (**144**) to the trichloroacetamido derivatives (equation 240). The latter can be hydrolysed with alkali at room temperature. Finally,



(144)



(61%) (240)

i, NaH, Et_2O; ii, CCl_3CN; iii, *o*-dichlorobenzene, reflux.

another [3,3]-sigmatropic reaction — the aliphatic Claisen rearrangement — provides an important and frequently stereoselective method of transferring a functionalized C_2 unit to the γ-position of an allylic or α-alkynic alcohol. Modern versions of the rearrangement are described in Ref. 330 and Section 4.3.6.2.

(*ix*) *Protection of hydroxy groups*

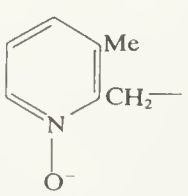
Recent compilations[25] and evaluations[342] of reactions applied to the protection and regeneration of hydroxy groups are available. Coverage of the topic here is therefore intended to be supplementary. Methods that involve the formation of cyclic derivatives from di- or poly-ols are deferred to Section 4.1.2.4. The major classes of derivatives used regularly for the protection of individual hydroxy groups are indicated and exemplified in Table 9.

TABLE 9

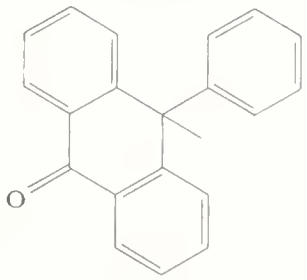
Major Derivatives Used for the Protection of Single Hydroxy Groups

Class of derivative	*Representative protecting groups*
Dialkyl ethers	t-Butyl, allylic groups, (**147**), *o*-nitribenzyl, (**145**), benzhydryl, triphenylmethyl, (**146**), *p*-anisyldiphenylmethyl, α-naphthyldiphenylmethyl
Alkyl silyl ethers	t-Butyldimethylsilyl, t-butyldiphenylsilyl, tri-isopropylsilyl
Acetals and hemithioacetals	Tetrahydropyran-2-yl, tetrahydrofuran-2-yl, 4-methoxytetrahydropyran-4-yl, 1-methoxyethyl, 1-methoxy-1-methylethyl, methoxymethyl, β-methoxyethoxymethyl, methylthiomethyl
Carboxylate esters	Acetyl, benzoyl, *o*-nitrobenzoyl, mesitoyl, 2,6-dimethoxybenzoyl, formyl, chloroacetyl, trichloroacetyl, trifluoroacetyl, phenoxyacetyl, dihydrocinnamoyl, 3-benzoylpropionyl, laevulinyl, crotonyl, pivaloyl, tigloyl
Carbonate esters	Ethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, allyloxycarbonyl
Other esters	Tosyl, phenylcarbamoyl

Although comparatively mild methods for the cleavage of simple dialkyl ethers are accumulating steadily (Section 4.3.4), greater selectivity of degradation favours others such as benzyl (*e.g.* catalytic hydrogenolysis) and trityl (*e.g.* mild, acid-catalysed C—O bond fission) ethers. The latter groups are also numbered amongst those for which electrochemical methods of removal have been established.[343] The selectivity and lability of arylalkyl groups are also amenable to modulation by varying the number and nature of the aryl substituents. Recent examples include the *o*-nitrobenzyl group (photolabile[344]) and the related group (**145**)[345] (both introduced *via* the aryldiazomethane and applied to the selective protection of secondary hydroxy groups in ribonucleosides), the tritylone



(**145**)



(**146**)

group (**146**) (removable by Wolff–Kishner reduction[346]), and the α-naphthyldiphenylmethyl group (susceptible to reductive cleavage by the anthracene radical anion in THF[347]). The trityl group and its *p*-methoxyphenyl analogues are widely used for the selective protection of primary hydroxy groups, and polymer-based versions of both have been devised.[348] The preparation of trityl ethers can be facilitated by using triphenylmethylium salts (in place of Ph_3CCl) with pyridine[349a] or its hindered 2,4,6-tri-t-butyl derivative;[349b] the second combination permits the rapid etherification of secondary hydroxy groups. When exceptionally mild conditions are required (*e.g.* to prevent the migration of a vicinal *O*-acyl group), the trityl group can be removed by chromatography on a silicic acid–'metaboric acid' column.[350] The complementary allylic groups (**147**) have been exploited extensively by Gigg and his colleagues for the 'temporary' etherification of hydroxy groups in carbohydrates. During treatment of a derivative with Bu^tOK in DMSO, the but-2-enyl group (**147c**) is rapidly eliminated whereas (**147a**) and, particularly, (**147b**)

$$R^1CH{=}CR^2CH_2{-}$$

(**147**) a; $R^1 = R^2 = H$
b; $R^1 = H$, $R^2 = Me$
c; $R^1 = Me$, $R^2 = H$

undergo slower prototropic rearrangement to give vinylic ethers. Migration of the double bond is also catalysed by $(Ph_3P)_3RhCl$[351] and Pd on charcoal,[352] and can be induced by an ene reaction with diethyl azodicarboxylate.[353] Removal of the protecting group is completed by acid or mercury(II) catalysed hydrolysis, or by oxidative cleavage of the vinylic ether. The potential value of 2-(phenylseleno)ethyl ethers in protection[354] is also based on the ease of formation of the selenoxide ($PhSeOCH_2CH_2OR$) and its fragmentation to a vinylic ether.

Because of their lability, trimethylsilyl ethers are seldom used in synthetic sequences, but certain related silyl ethers have recently come into prominence.[355] The most notable, Bu^tMe_2SiOR, are readily prepared by treating the hydroxy compounds with Bu^tMe_2SiCl and imidazole in DMF, and show useful stability to base, hydrogenolysis, and mild reduction. Desilylation is usually effected by treatment with Bu^n_4NF in THF — although this is inappropriate when *O*-acyl migration can occur — or by mild acid hydrolysis. The stability to acid of the related ethers, Bu^tPh_2SiOR, is sufficiently high to permit the selective removal of other protective groups such as trityl and tetrahydropyran-2-yl.[356] As expected, the bulky silylating agents are most reactive towards primary hydroxy groups, but can also be used to protect unhindered secondary groups.

The demand for a protecting group that is acid-labile but stable under a wide variety of other reaction conditions has frequently been met by the tetrahydropyran-2-yl group, readily introduced by acid-catalysed addition of the alcohol to 2,3-dihydro-4*H*-pyran (**88**). The same route is followed for the preparation of other acetals of varied acid lability from (**89a**), (**89b**), (**90**), and (**91**). The acetals from (**89**) avoid any problem resulting from the formation of diastereoisomers (*cf.* tetrahydropyran-2-yl ethers), and *product* stability follows the order (**89c**) > (**89a**) > (**89b**).[357] The extreme lability of acetone acetals [from (**91**)] leads only to specialized applications, whereas acetaldehyde acetals [from (**90**)] are used in a standard method[143] of locating *O*-acyl groups in polysaccharides by 'negative labelling' of free hydroxy groups. The rather stable formaldehyde acetals have not been

widely used, but an efficient method for the methoxymethylation of hydroxy groups by transacetalization has recently been described.[358] The imaginative step of 'replacing' the methoxy group of such acetals by a β-methoxyethoxy group[359] produces derivatives that are unusually sensitive to cleavage by a Lewis acid ($ZnCl_2$ or $TiCl_4$) in CH_2Cl_2 at or below room temperature, but remain resistant to bases, mild acids, and reagents used to remove many other protective groups. Other impressive advantages are the applicability of the method to tertiary as well as primary and secondary hydroxy groups, and the choice of synthetic routes: reaction of the chloroether (**148**) with the alkoxide in THF or glyme at 0 °C or with the alcohol and Pr^i_2EtN in CH_2Cl_2 at 25 °C, and reaction of the ammonium salt (**149**) with the alcohol in MeCN under reflux. Another innovative method for the

$MeOCH_2CH_2OCH_2Cl$ (**148**)

$MeOCH_2CH_2OCH_2\overset{+}{N}Et_3\ Cl^-$ (**149**)

protection of all classes of hydroxy groups is the formation of methylthiomethyl ethers (hemithioacetals, $MeSCH_2OR$).[360] Corey's method[360a] involves the reaction of a primary alkoxide in glyme with $MeSCH_2I$ (prepared *in situ* from $MeSCH_2Cl$ and NaI). Other groups[360b,c] have treated the alcohol with Ac_2O-activated DMSO (the inclusion of AcOH is also necessary for primary and secondary alcohols, to assist in diverting the reaction from oxidation to formation of the methylthiomethyl derivatives). Hydroxy groups can be selectively regenerated by treating the derivatives with a thiophilic metal ion (Hg^{II} or Ag^{I}) or with MeI in moist acetone. Following the discovery[361] of a simple and efficient method for their preparation *via* the chloroether [formed by the reaction of THF with SO_2Cl_2], tetrahydrofuran-2-yl derivatives should find applications in protection in competition with their less-labile tetrahydropyran-2-yl counterparts.

The protection of hydroxy groups against reactions occurring under neutral or acidic conditions by acetylation or benzoylation is commonplace (the protecting groups subsequently being removed by hydrolysis, alcoholysis, or ammonolysis). Easier and differential removal of the protecting group is possible with esters such as formates, trifluoroacetates, monochloroacetates, trichloroacetates, and phenoxyacetates, while groups such as mesitoyl and 2,6-dimethoxybenzoyl are relatively resistant to removal and *O*-acyl migration. Attention has also been focused on esters susceptible to alternative methods of degradation such as electrochemical reduction (benzoates[343]), hydrolysis by α-chymotrypsin (dihydrocinnamates[362]), reduction by Zn–NH_4Cl (*o*-nitrobenzoates[363]), and mild hydrazinolysis (3-benzoylpropionates,[364] laevulinates,[365] and crotonates[366]). The laevulinyl (4-oxovaleryl) group is also readily removed[367] by treating the ester with $NaBH_4$; the rationale behind the reduction (and the hydrazinolysis reactions) is the speed and selectivity of intramolecular attack at the ester carbonyl with cleavage of the protecting group as a lactone (or nitrogen heterocycle). Protecting groups in carbonate esters that can be selectively removed are allyloxycarbonyl [by heating the ester in MeCN or DMF with $Ni(CO)_4$ and $(Me_2NCH_2)_2$],[368] 2,2,2-trichloroethoxycarbonyl, and 2,2,2-tribromoethoxycarbonyl (by reductive fission of the esters with Zn or Zn–Cu in AcOH or MeOH; the chloro derivative has also been reduced electrochemically[343]). The main use of sulphonate esters is to provide durable protection for hydroxy groups, which are normally regenerated by reductive methods (*e.g.* with an alkali metal in NH_3 or HMPT, or with sodium naphthalenide). The introduction of electrochemical[343] and photochemical[369] methods for removing tosyl groups may modify this traditional role.

4.1.2 DIHYDRIC AND POLYHYDRIC ALCOHOLS

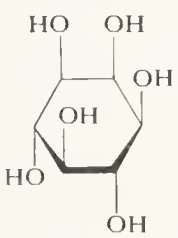
4.1.2.1 Introduction

This section is mainly concerned with novel chemical features that stem from the presence in a molecule of two or more hydroxy groups on different carbon atoms

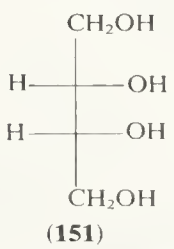
(*gem*-diols are excluded). Such features are most prominent for *vic*-diols, which will therefore be discussed in most detail. The coverage for other diols, in which the chemical independence of the hydroxy groups increases with their separation, and for polyols, in which hydroxy groups are usually present in a variety of skeletal relationships, will necessarily be selective and illustrative more than systematic and exhaustive. However, compensating reviews are available for the major classes of compounds: diols,[370a] triols,[370b] tetritols and higher alditols,[370c] and cyclitols.[370d]

Substitutive IUPAC nomenclature follows the rules exemplified for monohydric alcohols (Section 4.1.1.1), except that the incorporation of a multiplying affix obviates the need to elide a terminal 'e' from the name of the parent hydrocarbon, *e.g.* propane-1,2,3-triol [$CH_2(OH)CH(OH)CH_2OH$, glycerol]. The term *glycol* is a common synonym for diol, but its use in trivial nomenclature is strictly approved only for the C_2 and C_3 *vic*-diols (ethylene glycol and propylene glycol). Other simple compounds normally referred to by their trivial names include pinacol [$Me_2C(OH)C(OH)Me_2$], pentaerythritol [$C(CH_2OH)_4$], certain cyclitols, *e.g.* *myo*-inositol (**150**), and the stereoisomeric C_4 to C_6 sugar alcohols (alditols), *e.g.* erythritol (**151**), D-threitol (**152**), D-arabinitol (**153**), xylitol (**154**), D-glucitol (**155**), and D-mannitol (**156**). As indicated, stereochemical designations are frequently necessary. Chiral derivatives of glycerol are of central importance in lipid chemistry and biochemistry (Chapters 25.1 and 25.2), and a special system of 'stereospecific numbering' which recognizes the prochirality of C-2 in the parent triol (**157**) has been adopted for these compounds. Thus compound (**158**), alias a D-1,2-diglyceride, becomes a 2,3-di-*O*-acyl-*sn*-glycerol under this system.[371] The stereochemical designations for higher acyclic polyols and their derivatives are more conventional, being based on the D/L system, with additional aldose-related prefixes being used to signify particular configurational sequences as necessary.[372] Thus L-rhamnitol (**159**) is systematically named 1(6)-deoxy-L-mannitol, and (**160**) is L-*erythro*-D-*gluco*-octitol (the prefixes specifying the absolute configurations at C-6 and C-7, and C-2 to C-5, respectively). Special recommendations for the nomenclature of cyclitols have been issued.[373]

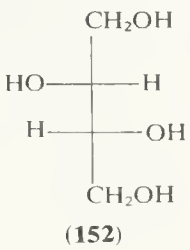
Ethylene glycol, and other simple diols, have numerous industrial applications, which include the formulation of anti-freeze solutions, hydraulic fluids, dyes, and inks, uses as humectants (*e.g.* in tobacco and certain comestibles), and the production of polyester



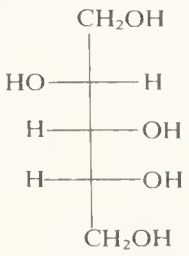
(**150**)



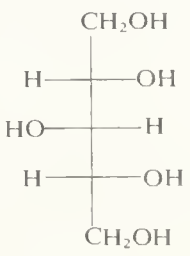
(**151**)



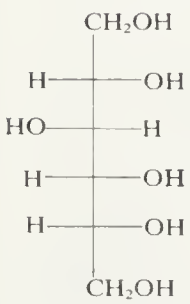
(**152**)



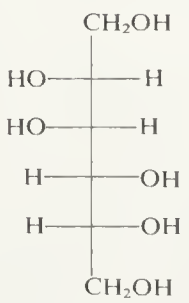
(**153**)



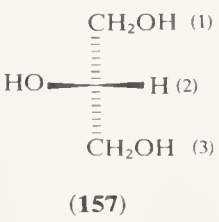
(**154**)



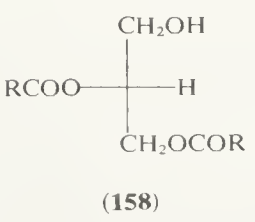
(**155**)



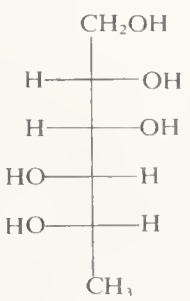
(**156**)



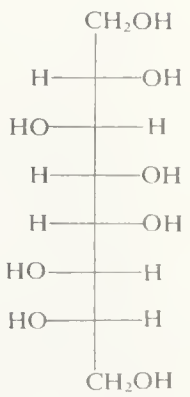
(**157**)



(**158**)



(**159**)



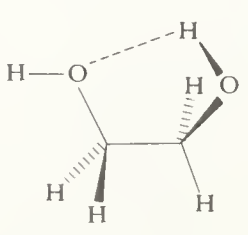
(**160**)

fibres and resins. Glycerol is typical of the polyols used in the production of cross-linked polyesters such as alkyd resins and polyurethane foams and, like ethylene glycol and pentaerythritol, is used for the preparation of explosive nitrate esters. The current interest in carbohydrates as raw materials for the chemical industry, *e.g.* for the production of surfactants, is likely to lead to more extensive use of the readily available alditols such as glucitol and, in the U.S.S.R. apparently,[374] xylitol.

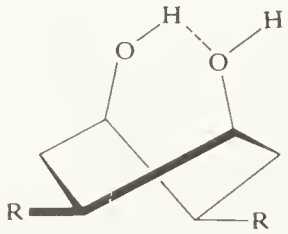
4.1.2.2 General characteristics

The physical properties of diols and polyols, compared with those of the corresponding monohydric alcohols, reflect their enhanced polarity and capacity for hydrogen bonding. The lower diols and triols are viscous, high-boiling, hygroscopic liquids, miscible with water in all proportions, but almost insoluble in diethyl ether.

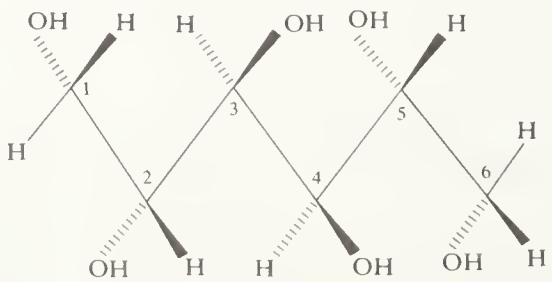
Molecular geometry permitting (*e.g.* in *trans*-cyclohexane-1,2-diol but not in *trans*-cyclopentane-1,2-diol), intramolecular hydrogen bonding may occur. In the series of n-alkane-α,ω-diols, the intramolecular hydrogen bond is strongest for butane-1,4-diol, though the proportion of bonded conformers is greatest for ethane-1,2-diol because of the more favourable entropy factor.[375] The orientation of the bonded hydroxy group in the conformer (**161**) of the latter diol is the result of interplay between the *gauche* effect and hydrogen bonding.[3] Bulky substituents that decrease the torsional angle between the C—O bonds in *vic*-diols (or distort the bond angles at carbon, also causing closer approach of the oxygen atoms) increase the strength of the hydrogen bond. Such substituents similarly promote bonded twist conformers (**162**) of certain cyclohexane-1,4-diols at the expense of the non-bonded chair structures. The conformational preferences of alditols, both in the crystalline state[376] and in aqueous solution,[377] are largely determined by the tendency of the carbon backbone to adopt an extended, planar, zigzag arrangement, except where this would lead to repulsive 1,3-interactions of parallel C—O bonds. The extended conformation of D-mannitol is indicated by (**163**), and the bent ('sickle') conformation of D-glucitol, produced from the extended conformation by a 120° rotation about the C-2 to C-3 bond to avoid interaction between the hydroxy groups at C-2 and C-4, is indicated by (**164**). Rotational deviations from these basic conformations can be attributed[378] to intramolecular hydrogen bonding between *gauche*-disposed hydroxy groups, *e.g.* the three consecutive pairs in mannitol.



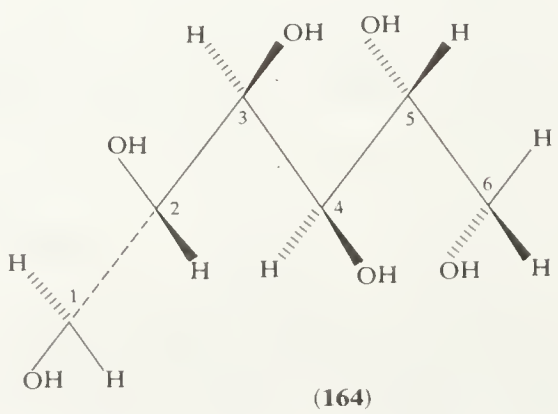
(**161**)



(**162**) R = Me, 5%
R = Bu^t, 100%

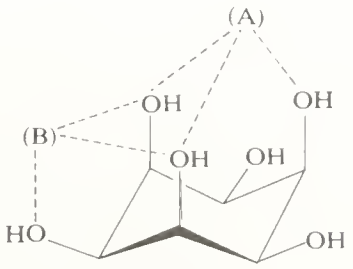


(**163**)



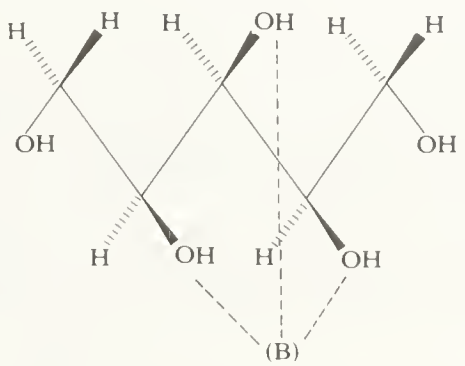
(**164**)

An aspect of polyol chemistry that has attracted much attention in recent years, because of its biological implications and possible commercial importance, is the complexing of metal cations[379] (*cf.* complexing by macrocyclic crown ethers and other cryptands). The steric arrangements of hydroxy groups that favour tridentate complexation by cyclohexitols are the *syn*-triaxial arrangement (A) and the consecutive axial-equatorial-axial arrangement (B), both of which occur in *cis*-inositol (**165**). Arrangement (A) permits



(165)

coordination to cations of ionic radius greater than *ca.* 60 pm, whereas with (B) the lower limit is *ca.* 80 pm. The efficiency of complexation by acyclic polyols depends on the accessibility of conformers with hydroxyl arrangements equivalent to (B), and is greatest for alditols containing the *xylo* configuration, *e.g.* xylitol and glucitol (C-2 to C-4).[377,378] Thus complexing by xylitol involves the secondary hydroxy groups and a sickle→zigzag conformational change (**166**). The interactions are conveniently monitored by n.m.r.



(166)

spectroscopic techniques and the use of a paramagnetic lanthanide salt (*e.g.* of Eu^{III}, Pr^{III}, or Yb^{III}) in ^2H_2O.[377–380] Practical applications of complexing include the separation and identification of polyols by electrophoresis in the presence of metal salts and by column chromatography on a cation-exchange resin,[381] and the determination of configuration for *diols* (usually vicinal) from chiroptical measurements. The latter include the applications of circular dichroism to the well-known cuprammonium solutions of glycols[382] and to the complexes formed with nickel(II) acetylacetonate (mainly useful for acyclic *vic*-diols in an aprotic solvent or Bu^tOH)[383a] or the praseodymium analogue of the paramagnetic shift reagent (**16a**) (mainly useful for cyclic or hindered acyclic *vic*-diols in dry $CHCl_3$ or CCl_4).[383b] Other derivatives of diols for which chiroptical properties can be correlated with configuration are the cycle osmates[384a] and thionocarbonates,[384b] and the dibenzoate esters of cyclic diols.[384c] The conversion of diols to cyclic derivatives such as sulphites, thionocarbonates, 1,3-dioxolans, and 1,3-dioxans often facilitates the determination of their configuration by n.m.r. spectroscopic techniques.[385]

4.1.2.3 Methods of preparation

Although the reactions already described for the preparation of monohydric alcohols (Section 4.1.1.3) can obviously be used to synthesize diols and polyols, their straightforward applications are excluded from the following accounts. Instead, the focus is on methods specific to the different classes of compounds.

(*i*) *Preparation of 1,2-diols*

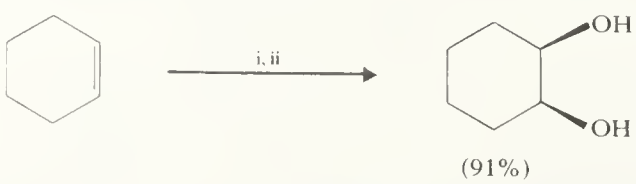
Reactions involving the stereoselective hydroxylation of alkenes[47,386] are prominent among the standard routes to 1,2-diols. Of the two classic reagents for *syn* hydroxylation *via* the formation of cyclic esters, $KMnO_4$ and OsO_4, the latter is more efficient and reliable, but costly and hazardous. With care, *alkaline* $KMnO_4$ gives good results with alkenic acids (equation 241), but yields are generally moderate with more lipophilic substrates. The latter are usually hydroxylated in aqueous solution, *e.g.* using acetone–water, 7:1 (v/v),[387a] though phase-transfer catalysis is possible with heterogeneous reaction mixtures.[387b] The problems associated with OsO_4 can be minimized by using it (or K_2OsO_4 neutralized with acetic acid[388]) catalytically along with a co-oxidant — a metal chlorate (Hofmann) or H_2O_2 (Milas) — though with some loss of efficiency compared with stoichiometric use of the OsO_4–pyridine reagent. The recently introduced co-oxidants Bu^{t}OOH (equation 242)[389a] and *N*-methylmorpholine *N*-oxide (**132**) (equation 243)[389b] appear to remove this disadvantage. With both the Mn^{VII} and Os^{VIII} reagents, hydroxylation of a double bond normally takes place from the less-hindered side.

$$\underset{(Z)}{Me(CH_2)_7CH{=}CH(CH_2)_7CO_2H} \xrightarrow{\text{i, ii, iii}} \underset{\textit{erythro}\ (75\%)}{Me(CH_2)_7CH(OH)CH(OH)(CH_2)_7CO_2H} \qquad (241)$$

i, aq. $KMnO_4$–KOH, 5 °C, 10 min; ii, SO_2; iii, HCl.

$$\underset{(E)}{Pr^nCH{=}CHPr^n} \xrightarrow{\text{i, ii}} \underset{\textit{threo}\ (73\%)}{Pr^nCH(OH)CH(OH)Pr^n} \qquad (242)$$

i, OsO_4, Bu^{t}OOH, Et_4NOOH, aq. Bu^{t}OH; ii, $NaHSO_3$.



(243)

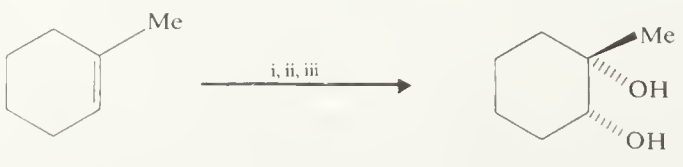
(91%)

i, OsO_4, (**132**), aq. Bu^{t}OH–Me_2CO, 25 °C; ii, $NaHSO_3$.

Halohydrin esters (**167**) are the key intermediates in a growing range of diol syntheses of which the Prévost reaction (equation 244) and the Woodward reaction (equation 245)

$$PhCH_2CH{=}CH_2 \xrightarrow{\text{i, ii}} \underset{(85\%)}{PhCH_2CH(OH)CH_2OH} \qquad (244)$$

i, I_2, $PhCO_2Ag$, benzene, reflux; ii, NaOH.

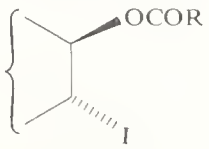


(245)

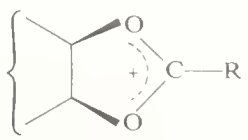
(60%)

i, I_2, $MeCO_2Ag$, AcOH, 25 °C; ii, H_2O added; iii, KOH, MeOH.

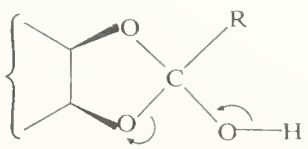
are the prototypes. The initial steps common to these two reactions are: (a) the formation of an acyl hypoiodite (or its Simonini complex[386]) from I_2 and a silver(I) carboxylate; (b) electrophilic *anti* addition of the acyl hypoiodite to the alkene, giving (**167**) *via* an iodonium ion; (c) silver(I)-assisted anchimeric displacement of iodide, giving a 1,3-dioxolan-2-ylium cation (**168**). Under anhydrous (Prévost) conditions, ring-opening S_N2 attack on (**168**) by a carboxylate ion gives the diester(s) corresponding to *anti* hydroxylation of the alkene. In the presence of water (Woodward), (**168**) is hydrated to the orthoester (**169**), which decomposes to diol monoesters corresponding to *syn* addition to



(**167**)

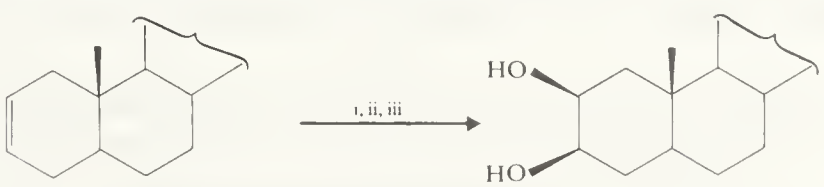


(**168**)



(**169**)

the alkene, usually from the more hindered side (a consequence of the initial formation of an iodonium ion). Other mechanistic aspects of the reactions with cyclic alkenes are discussed in recent papers.[390] Alternative methods for the preparation of halohydrin esters and for their conversion to diol esters are now available. For the preparation of (**167**), suitably economical reagents are: (a) I_2 with (i) a thallium(I) carboxylate,[391a] (ii) NaOAc in anhydrous tetramethylene sulphone,[107b] or (iii) KIO_3 in acetic acid;[391b] (b) *N*-iodosuccinimide and a carboxylic acid in chloroform.[391c] Similarly, *N*-bromoacetamide and silver(I) acetate have been used under Woodward conditions for the preparation of bromohydrin acetates.[392] For the conversion of iodohydrin acetates to the diol monoesters, adequate treatments[391a,b] include heating under reflux with DMSO, aqueous AcOH, or KOAc in AcOH. Equation (246) illustrates the application to 5α-cholest-2-ene of one of these various alternatives to Woodward hydroxylation. A comparable result has been obtained[393a] with thallium(III) acetate in AcOH, while thallium(III) sulphate in water has been recommended[393b] for the *anti* hydroxylation of rigid cyclic alkenes. The diol esters formed by treating an alkene with iodine(III) trifluoroacetate[394] correspond predominantly to net *syn* addition (equation 247).



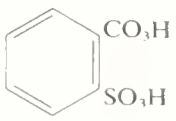
(70%) (246)

i, I_2, KIO_3, AcOH, 60 °C, 3 h; ii, AcOK, AcOH, reflux, 3 h; iii, KOH, MeOH.

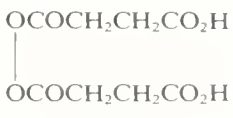
$$\underset{(Z)}{MeCH{=}CHMe} \xrightarrow[25\,^{\circ}C]{I(OCOCF_3)_3,\ pentane} \underset{erythro\ (97\%)}{MeCH(OCOCF_3)CH(OCOCF_3)Me} \qquad (247)$$

Reverting to classical methods, peroxy acids are routinely used for the hydroxylation of alkenes *via* epoxidation (*syn* addition), acid-catalysed ring-opening of the oxiran (most commonly with inversion of configuration, see Section 4.4.4.2) and hydrolysis of the diol monoester formed. The reagent (usually prepared *in situ*) is conventionally chosen from

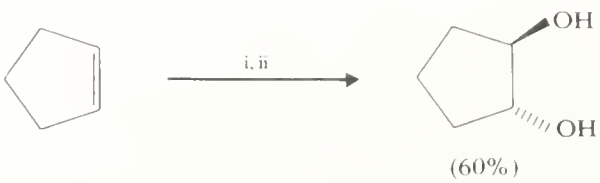
HCO_3H, CF_3CO_3H, and $MeCO_3H$–H_2SO_4, though the ability to obtain free diols directly from reactions employing *o*-sulphoperbenzoic acid (**170**)[395a] or disuccinoyl peroxide (**171**) (a stable solid)[395b] may be considered an advantage. Equations (248) and (249)



(**170**)

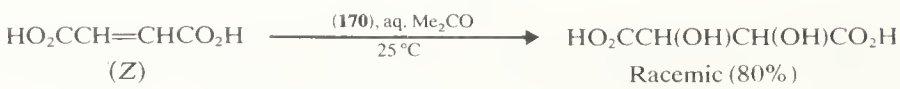


(**171**)



(60%) (248)

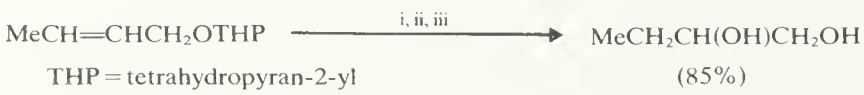
i, HCO_2H, 30% H_2O_2, 40 °C; ii, aq. NaOH, reflux.



(*Z*) Racemic (80%) (249)

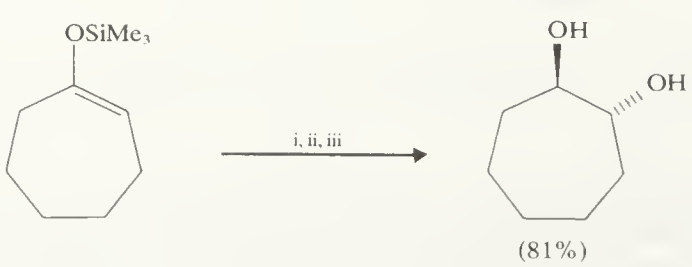
show representative *anti* hydroxylations using peroxy acids. Pre-formed oxirans can be used similarly to obtain 1,2-diols directly by hydrolysis (catalysis normally being supplied by acid, but sometimes by base) or indirectly *via* acid-catalysed reaction with other nucleophiles, *e.g.* DMSO.[396] Structural influences on the mechanisms of these reactions — including regio- and stereo-selectivity — are discussed elsewhere.[397]

Both the hydroboration–oxidation and oxymercuration–demercuration reaction sequences can be used for the preparation of *vic*-diols. Electronegative allylic substituents such as hydroxyl promote the formation of a proximal C—B bond on hydroboration of alkenes of the type $RCH{=}CHCH_2X$. By protecting the hydroxy group against subsequent elimination (*e.g.* by the use of the disiamylborinate ester or tetrahydropyran-2-yl ether), crotyl and similar alcohols can be efficiently converted into 1,2-diols (equation 250).[38b,86] Enol derivatives of various types have also been subjected to hydroboration–oxidation. Applied to the silyl ethers,[398] the sequence provides a useful route to *trans*-1,2-diols from certain cyclanones (equation 251). The scope of oxymercuration–demercuration for the



THP = tetrahydropyran-2-yl (85%) (250)

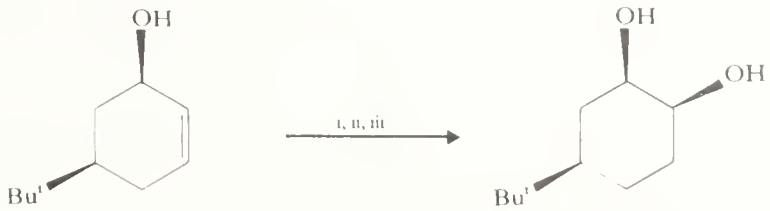
i, B_2H_6, THF: ii, NaOH, H_2O_2; iii. TsOH, MeOH.



(81%) (251)

i, B_2H_6, THF; ii, NaOH, H_2O_2; iii, MeOH, MeONa.

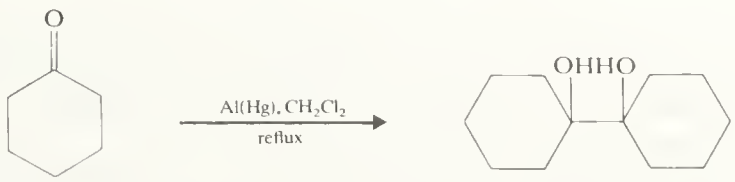
synthesis of *vic*-diols is mainly restricted to the use of such alkenols, *e.g.* CH_2=$CHCH(OH)Me$, as give the appropriate Markownikov addition. With other allylic alcohols, *e.g.* $MeCH$=$CHCH_2OH$, 1,3-diols are the major products.[399] An alternative approach,[400] in which oxymercuration involves the directed intramolecular addition of a hemiacetal hydroxy group, has proved successful with various *cyclic* allylic alcohols, *e.g.* equation (252).



(70%) (252)

i, CCl_3CHO, $Hg(OCOCF_3)_2$, THF; ii, NaOH, $NaBH_4$; iii, Na, Et_2O.

A classic method of preparing constitutionally symmetrical 1,2-diols is the reductive self-coupling (hydrodimerization, pinacolic reduction) of carbonyl compounds (particularly ketones).[47] With the usual reagents (*e.g.* an amalgam of Mg, Al, or Zn in benzene), yields are only moderate, but can be improved[401] by using THF or CH_2Cl_2 as the solvent (equation 253). More significantly, a range of effective Ti-based reagents has been developed.[402] Mukaiyama's reagent ($TiCl_4$–Zn) appears to give good results with aromatic aldehydes and ketones, *e.g.* equation (254), but to be less satisfactory with aliphatic carbonyl compounds. Equations (255)–(257) illustrate the greater versatility of the related



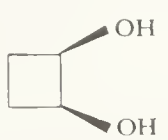
(55%) (253)

PhCOMe $\xrightarrow[25\,°C,\,2\,h]{TiCl_4,\,Zn,\,THF}$ PhMeC(OH)C(OH)MePh (254)

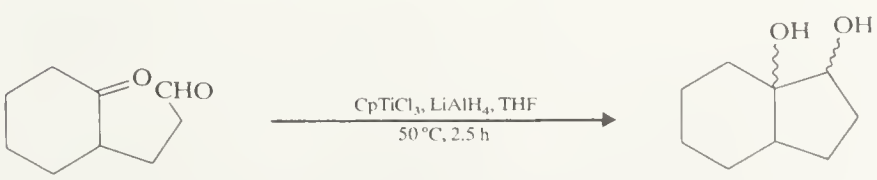
(91%)

n-$C_7H_{15}CHO$ $\xrightarrow[0\,°C,\,13\,h]{TiCl_4,\,Mg(Hg),\,THF}$ $C_7H_{15}CH(OH)CH(OH)C_7H_{15}$ (255)

(80%)

$MeCOCH_2CH_2COMe$ $\xrightarrow[0\,°C,\,2.5\,h]{TiCl_4,\,Mg(Hg),\,THF}$  (256)

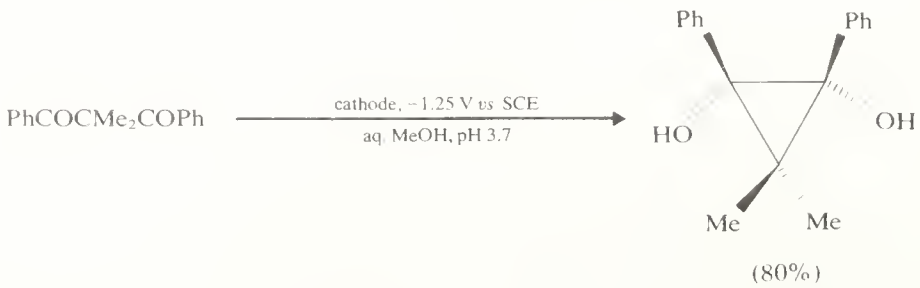
(81%)



(49%) (257)

Cp = Cyclopentadienyl

reagents introduced by Corey's group. Constitutionally symmetrical *vic*-diols are also formed — though in moderate yields — when carboxylic acids are treated with an alkyllithium and $TiCl_3$ at low temperature,[403] and (efficiently) when PhCHO or PhCOMe is heated in HMPT with Mg and Me_3SiCl, followed by hydrolysis of the products.[404] The extensive studies of pinacol formation by the electrochemical[405] or photochemical[406] reduction of carbonyl compounds are described in the references cited, and are exemplified by equations (258) and (259). Methods other than intramolecular reductive coupling that have been successfully applied to the synthesis of small-ring diols have been summarized for cyclopropanediols[407a] and cyclobutane-1,2-diols.[407b]



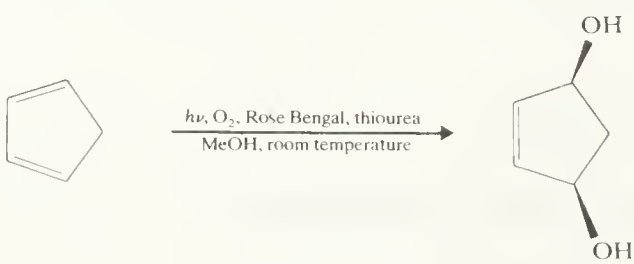
(80%) (258)

(95%) (259)

(ii) Preparation of other diols

No attempt will be made to segregate reactions for the preparation of individual classes of diols, routes to which depend on the availability of suitably functionalized precursors or the use of appropriate C—C bond-forming reactions. As a full account of either approach is impossible, both are exemplified by a number of reactions, most of which represent recent developments.

The [4+2] cycloaddition of singlet oxygen to a conjugated diene[35] — usually a *cisoid* cyclic diene — produces a 1,4-epidioxide (*endo*-peroxide) that can be reduced, subsequently or *in situ* (equation 260) to the unsaturated diol. Barton's group has discovered catalysts that induce the formation of an *endo*-peroxide by a photochemical or a thermal reaction of a diene with *triplet* oxygen.[408] The triphenylmethylium cation catalyses reactions of the first type, and the tris-(*p*-bromophenyl)ammoniumyl radical cation those of the second (equation 261).



(59%) (260)

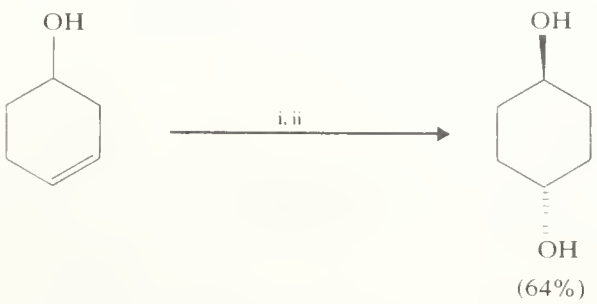
(56%) (261)

i, O_2, $(p\text{-}BrC_6H_4)_3\overset{\cdot\cdot}{N}BF_4$, CH_2Cl_2, −78 °C, dark; ii, H_2, Raney Ni.

As noted previously (p. 669), 1,3-diols are the major products from the oxymercuration–demercuration reactions of allylic alcohols to which the formal Markownikov rule is inapplicable.[399] The situation is further illustrated by equation (262): the hydroxy group attached to C-2 during initial oxymercuration at the more reactive, terminal double bond directs the second hydroxy group to the more remote C-4 position. Similarly, *trans*-cyclohexane-1,4-diol is the major product from cyclohex-3-en-1-ol (equation 263). For the preparation of 1,4- and 1,5-diols from acyclic alkenols, the hydroxy group of the latter should first be acetylated to prevent the formation of a cyclic ether during oxymercuration.

$$\underset{(E)}{CH_2{=}CHCH{=}CHMe} \xrightarrow{\text{i, ii}} \underset{(79\%)}{MeCH(OH)CH_2CH(OH)Me} \qquad (262)$$

i, $Hg(OAc)_2$, THF, H_2O; ii, NaOH, $NaBH_4$.



(263)

(64%)

i, $Hg(OAc)_2$, THF, H_2O; ii, NaOH, $NaBH_4$.

Several applications of hydroboration–oxidation to the synthesis of non-vicinal diols have been described.[38b,86] Applied to lithiated allylbenzenes, the reaction sequence gives 1,3-diols (equation 264). 1,5-Diols can be obtained in good yield from acyclic alk-1-enes containing a primary hydrogen at C-5 *via* the thermal cyclization of the dialkylborane formed by reaction with thexylborane (**32**) (equation 265). More generally, cyclic intermediates suitable for oxidation to diols can be obtained by the reaction of a diene with

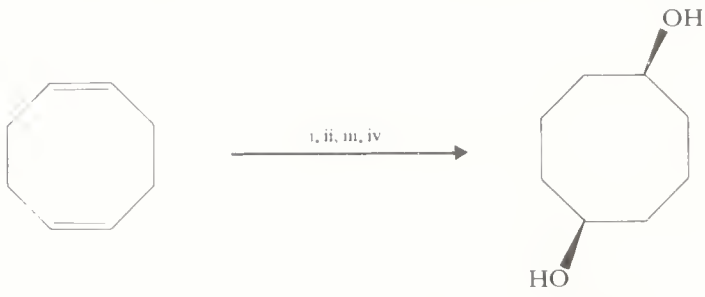
$$PhCH_2CH{=}CH_2 \xrightarrow{\text{i, ii, iii}} \underset{(65\%)}{PhCH(OH)CH_2CH_2OH} \qquad (264)$$

i, Bu^nLi, Et_2O; ii, B_2H_6, THF; iii, NaOH, H_2O_2.

$$Me_3CCH_2CMe{=}CH_2 \xrightarrow{\text{i, ii, iii}} \underset{(81\%)}{CH_2(OH)CMe_2CH_2CHMeCH_2OH} \qquad (265)$$

i, (**32**), THF; ii, 200 °C; iii, NaOH, H_2O_2.

B_2H_6 or a monosubstituted borane, *e.g.* thexylborane or monochloroborane etherate (**35**).[409] Thus *cis*-cyclo-octane-1,5-diol can be prepared from cyclo-octa-1,5-diene *via* 9-BBN (**34**) (equation 266). Further syntheses involving cyclic hydroboration are shown in equations (267) and (268), the latter illustrating the stereo- and regio-selective control attainable. Constructional syntheses of 1,3- and 1,4-diols using organoboron reagents have also been devised. The reaction of a trialkylborane with α-lithiofuran, followed by the usual oxidative work-up, gives an unsaturated 1,4-diol (equation 269).[410] Saturated 1,4-diols are obtained by oxidation of the products from reactions of lithium trialkylvinylborates with oxirans (equation 270),[411a] and 1,3-diols from the corresponding reactions with aldehydes (equation 271).[411b]



(266)

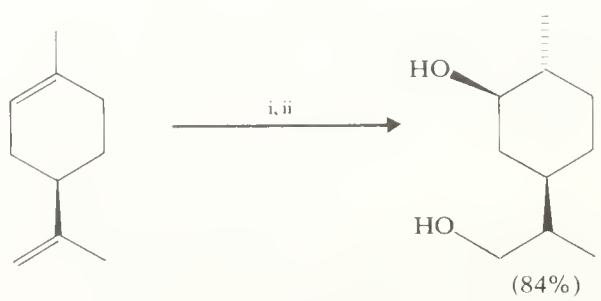
(100%)

i, B_2H_6, THF, 0 °C; ii, THF, reflux; iii, EtOH; iv, NaOH, H_2O_2.

$$CH_2{=}CMeCH_2CH_2CMe{=}CH_2 \xrightarrow{\text{i, ii}} CH_2(OH)CHMeCH_2CH_2CHMeCH_2OH \quad (267)$$

(99%)

i, (**35**), Et_2O, 0 °C; ii, NaOH, H_2O_2.



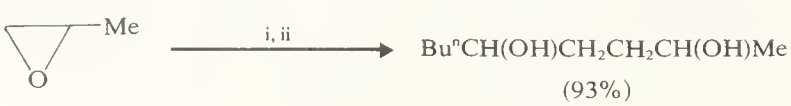
(268)

(84%)

i, (**32**), THF, 0 °C; NaOH, H_2O_2.

(269)

i, Bu^nLi, Et_2O; ii, Et_3B, THF; iii, NaOH, H_2O_2.



(270)

i, $Li^+(Bu^n_3BCH{=}CH_2)^-$, THF; ii, NaOH, H_2O_2.

(271)

i, $Li^+(Et_3BCH{=}CH_2)^-$, Et_2O; ii, NaOH, H_2O_2.

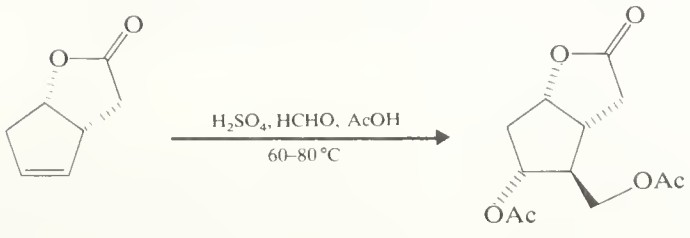
Two classic methods for preparing 1,3-diols *via* carbonyl addition reactions are adolization–reduction and the Prins reaction between an alkene and a carbonyl compound (most commonly HCHO) under acid catalysis. The self-condensation of an unbranched aliphatic aldehyde catalysed by a magnesium phenoxide in HMPT produces directly a mixture of the 1,3-diol monoesters. As the efficiency of the reaction approaches the theoretical value of 66% (based on the aldehyde to diol stoichiometry), this route to 1,3-diols (equation 272) is a competitive alternative to aldolization–reduction.[412] Prins reactions are intrinsically complex, and the products and yields therefrom dependent on

the reactants and conditions.[413] The major products are commonly 1,3-dioxans (equation 273) or diesters (equation 274) from which the 1,3-diols can be recovered by hydrolysis or alcoholysis. An unusual synthesis of 1,3-diols is provided by the reaction between an enol ester and Bu^i_2AlH (equation 275).[63] The reaction, which contrasts markedly with the

$$EtCH_2CHO \xrightarrow{\text{i, ii}} EtCH_2CH(OH)CHEtCH_2OH \quad (57\%) \qquad (272)$$

i, PhOMgBr, HMPT, 40 °C; ii, KOH, EtOH.

$$Me_2C{=}CH_2 \xrightarrow{25\%\ H_2SO_4,\ HCHO,\ 25\ ^\circ C} \text{Me, Me, O, O} \quad (60\%) \qquad (273)$$

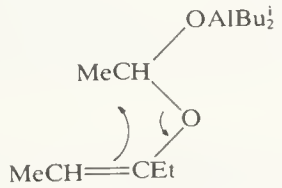


(85%) (274)

$$MeCH{=}CEtOAc \xrightarrow{\text{i, ii}} EtCH(OAc)CHMeCH(OAc)Me \quad (66\%) \qquad (275)$$

i, Bu^i_2AlH, light petroleum, 20 °C; ii, Ac_2O, reflux.

behaviour of enol esters on hydroboration, is considered to involve addition of the reagent to the ester carbonyl, followed by a rearrangement (**172**) regenerating the keto carbonyl group, and further reduction.



(**172**)

(*iii*) *Preparation of polyols*

Reactions in which three or more hydroxy groups are generated, *e.g.* the formation of pentaerythritol by a Tollens reaction (equation 276), or incorporated, *e.g.* the diol version of the Guerbet reaction (equation 277), in a single step have relatively limited synthetic scope. More typically, the hydroxy groups of polyols are accumulated progressively by the functional transformations described for mono- and di-hydric alcohols. Their applications

$$HCHO \xrightarrow{MeCHO,\ Ca(OH)_2,\ 15\text{–}45\ ^\circ C} C(CH_2OH)_4 \quad (74\%) \qquad (276)$$

$$HO(CH_2)_4OH \xrightarrow{\text{i, ii}} HO(CH_2)_4CH(CH_2OH)(CH_2)_2OH \quad (277)$$
(50%)

i, Na; ii, Ni, Cr_2O_3, xylene, reflux.

to representative triols, tetritols, and higher alditols are described elsewhere.[370b,c] The ready availability of glycerol and certain alditols from natural sources (lipids and carbohydrates, respectively) also simplifies the preparation of related polyols by reactions such as epimerization and deoxygenation applied to hydroxy groups selected by appropriate blocking procedures. Similar considerations apply to the cyclitols of which *myo*-inositol, the most abundant, is widely distributed in the form of its hexaphosphate ester (phytic acid) and as a component of various phospholipids.[370d,414]

4.1.2.4 Reactions

The reactions and products selected for discussion are categorized by *type*, and are mainly those peculiar to diols or polyols. The further consideration of standard hydroxy reactions is largely restricted to the section on selective functionalization.

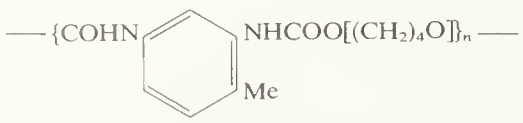
(*i*) *Formation of polymeric derivatives*

A characteristic dimension to the chemistry of difunctional compounds is that of polymer formation. Both homo- and hetero-polymers are well known for simple diols. Polymers of the former type (**173**), produced by controlled glycolysis of the appropriate

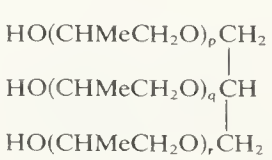
$HO(CHRCH_2O)_nH$

(**173**) R = Me or H

oxiran, have many and varied applications in both industry and the laboratory.[1,415] The lower oligomers ($n = 2$ or 3) and their simple ethers, *e.g.* diglyme, have properties and uses similar to those of the monomeric compounds. Industrial applications of the higher polyethers include their use as lubricants, bases for various cosmetic and pharmaceutical preparations, hydraulic fluids, plasticizers, dispersants, and antifoam agents. They are also important as chemical intermediates in the manufacture of non-ionic surfactants, polyurethane elastomers, *e.g.* (**174**), and cross-linked foams, *e.g.* incorporating residues of glycerol-derived polyethers (**175**), and the alkyd polyester resins used as surface coatings and in glass-reinforced plastics.

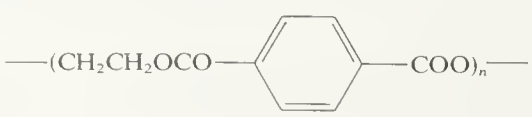


(**174**)



(**175**)

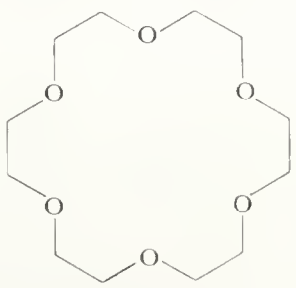
The range of synthetic polyester fibres is still dominated by the familiar polymer of ethylene glycol and terephthalic acid (**176**). The corresponding polyester of 1,4-bis(hydroxymethyl)cyclohexane — mainly the *trans*-isomer — also has established textile



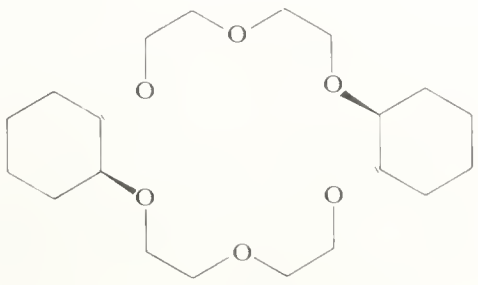
(**176**)

applications. Relatively low-molecular-weight, hydroxy-terminated polyesters, *e.g.* of propylene glycol or diethylene glycol, are also used in the production of some flexible polyurethane foams, and similar esters incorporating residues of an unsaturated acid, *e.g.* maleic, are important as thermosetting resins. Alkyd resins are a family of complex, cross-linked polyesters, typically including phthalate esters of polyols such as glycerol.

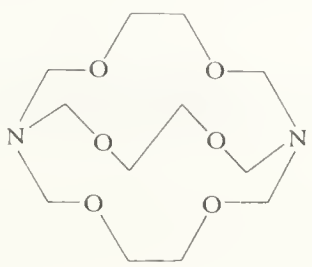
Following Pedersen's discovery of the so-called 'crown ethers' and their cation-binding properties, various classes of macro(bi)cyclic polyethers have risen to prominence in the last decade.[416] They include ethers such as 18-crown-6 [(**177**), the name indicating the size of the ring and the number of heteroatoms therein] and its chiral analogue (**178**) derived from (+)-(1*S*,2*S*)-*trans*-cyclohexane-1,2-diol, the bicyclic 'cryptand' (**179**), and its analogue (**180**) with bridgehead residues derived from pentaerythritol. The surprisingly



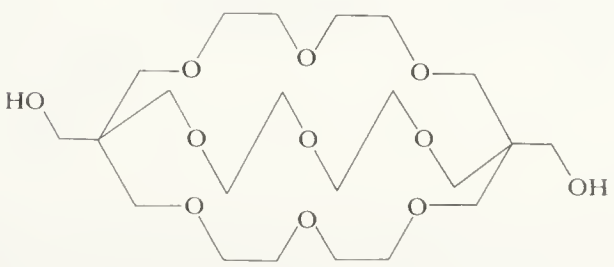
(**177**)



(**178**)



(**179**)



(**180**)

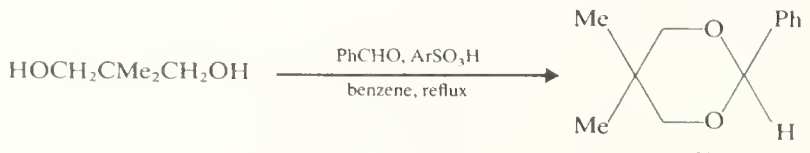
high yields often attained in syntheses of these macrocyclic compounds in base-catalysed Williamson-type reactions between diols and dihalides or ditosylates indicate that complexing encirclement of metal cations present — and acting as templates — facilitates cyclization. The 'fit' of a metal cation into the cavity provided by a polyether is a significant factor in the strength or selectivity of complexing. The ability of crown ethers and related compounds to dissolve metal salts (particularly those of alkali and alkaline earth metals) in non-polar solvents, with concomitant 'activation' of the relatively unsolved anion, has found many applications in synthesis:[416a] examples of such assisted reactions are included in Section 4.1.1. A further aspect of this rapidly developing area of chemistry is the use of chiral macrocyclic polyethers[416b,c] (i) in the resolution of racemates of primary alkylammonium salts through diastereoisomeric complexing and (ii) in the elaboration of enzyme analogues.

(ii) Formation of cyclic derivatives

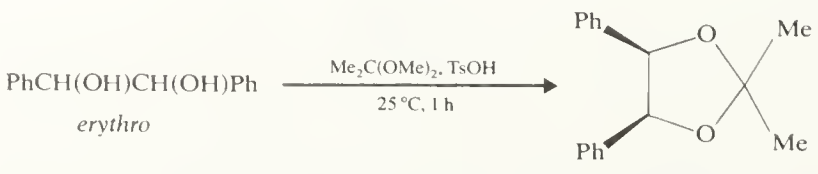
Compounds and complexes of medium ring-size and different structural types are readily formed by diols and polyols, *e.g.* through interaction with metal cations (Section 4.1.2.2), oxyanions, carbonyl compounds, and a variety of di- or poly-functional reagents. Apart from their intrinsically interesting stereochemistry and properties, such cyclic derivatives have a number of important applications, including the separation and identification of polyols (p. 665), the assignment of configuration to diols (p. 665), the protection of diols (p. 677), the differential functionalization of diols (p. 681), and the dehydroxylation of diols (p. 692).

(a) Cyclic acetals and orthoesters. As with most other cyclizations, five- and six-membered rings are the most readily and efficiently formed, and are the most widely studied. The standard methods for preparing the derivatives are drawn from those described for their acyclic counterparts (Section 4.1.1.4).

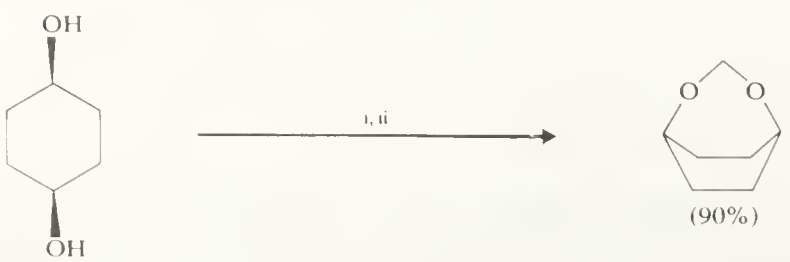
Cyclic acetals of 1,2-diols and 1,3-diols (1,3-dioxolans and 1,3-dioxans, respectively) are usually prepared by acid-catalysed reaction of the diol with the carbonyl compound (equation 278) or an acyclic acetal (equation 279). Recent additions to the extensive list of suitable catalysts, *e.g.* HCl, $HClO_4$, TsOH, sulphonated polystyrene resin, $ZnCl_2$, BF_3, $SnCl_4$, are oxalic acid[417a] in MeCN, and pyridinium chloride.[417b] Cyclic acetals difficult to prepare by the above methods can be obtained *via* the disproportionation of mixed acyclic acetals (equation 280)[418] or by reaction of the diol with a trimethylsilyl enol ether (equation 281).[419] Standard reactions less widely used are acid-catalysed addition of a diol



(83%) (278)

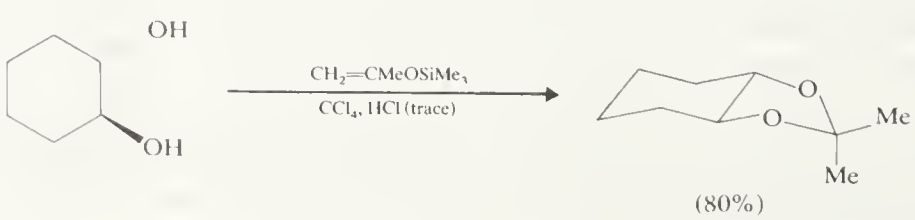


(86%) (279)



(90%) (280)

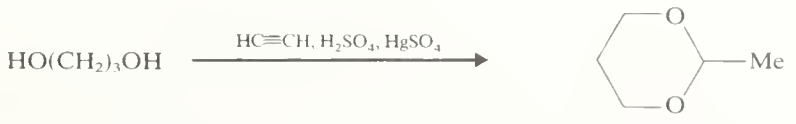
i, HCHO, EtOH, TsOH, benzene; ii, TsOH, heat.



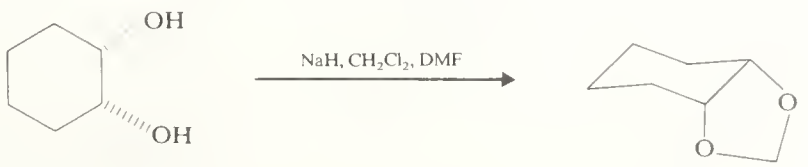
(80%) (281)

to an alkyne (equation 282) and base-catalysed reaction with a *gem*-dihalide (equation 283). Newer methods for the acetalation of acid-sensitive diols are (i) heating the diol with DMSO, alone or with *N*-bromosuccinimide[420] (giving methylene acetals), and (ii) thioacetal–acetal exchange involving the disulphonium salt (**181**) (equation 284).[421]

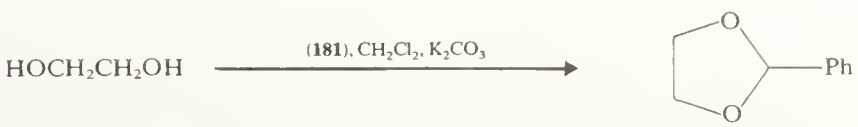
The stability of acetals under many reaction conditions makes them useful for the protection of both carbonyl compounds and diols. 1,2-Diols used for the former purpose include ethylene glycol (much the commonest reagent[422]), 3-bromopropane-1,2-diol (permitting reductive cleavage of the 1,3-dioxolan[423a]), and *o*-nitrophenylethylene glycol (photolabile[423b]). 1,3-Diols used as reagents include 2,2-dimethylpropane-1,3-diol (giving relatively acid-stable 1,3-dioxans), diol (**182**) (giving 5-methylene-1,3-dioxans that can be



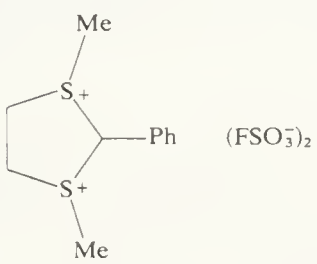
(75%) (282)



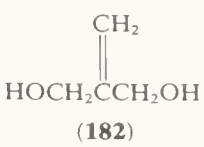
(46%) (283)



(60%) (284)



(**181**)

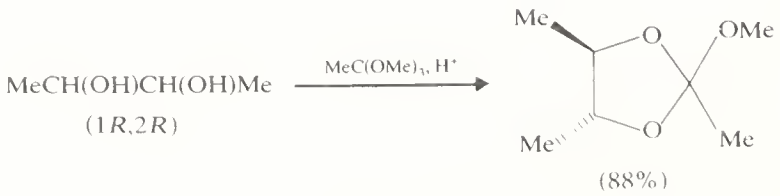


(**182**)

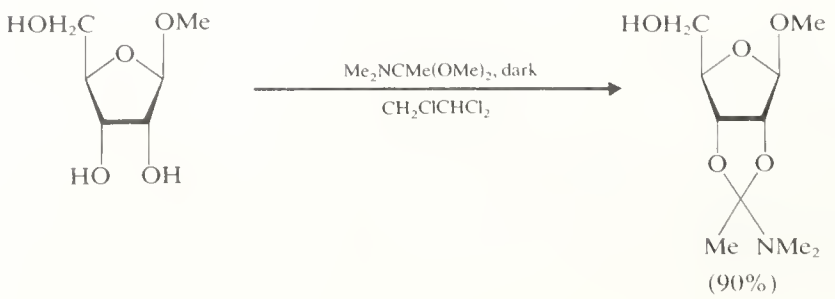
isomerized to acid-labile enol ethers with a soluble rhodium(I) catalyst[424a]), 2,2-dibromopropane-1,3-diol (permitting reductive de-protection[424b]), and a polymer-based diol (used for the monoacetalation of constitutionally symmetrical dialdehydes[424c]). Diols themselves are normally protected[342] as the methylene, ethylidene, benzylidene, isopropylidene, or cyclohexylidene derivatives; the use of a formylated polystyrene resin in heterogeneous reactions has also been reported.[425] Two problems that can arise in acetalation are the formation of diastereoisomeric mixtures (of ethylidene and benzylidene derivatives), and the formation of both 1,3-dioxolans and 1,3-dioxans (from triols and higher polyols). In general, thermodynamic control of the reactions leads mainly to 1,3-dioxans from aldehydes and 1,3-dioxolans from ketones, though complex patterns of products can arise with alditols. These specialized aspects of acetalation are discussed elsewhere.[426]

Cyclic orthocarboxylates (2-alkoxy-1,3-dioxolans and related heterocycles) are normally prepared by acid-catalysed exchange with an acyclic orthoester (equation 285). Applications of these derivatives and the corresponding orthocarbonates to the protection

of diols appear to be limited — or dictated — by their exceptional acid-lability. More durable protection can be provided by the related 1-*N*,*N*-dimethylaminoethylidene group (equation 286) and its benzylidene equivalent.[427] The involvement of cyclic derivatives of orthoacids in the formation and reactions of 1,3-dioxolan-2-ylium and related salts is considered below and in Section 4.1.2.4 (p. 681); general reviews of their chemistry are also available.[428]

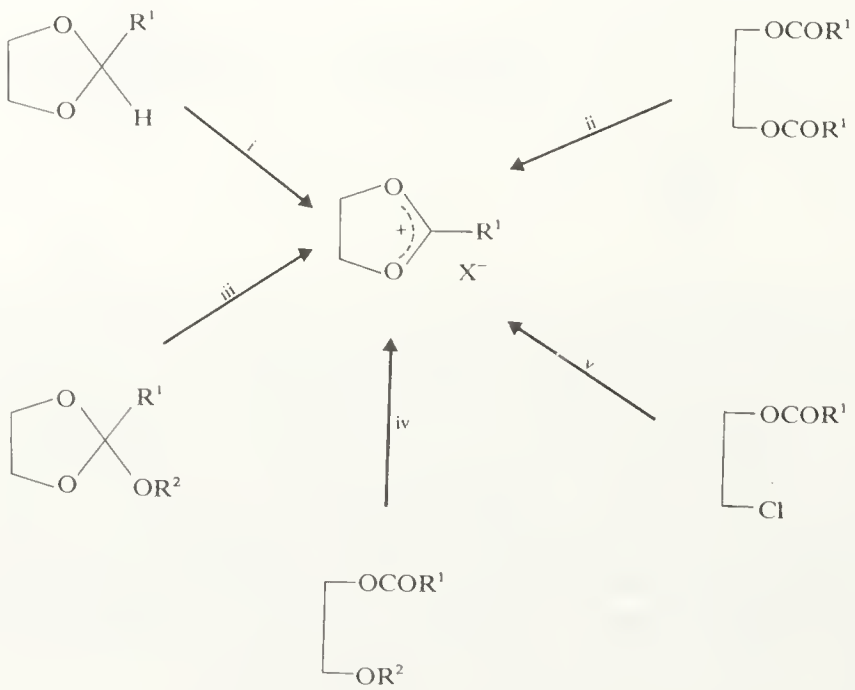


(285)



(286)

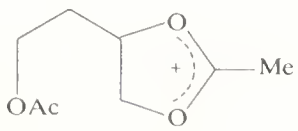
(*b*) *1,3-Dioxolan-2-ylium and related salts.* Cyclic carboxonium ions have been recognized or postulated as intermediates in many organic reactions, and methods for the preparation of their stable salts have been developed.[429] Scheme 25 indicates the major routes to 1,3-dioxolan-2-ylium (dioxolenium, acyloxonium) salts from derivatives of 1,2-diols. Similar methods apply to the preparation of 1,3-dioxan-2-ylium (dioxenium) salts, the lower stability of which is illustrated by the reaction of butane-1,2,4-triol



i, $Ph_3C^+ BF_4^-$; ii, HF, $SbCl_5$, or CF_3SO_3H; iii, BF_3 or $SbCl_5$; iv, $Et_3O^+ BF_4^-$; v, $SbCl_5$ or $AgBF_4$.

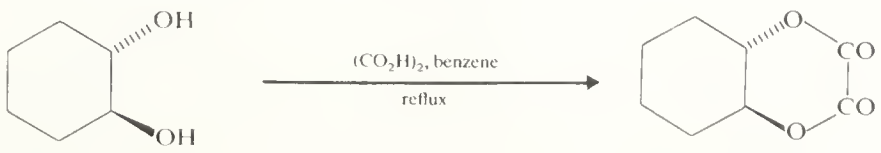
SCHEME 25

triacetate with $SbCl_5$: at equilibrium, only the dioxolenium cation (**183**) is detectable in solution.[430] Ring-opening reactions of these heterocyclic cations that are relevant to the selective functionalization of diols are described in Section 4.1.2.4 (p. 681); their intervention in rearrangements of polyol and monosaccharide esters[430] and in glycosidation reactions[431] has been reviewed.



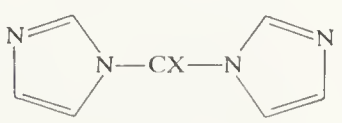
(**183**)

(*c*) *Cyclic carbonates and related esters.* Although cyclic esters of dicarboxylic acids are known, *e.g.* equation (287), they are not of major importance. On the other hand, cyclic carbonates — readily degraded under mild, basic conditions — are regularly used for the

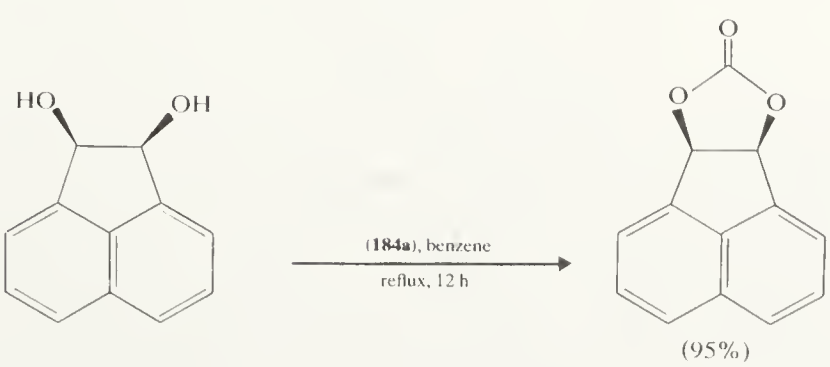


(287)

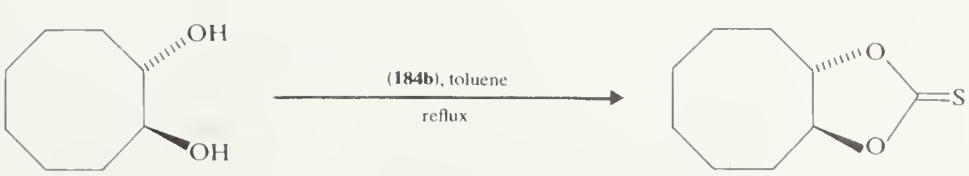
protection of diols (mainly *cis*-1,2). Esterification is conventionally achieved by base-catalysed reaction of the diol with $COCl_2$ or a chloroformate ester, though the imidazole derivative (**184a**) gives efficient acylation under neutral conditions (equation 288).[432] The corresponding reaction of a diol with (**184b**) constitutes one of the major routes to thionocarbonates (equation 289). Other methods[433] for preparing these cyclic derivatives are indicated by equations (290)–(292). These reactions, and methods for the preparation of cyclic esters from the oxoacids of phosphorus and sulphur, are also discussed in Volumes 3 and 4 of this work.



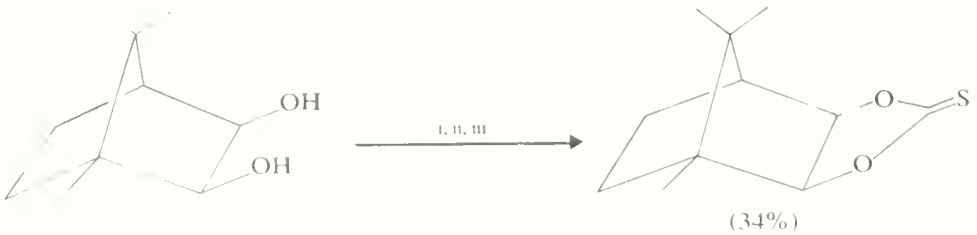
(**184**) a; X = O
b; X = S



(288)

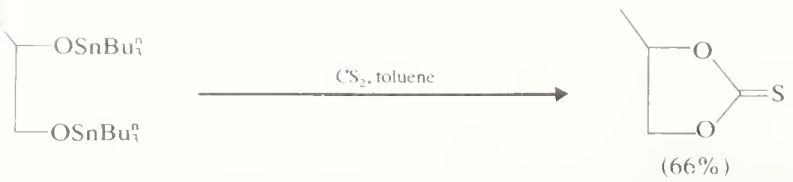


(289)

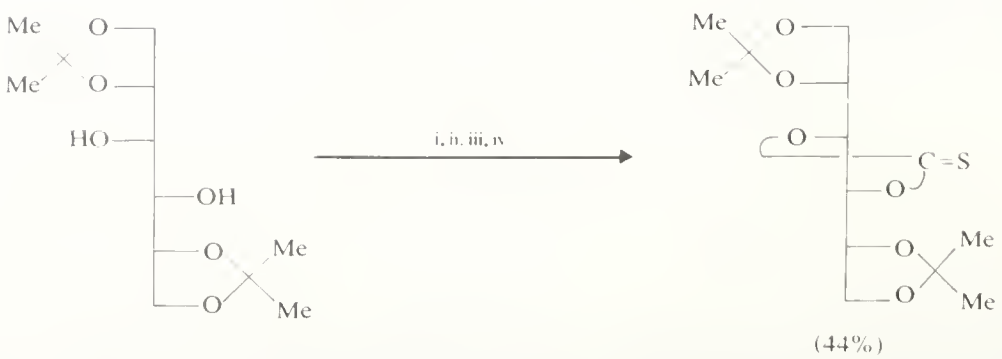


(34%) (290)

i, Bu^nLi, hexane; ii, CS_2, iii, MeI.



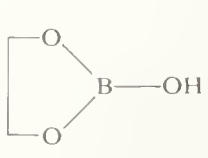
(66%) (291)



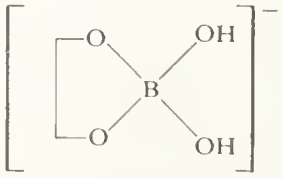
(44%) (292)

i, NaOH, aq. dioxan; ii, CS_2; iii, I_2; iv, pyridine.

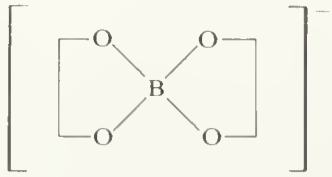
(*d*) *Borate complexes and related derivatives.* The formation of 'complexes' between polyhydroxy compounds and various inorganic oxoacids or their anions is a well-known phenomenon. The most extensively studied and exploited of these complexes are those containing boron, but molybdate, tungstate, germanate, and arsenite complexes have also found applications. Complexation is usually interpreted as dynamic esterification, and has mainly been studied with aqueous solutions of the reactants. Borate esters of several types are postulated: weakly ionizing esters (**185**) formed by boric acid, the 1 : 1 and 2 : 1 anionic esters (**186**) and (**187**) formed by tetraborate with a diol, and 'tridentate' complexes exemplified by the derivatives of *cis*-inositol (**188**) (and other cyclitols with an accessible conformation having the same *syn*-triaxial arrangement of hydroxy groups) and acyclic triols such as (**189**).[434] In general, *threo*-1,2-diols complex more strongly than do the



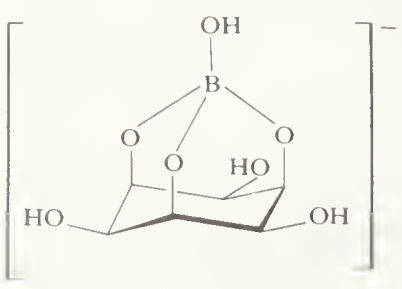
(**185**)



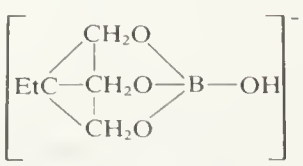
(**186**)



(**187**)



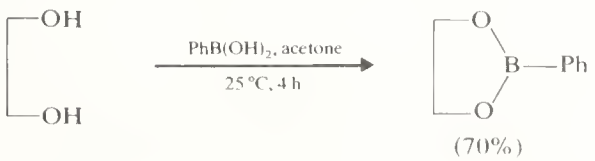
(**188**)



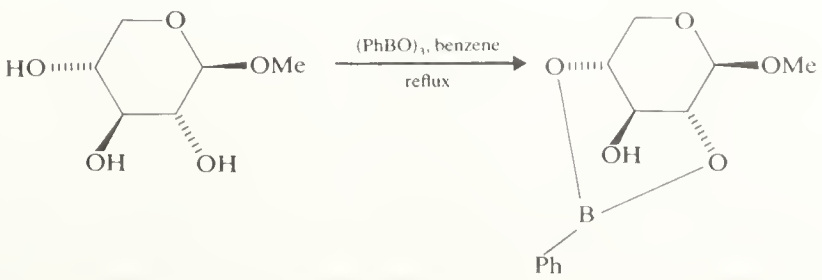
(**189**)

erythro-isomers. Partition chromatography, electrophoresis,[370c] and anion-exchange chromatography[435] of polyols and carbohydrates in the presence of complexing anions are used routinely for the separation, identification, and estimation of these compounds.

In marked contrast to borate complexes, the boronate esters of diols and polyols can often be obtained as pure, crystalline, and relatively stable compounds. Benzeneboronates are readily formed by both 1,2- and 1,3-diols by reaction with $PhB(OH)_2$ (equation 293) or its cyclic trimeric anhydride, triphenylboroxole, $(PhBO)_3$ (equation 294). Although



(70%) (293)



(89%) (294)

five- and six-membered rings are preferred, cyclic boronates of larger ring sizes can also be formed.[436] Mixed products are often obtained from acyclic 1,2,3-triols, with the six-membered-ring products predominating in the absence of axial substitution.[437] The facile preparation and hydrolysis or alcoholysis of benzeneboronates makes them useful in protection.[342,438] Polymer-based boronic acids have also been used for the selective blocking of polyols in solid-state syntheses,[439a] the separation of the components of *cis–trans* mixtures of alicyclic diols,[439b] and the fractionation of polyols by column chromatography.[439a,c] The volatile benzene- and butane-boronates of diols and polyols are useful for the analysis of these compounds by gas–liquid chromatography and mass spectrometry.[440] The anionic complexes formed with areneboronic acids and the corresponding borinic acids (Ar_2BOH)[441] in aqueous solution are, like the borate complexes, amenable to chromatographic and electrophoretic separation.

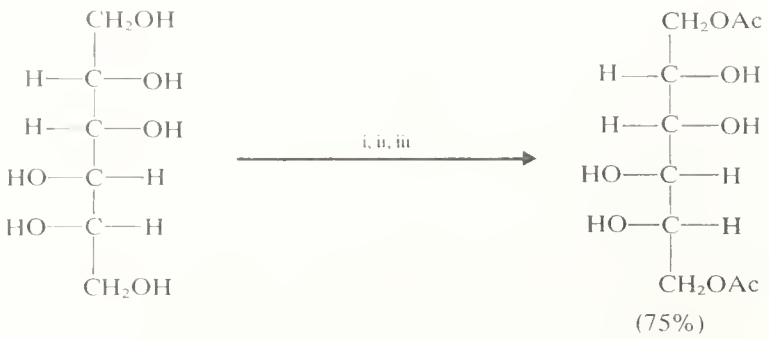
(*iii*) *Selective and differential functionalization of hydroxy groups*

The selective functionalization of a specific hydroxy group in a polyol is a perennial challenge to the synthetic chemist. In the simplest cases, where stereoelectronic or conformational factors are favourable, the use of a limited amount of reagent and kinetic control of the reaction will provide adequate regioselectivity. Where direct, selective reaction at the chosen site is impracticable, the differential protection of other hydroxy groups commonly provides a solution. A valuable survey of the relative reactivities of hydroxy groups — specifically relating to carbohydrates, but of general interest — towards esterification, etherification, halogenation, and oxidation is available.[442] Methods and reagents that differentiate effectively between the various classes of hydroxy groups have been exemplified in Section 4.1.1, and are supplemented below. Several approaches to the difficult problem of efficient monofunctionalization of diols containing similar or equivalent hydroxy groups are also considered here.

Bimolecular reactions in which steric retardation is a major influence naturally favour the selection of primary hydroxy groups and discriminate between equatorial and axial secondary hydroxy groups. Such selectivity is commonly exploited in acylation, alkylation,

and certain halogenation reactions. Recent examples are partial esterification by the Ph_3P–azodicarboxylate method[443] (equation 295) and selective acetolysis of pertrimethylsilyl ethers[444] (equation 296). Although respectable yields of monoesters can be obtained

$$MeCH(OH)CH_2CH_2OH \xrightarrow[PhCO_2H,\ THF,\ 25\,^\circ C]{Ph_3P,\ EtO_2CN{=}NCO_2Et} MeCH(OH)CH_2CH_2OBz \quad (70\%) \qquad (295)$$



(296)

i, Me_3SiCl, pyridine; ii, Ac_2O, AcOH, pyridine; iii, aq. AcOH, MeOH, 25 °C.

from some constitutionally symmetrical diols by the former method, *e.g.* from butane-1,4-diol (66%) and pentane-2,4-diol (57%),[443] intramolecular reactions of the intermediate alkoxyphosphonium salts leading to oxirans or spirophosphoranes predominate in other cases.[443,445] The synthetic versatility of the alkoxyphosphonium salts (**85b**) derived from primary alcohols (Section 4.1.1.4, p. 618) extends to the efficient monofunctionalization of constitutionally symmetrical di-primary diols in other ways (1,2-diols excepted).[446] With 1,3-diols, the use of an equimolar amount of $(Me_2N)_3P$ leads uniquely to the 3-hydroxyalkoxyphosphonium salt, which can be decomposed directly to the chloroalcohol (equation 297), or converted to the perchlorate or fluorophosphate, and then subjected to alternative nucleophilic displacements. Similar results can be obtained with other diols (equation 298) by preparing the salt in THF (in which it is insoluble), but not in CH_2Cl_2. The yields of monofunctionalized products obtained from diols by classical

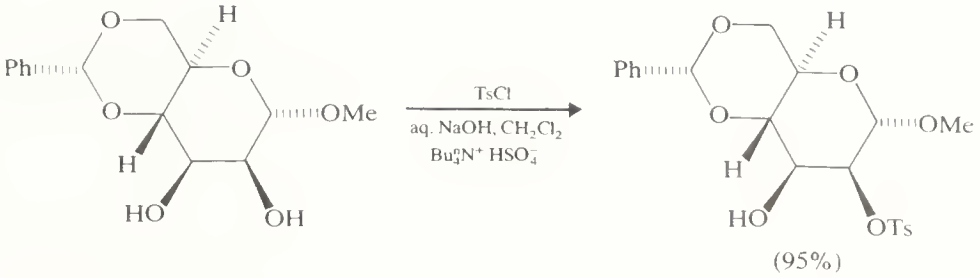
$$Me_2C(CH_2OH)_2 \xrightarrow{i,\ ii} HOCH_2CMe_2CH_2Cl \quad (85\%) \qquad (297)$$

i, $(Me_2N)_3P$, CCl_4, THF, −30 °C; ii, DMF, 100 °C, 6 h.

$$HO(CH_2)_{10}OH \xrightarrow{i,\ ii,\ iii} HO(CH_2)_{10}CN \quad (70\%) \qquad (298)$$

i, $(Me_2N)_3P$, CCl_4, THF, −20 °C; ii, KPF_6; iii, KCN, DMF, 80 °C.

methods of acylation and alkylation can be improved by resorting to heterogeneous reactions. One approach[447] is to use a two-phase system with a phase-transfer catalyst, whereby the initial product becomes relatively inaccessible to further reaction, *e.g.* equation (299). A second approach[448] is to use a sparsely functionalized, insoluble polymer — effectively a dilute reagent — to block selectively one hydroxy group of a constitutionally symmetrical diol, allowing further manipulation to be carried out at the remaining site. Polystyrene resins carrying residues of either trityl chloride or an acid chloride have been prepared and used for the synthesis of simple diol derivatives (equation 300) and also of insect pheromones.[448b]



(95%) (299)

$$HO(CH_2)_8OH \xrightarrow{\text{i, ii, iii}} HO(CH_2)_8OCPh_3 \quad (51\%) \qquad (300)$$

i, ⓟ$C_6H_4CH_2COCl$, pyridine; ii, Ph_3CCl, pyridine; iii, NH_3, dioxan.

Several methods for the selective oxidation of primary hydroxy groups (*e.g.* with CrO_3–graphite or Pt–O_2) and secondary hydroxy groups (*e.g.* with various halogen-based derivatives or dehydrated Al_2O_3) have been indicated in Section 4.1.1.4 (p. 644). Hydroxyketones can also be obtained selectively from primary–secondary diols by treating the bistrityl ethers with a triphenylmethylium salt[449] (equation 301). However, yields from 1,2-diols are poor. α-Ketols have been obtained from several such diols by a related reaction[245a,450] involving hydride abstraction from the derived 1,3-dioxolans (equation 302). Other oxidants used for the preparation of α-ketols are *N*-chlorosuccinimide–dimethyl sulphide[451a] and silver(I) carbonate–Celite (the Fétizon reagent);[451b] instances of

(85%) (301)

i, Ph_3CCl, pyridine; ii, $Ph_3C^+ BF_4^-$, CH_2Cl_2, 25 °C; iii, aq. $NaHCO_3$.

(302)

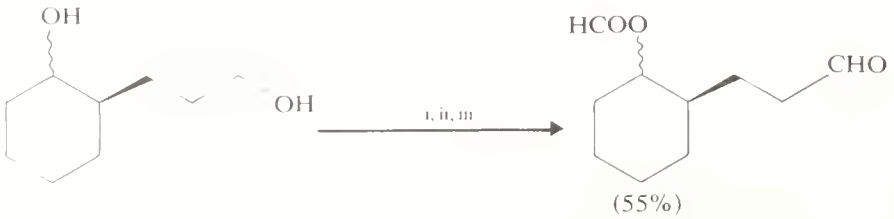
i, $Ph_3C^+ BF_4^-$, CH_2Cl_2; ii, aq. $NaHCO_3$.

preferential cleavage of the C—C bond, *e.g.* with *threo*-diols of structure $ArCH(OH)CH(OH)CMe{=}CH_2$, have, however, been reported[451c] for the latter reagent. The Fétizon reagent has also proved useful for the partial oxidation of constitutionally symmetrical, non-vicinal diols and for the selective oxidation of secondary hydroxy groups (equation 303).[452a] Lactones are obtained in high yield by the oxidation of di-primary and primary-tertiary 1,4-, 1,5-, and 1,6-diols (equation 304).[452b] A novel method[453] for the

$$MeCH(OH)CH_2CH_2OH \xrightarrow[\text{benzene, reflux, 2 h}]{Ag_2CO_3/\text{Celite}} MeCOCH_2CH_2OH \quad (80\%) \qquad (303)$$

$$HO(CH_2)_6OH \xrightarrow[\text{benzene, reflux, 2.5 h}]{Ag_2CO_3/\text{Celite}} \text{(O, CO)} \quad (96\%) \qquad (304)$$

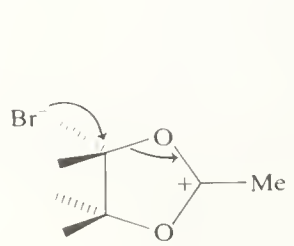
selective oxidation of primary hydroxy groups stems from the fact that, at low temperature, secondary alcohols react with Ph_3PBr_2 in DMF to give formate esters in place of bromides. The bromoformates obtained from primary-secondary diols can then be oxidized to hydroxyaldehyde formates (equation 305).



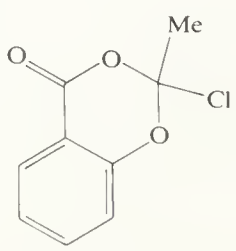
(305)

i, Ph_3PBr_2, DMF, −5 °C; ii, DMSO, $AgBF_4$; iii, Et_3N.

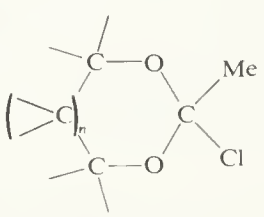
An important and growing group of reactions leading to the differential functionalization of the hydroxy groups of 1,2- and 1,3-diols proceed through the formation and cleavage of cyclic derivatives. The halohydrin-forming reactions of the diols with hydrogen halides, and the catalysis of these reactions by acetic acid, have been extensively studied. The catalysis is usually[454] interpreted as evidence for reaction *via* an acyloxonium cation. The corresponding reactions of acyclic diols or cyclic *cis*-diols with HBr in acetic acid,[455] involving nucleophilic ring-opening of the intermediate cation, *e.g.* (**190**), provide simple and efficient syntheses of bromohydrin acetates. High regio- and stereoselectivities consistent with S_N2 displacement are observed (equation 306) for attack at non-benzylic, primary or secondary carbon atoms. Analogous results are obtained in reactions of 1,2-, 1,3-, and 1,4-diols with *O*-acetylsalicyloyl chloride in the absence of base, *e.g.* equation (307).[456] Postulated intermediates are the cyclic tautomer (**191**) of the acid chloride,[456a,457] and the chloroheterocycle (**192**).



(**190**)

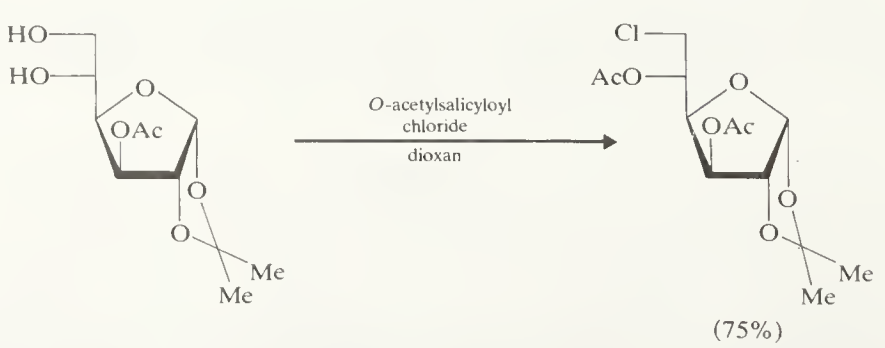


(**191**)



(**192**) $n = 0$, 1, or 2

$$\underset{(S)}{MeCH(OH)CH_2OH} \xrightarrow[\text{room temperature}]{HBr,\ AcOH} \underset{(S)\ (84\%)}{MeCH(OAc)CH_2Br} + \underset{(S)\ 5\%}{MeCHBrCH_2OAc} \qquad (306)$$



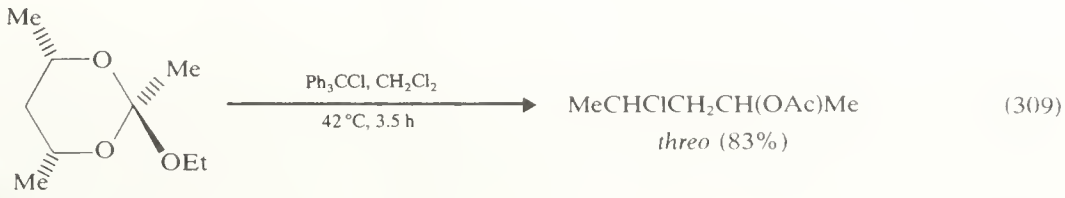
(307)

Compounds of type (**192**) are also formed by the action of PCl_5 on the cyclic acetals of pyruvic acid;[458] at room temperature, they rapidly rearrange to chlorohydrin esters, presumably *via* heterolysis of the C—Cl bond and S_N2 displacement on the acetoxonium

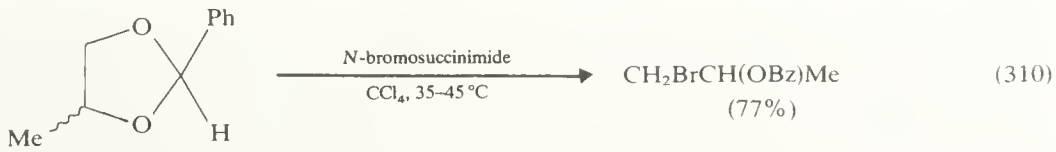
$$\underset{(-)\text{-}threo}{MeCH(OH)CH(OH)Me} \xrightarrow{\text{i, ii}} \underset{(+)\text{-}erythro\ (46\%)}{MeCHClCH(OAc)Me} \qquad (308)$$

i, $MeCOCO_2H$, $ArSO_3H$, benzene, reflux; ii, PCl_5, CH_2Cl_2

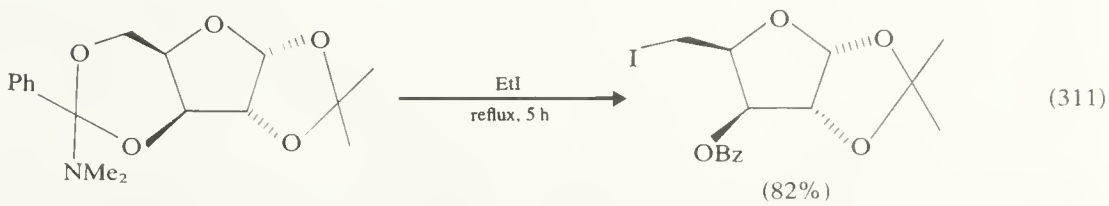
ion or (**192**) itself (equation 308). The modest overall yields are mainly caused by the relative inefficiency of the first stage. Varying degrees of improvement in yield or applicability emanate from related reaction sequences in which acyloxonium cations are generated from cyclic orthoesters by treatment with Ph_3CCl,[459a] Me_3SiCl,[459b] or Me_3CCOCl (pivalyl chloride),[459c] from benzylidene acetals by treatment with *N*-bromosuccinimide (the Hanessian–Hullar reaction),[460a] from *N*,*N*-dimethylbenzamide acetals by treatment with an alkyl halide,[460b] and from cyclic thionocarbonates by treatment with methyl iodide.[460c] Examples of some of these reactions are given in equations (309)–(312). Still



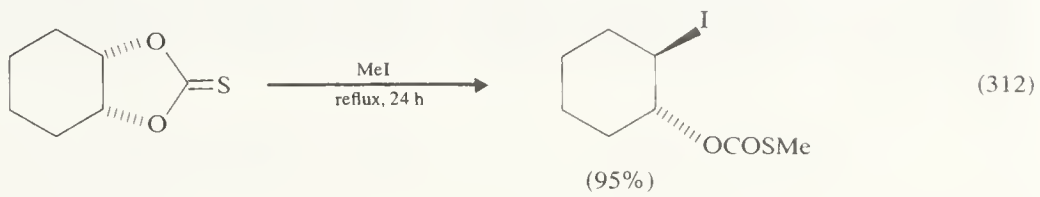
(309)



(310)



(311)



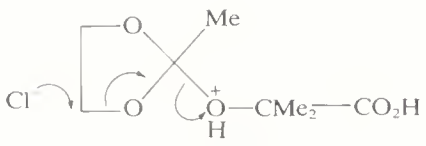
(312)

more reactions in this category, that produce halohydrin esters directly from diols, include those with acetyl bromide[461a] or 2-acetoxy-2-methylpropanoyl chloride (**193**)[461b] in the absence of base (both reactions giving acetates), with cyanogen chloride and HCl (giving carbamates),[461c] with *N*-dichloromethylene-*N*,*N*-dimethylammonium chloride (**194**) (giving *N*,*N*-dimethylcarbamates),[461c] and with *N*-α-chlorobenzylidene-*N*,*N*-dimethylammonium chloride (**195**) (giving benzoates).[461d] The likely intermediates leading to the halohydrin esters, either directly or *via* acyloxonium cations, in the reactions of diols with (**193**), (**194**), and (**195**) are indicated by (**196**), (**197**), and (**198**), respectively. Excellent yields have been recorded for simple 1,2- and 1,3-diols, and both these and the preceding reactions are finding many applications in the selective functionalization of carbohydrates and nucleosides. Apart from their intrinsic interest, halogenated sugars are useful intermediates for the preparation of deoxy derivatives. Because the ring-opening step in the reactions described above involves an S_N2 displacement, the formation of primary halides is normally favoured over secondary, *e.g.* equation (311). The reverse regioselectivity

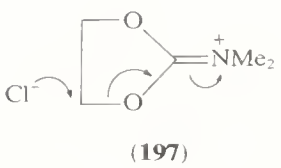
$Me_2C(OAc)COCl$ (193)

$Me_2\overset{+}{N}{=}CCl_2\ Cl^-$ (194)

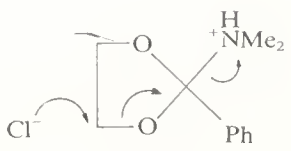
$Me_2\overset{+}{N}{=}CPhCl\ Cl^-$ (195)



(196)



(197)

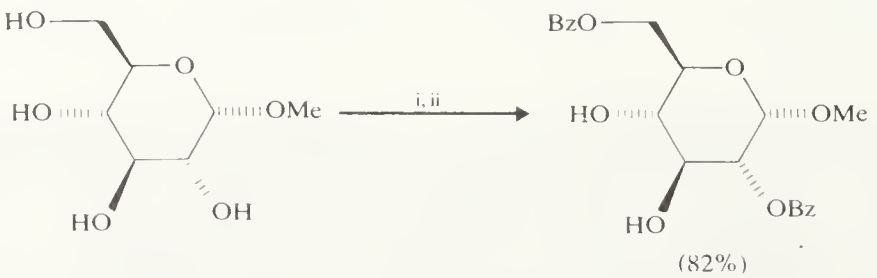


(198)

applies to the opening of thionocarbonate rings with Bu^n_3SnH, giving secondary deoxy derivatives directly from primary-secondary diol esters in a radical-mediated reaction.[462] The stereoselectivity of the acyloxonium-cation-mediated reactions also makes them useful for the conversion of chiral diols to chiral oxirans of the same configuration — the net result of inversion both during the ring-opening and during cyclization of the halohydrin ester.

The ambident nature of acyloxonium cations[429] provides an alternative pathway for reaction with some nucleophiles. Thus hydration of the cations, *via* orthoacid derivatives such as (**169**), leads to diol monoesters with retention of configuration. Examples of partial esterification by this method are the reactions of orthoesters with water or dilute acid,[428,459a] of *N,N*-dimethylbenzamide acetals with dilute acetic acid,[427] and of benzylidene acetals with *N*-bromosuccinimide[460a] or $Ph_3C^+BF_4^-$ followed by aqueous work-up.[463] The ozonolysis of cyclic acetals is another means of converting diols into their monoesters.[464] Still further possibilities for selective functionalization are offered by other ring-opening reactions of cyclic orthoesters[428] and acetals.

A new development in selective functionalization is the use of specifically activated organotin derivatives. The enhanced nucleophilicity of such derivatives was noted in Section 4.1.1.4 (p. 618) and their use in (selective) oxidation of alcohols[292,309] was also described (p. 649). Preliminary studies[465] also indicate the feasibility of regioselective acylation of individual hydroxy groups of polyols under thermodynamic control. In the example shown (equation 313), selective stannylation (and ultimate acylation) of the

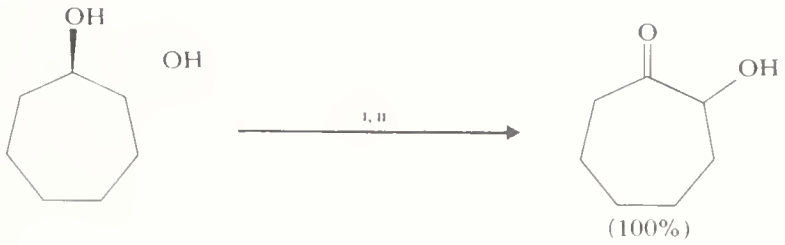


(313)

(82%)

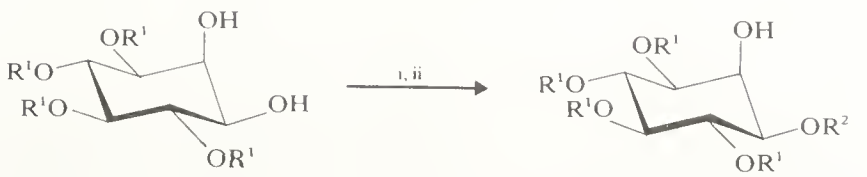
i, $(Bu^n_3Sn)_2O$, toluene, reflux; ii, BzCl, room temperature.

2-position of the glucoside is dictated by stabilizing coordination of metal to the suitably disposed methoxy group. More extensively explored are the cyclic stannylidene derivatives formed by the reaction of Bu^n_2SnO with 1,2- and 1,3-diols.[466] Equations (314) and (315) illustrate applications of these derivatives to the partial oxidation and selective alkylation of simple diols, but the most attractive applications appear to lie in the fields of carbohydrate and nucleoside chemistry.



(100%) (314)

i, Bu^n_2SnO, benzene, reflux; ii, Br_2, CH_2Cl_2.



(73%) R^1 = benzyl, R^2 = allyl (315)

i, Bu^n_2SnO, MeOH, reflux; ii, $CH_2{=}CHCH_2I$, DMF, 100 °C.

(*iv*) *Dehydration, rearrangement, and cyclization*

Various reactions are possible when a diol or polyol is treated with a dehydrating agent, and not surprisingly the products are frequently complex and dependent on the reagent and conditions, as well as on the type and structure of the hydroxy compound. In these circumstances the discussion will mainly be focused on reactions that are relatively clear-cut and of synthetic value. The potential complexity of the acid-catalysed, carbenium-ion-mediated reactions of even simple diols is exemplified by the effect of pyridinium halides on hexane-1,6-diol under reflux.[467] The 24 products identified included five conjugated dienes, three non-conjugated dienes, cyclohexene, unsaturated alcohols and halides, and both cyclic and acyclic ethers.

(*a*) *Dehydration of diols to dienes.* Conjugated dienes are the main products of interest (*cf.* Section 2.3.1) and can be prepared from 1,2-, 1,3-, and 1,4-diols by direct dehydration. The extensive studies of such reactions[468] will not be considered in detail here. Equations (316)–(318) exemplify the use of some classical reagents in representative

$$Me_2C(OH)C(OH)Me_2 \xrightarrow[400\text{–}470\,^\circ C]{Al_2O_3} CH_2{=}CMeCMe{=}CH_2 \quad (70\text{–}85\%) \qquad (316)$$

$$MeCH(OH)CH_2CH(OH)Me \xrightarrow[\text{heat}]{48\%\ HBr} MeCH{=}CHCH{=}CH_2 \quad (50\%) \qquad (317)$$

(50%) (318)

transformations. In general, 1,3-diols give least by-products. 1,4-Diols tend to undergo preferential cyclization, particularly in acid-catalysed, liquid-phase reactions, except where this is sterically prevented or hindered. Constitutionally symmetrical, di-tertiary 1,2-diols can often be dehydrated readily and efficiently; dehydration, as opposed to pinacolic rearrangement, is encouraged by the use of hot, relatively strong, concentrated acids.

(*b*) *Dehydration–rearrangement.* The acid-catalysed partial dehydration–rearrangement of 1,2-diols (pinacolic rearrangement) is a well-known reaction. Standard treatments[24,469] include the use of Lewis acids (*e.g.* BF_3, $ZnCl_2$, I_2), the use of concentrated, strong acids (*e.g.* H_2SO_4, $HClO_4$) in the cold, and heating with more dilute or weaker Brønsted acids. The products may be aldehydes (from diols containing a primary or — in some cases — secondary hydroxy group) or ketones (formed directly, or indirectly *via* aldehydes, where the conditions are sufficiently vigorous to cause rearrangement of the latter). Examples of the rearrangement for primary-tertiary and di-secondary diols are given in equations (319) and (320). Of greater preparative importance, and more extensively studied from the viewpoint of mechanism,[470] are the rearrangements of di-tertiary and secondary-tertiary diols, *e.g.* equations (321)–(325).

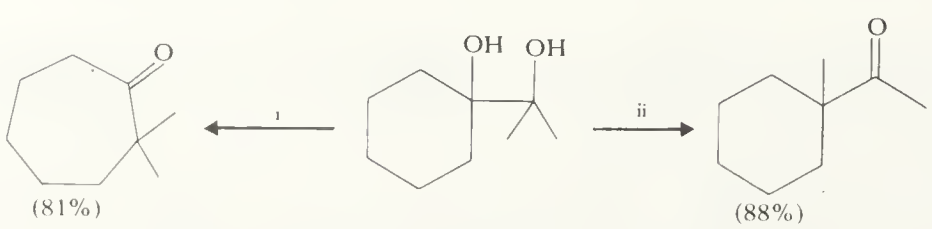
$$Me_2C(OH)CH_2OH \xrightarrow[\text{distillation}]{12\%\ H_2SO_4} Me_2CHCHO \quad (100\%) \tag{319}$$

$$MeCH(OH)CH(OH)Me \xrightarrow[\text{distillation}]{35\%\ H_2SO_4} MeCOCH_2Me \quad (81\%) \tag{320}$$

$$Ph_2C(OH)CH(OH)Ph \xrightarrow[0\,^\circ C]{\text{conc. } H_2SO_4} Ph_2CHCOPh \quad (100\%) \tag{321}$$

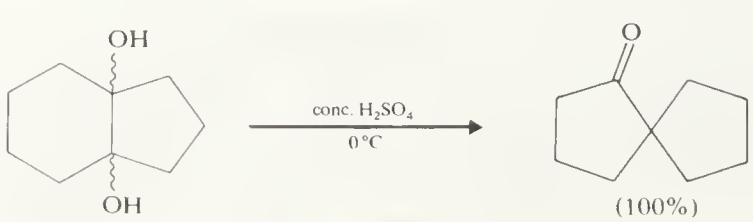
$$Bu^tMeC(OH)C(OH)Me_2\ (S) \xrightarrow[\text{reflux}]{40\%\ H_2SO_4} MeCOCMe_2Bu^t\ (S)\ (66\%) \tag{322}$$

(100%) (323)

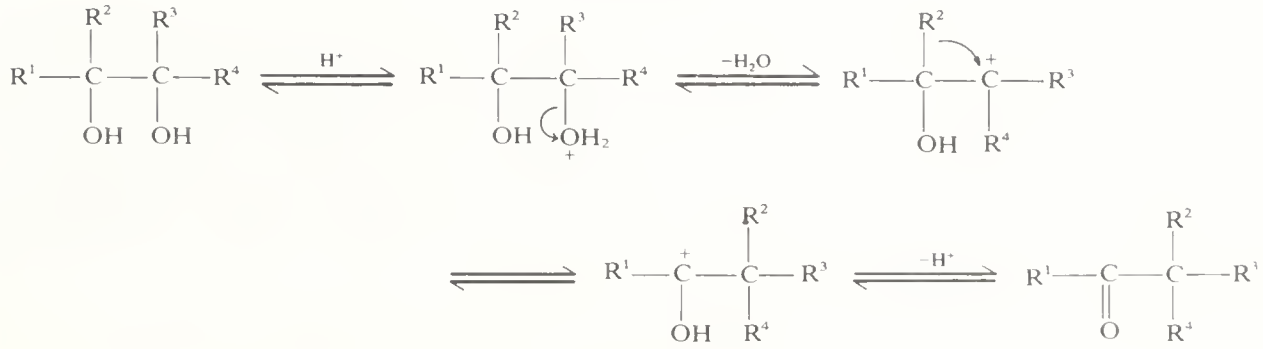


(81%) (88%) (324)

i, 70% $HClO_4$, −20 °C; ii, $BF_3.OEt_2$, CH_2Cl_2, 0 °C.



(100%) (325)



SCHEME 26

At its simplest, the pinacol rearrangement follows the mechanism indicated by Scheme 26, involving an intramolecular, nucleophilic 1,2-shift, with retention of configuration by the migrating group, *e.g.* equation (322). With constitutionally unsymmetrical diols, the course of the reaction depends on the balance of importance between the relative migratory aptitudes of the different groups, and their abilities to stabilize the initial carbenium ion,[470] and also on the reaction conditions, *e.g.* equation (324). No useful account of the mechanistic subtleties and variants can be given in the space available.

Acid-catalysed rearrangements of 1,3-diols have not achieved synthetic prominence. The neopentylic rearrangements of di-primary diols, producing mainly carbonyl compounds, have been examined by Mazet and his co-workers.[471a] Individual aldehydes can be obtained in good yield from diols in which the alternative groups differ significantly in migratory aptitude (equation 326). With the primary-secondary 1,3-diols, increasing competition from cyclization is observed.[471b] Pyridinium bromide is a relatively mild reagent for promoting rearrangements of 1,3-diols,[472] and rhodium catalysts appear to be selective for the formation of ketones (equation 327).[473]

$$HOCH_2CR^1R^2CH_2OH \xrightarrow[\text{distillation}]{50\%\ H_2SO_4} R^1CH_2CHR^2CHO \qquad (326)$$

$R^1 = Ph,\ R^2 = Me$ (95%)
$R^1 = Me,\ R^2 = Bu^s$ (80%)

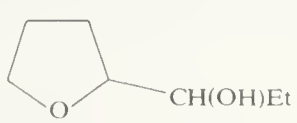
$$MeCH(OH)CH_2CH_2OH \xrightarrow[80\,^\circ C,\ 48\ h]{RhCl_3\text{-}Ph_3P} MeCOCH_2Me \qquad (327)$$

(89%)

(*c*) *Cyclization.* Applied to diols, standard methods of etherification often lead to cyclic products (Chapter 4.4). In view of discussion elsewhere, treatment of the topic here will be brief.

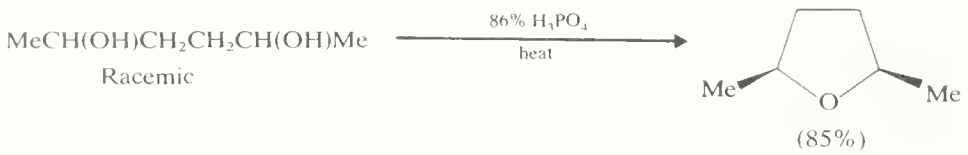
Oxirans are sometimes formed from 1,2-diols — particularly tetra-aryl substituted diols — under the conditions of pinacolic rearrangement, but this is not a general method of preparation. Both oxirans and oxetans, formed similarly from 1,3-diols,[474] readily undergo acid-catalysed rearrangement or further dehydration. In contrast, the cyclization of 1,4-diols is a major route to tetrahydrofurans, and 1,5-diols can similarly be converted to tetrahydropyrans. Where both classes of product are possible, the formation of tetrahydrofurans is normally preferred, *e.g.* from the triol in equation (328) and from

$$HOCH_2CH_2CH_2CH_2CH(OH)CH(OH)Et \xrightarrow[\text{heat}]{\text{aq } HCO_2H} \qquad (328)$$



(*ca.* 40%)

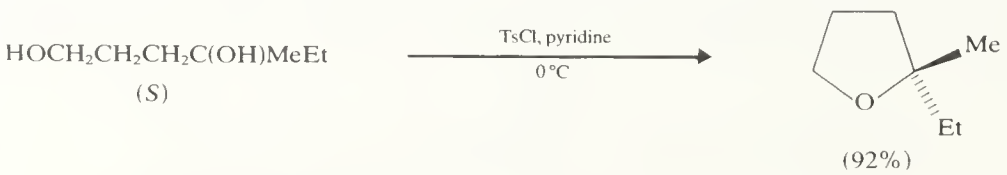
alditols generally. In addition to the usual acid catalysts (*e.g.* H_2SO_4, H_3PO_4, TsOH),[475a] relatively mild or convenient reagents such as DMSO,[255,475b] pyridinium chloride,[475c] and sulphonated polystyrene resins[475d] are also effective. Several groups[476] have recently scrutinized the stereochemistry of cyclizations catalysed by acid and other reagents. With simple aliphatic di-secondary 1,4-diols, reaction proceeds by way of a stereoselective, intramolecular S_N2 displacement (equation 329). When the diol contains a tertiary or



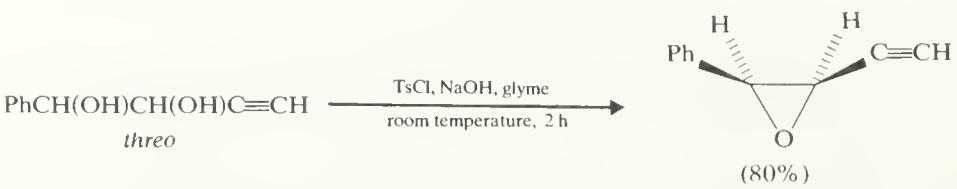
(329)

benzylic hydroxy group, this is preferentially lost in reaction under mild conditions by a carbenium ion mechanism. Under the more drastic conditions used for the cyclodehydration of alditols, the 1,4-anhydro derivatives of pentitols and hexitols are typically formed with retention of configuration *via* S_N2 displacement of the protonated *primary* hydroxy group.[477] Steric influences on the ease, direction, and site of cyclization have been assessed,[477] and the chemistry of both mono- and poly-cyclic anhydro derivatives has been reviewed.[478]

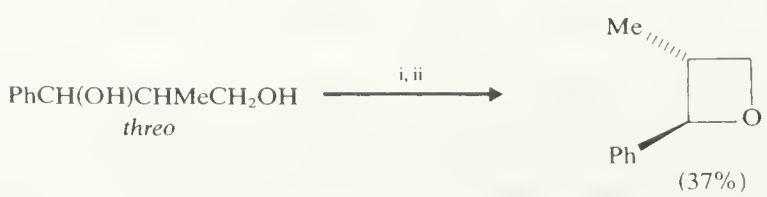
A widely used, stereoselective method of preparing cyclic ethers from diols containing a primary or secondary hydroxy group consists of the base-catalysed ring closure of a monosulphonate ester. Yields of tetrahydrofurans from one-step reactions, *e.g.* equation (330), are generally good, and a similarly efficient direct preparation of oxiranes has also been described[479] (equation 331). Equations (332) and (333) exemplify two-step syntheses



(330)

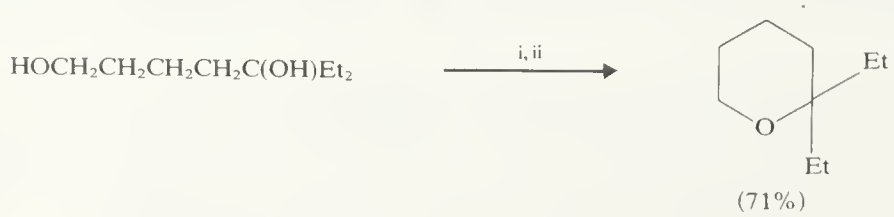


(331)



(332)

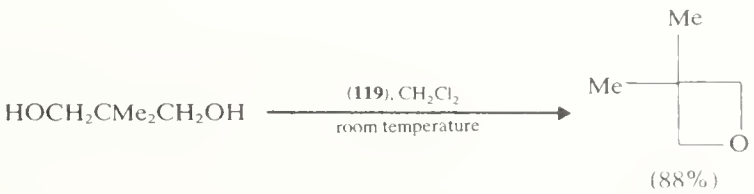
i, TsCl, pyridine, 5 °C; ii, Bu^{t}OK, Bu^{t}OH, room temperature.



(333)

i, TsCl, pyridine, 0 °C; ii, HMPT, 80 °C, 6 h.

of oxetans[480] and tetrahydropyrans,[481] respectively. Traditional Williamson reactions of halogeno-alcohols are, of course, equally servicable for cyclizations, and organotin derivatives of such alcohols have similar applications.[482] Other novel methods of cyclodehydration are the reaction of a diol with the sulphurane (**119**), best suited[483] to the preparation of oxirans and some oxetans (equation 334), and reactions involving rhodium[473] or palladium[484] catalysts, both applicable to the preparation of tetrahydrofurans and tetrahydropyrans.

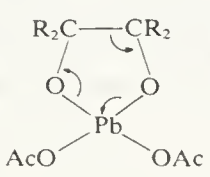


(334)

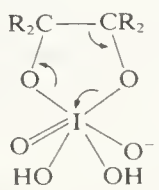
(*v*) *Oxidative cleavage of vicinal diols*

Many oxidants are capable of cleaving the C—C bond of 1,2-diols and related functional combinations, *e.g.* —COCH(OH)—, —COCO—, —CH(OH)CH(NH_2)—.[485] However, only lead(IV) acetate, paraperiodic acid (H_5IO_6), and alkali metal metaperiodates ($NaIO_4$ and KIO_4) are established as reagents of choice; studies of other reagents have mainly been exploratory or mechanistic. Whereas $Pb(OAc)_4$ in AcOH is mainly used for the cleavage of hydrophobic diols, the water-soluble periodates are preferred for the cleavage of polyols and other hydrophilic substrates. Chloroform-soluble quaternary ammonium periodates also find occasional applications.[486] The reactions are usually stoichiometric, with one mole of oxidant being consumed for each bond cleaved. Where two adjacent bonds are cleaved, the central —$\overset{|}{\underset{|}{C}}$OH is oxidized to —$CO_2H$ (equation 335). Such reactions, monitored both for the consumption of periodate and the identities and quantities of products, are widely used in degradative studies of carbohydrates. Cyclic esters such as (**199**) and (**200**) are intermediates in the oxidative cleavage of diols by the

(335)



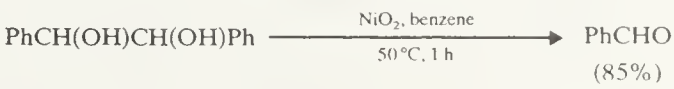
(**199**)



(**200**)

two types of reagent. The involvement of such esters explains the relatively fast oxidation of the *cis*-isomers of cyclic diols (compared with the *trans*-isomers) and likewise the faster oxidation of the *threo*-isomers of acyclic diols, in accordance with the greater torsional strain introduced during the cyclization of the *erythro*-isomers.

The general excellence of the above reagents for selective cleavages under mild conditions, particularly in oxidations with periodate, has discouraged the development of alternatives. Such reagents 'on the shelf' include[485] sodium bismuthate, phenyliodosoacetate [$PhI(OAc)_2$], the peroxydisulphate–silver(I) salt combination (for which two reaction pathways are postulated[487]), cerium(IV) salts (involving radical decomposition of acyclic complexes[488]), vanadium(V) and manganese(III) salts. More recent accessions to the list are nickel peroxide[286,489] (equation 336), mercury(II) oxide–iodine[490] (equation

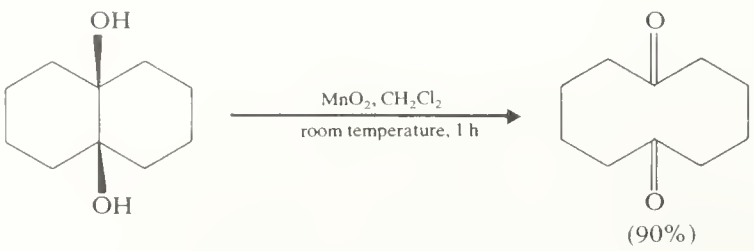


(336)

337), thallium(III) salts[491] (equation 338), activated manganese(IV) oxide[492] (equation 339), and oxygen with a copper(II) catalyst[493] (equation 340). The anodic cleavage of 1,2-diols has also been reported briefly.[494]

$$n\text{-}C_{16}H_{33}CH(OH)CH_2OH \xrightarrow[\text{dark, 24 h}]{HgO,\ I_2,\ CHCl_3} n\text{-}C_{16}H_{33}CHO\ (70\%) + HCHO \quad (337)$$

$$Ph_2C(OH)C(OH)Ph_2 \xrightarrow[75\,^\circ C,\ 30\ min]{Tl(NO_3)_3,\ AcOH} Ph_2CO\ (91\%) \quad (338)$$



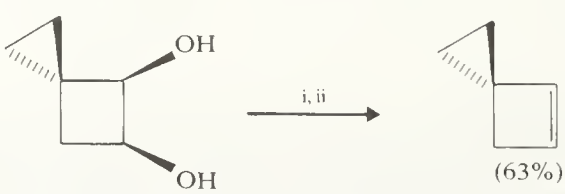
(90%) (339)

$$n\text{-}C_8H_{17}CH(OH)CH_2OH \xrightarrow[PhCN,\ 100\,^\circ C]{Cu^{II}\ laurate,\ O_2} n\text{-}C_8H_{17}CO_2H\ (70\%) + HCHO \quad (340)$$

(*vi*) *Dehydroxylation of vicinal diols*

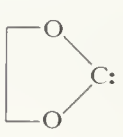
Although not a synthetic highway, the dehydroxylation ('deoxygenation') of 1,2-diols to alkenes is a useful way of introducing unsaturation. Excluded from the present account are routes proceeding *via* oxirans or *vic*-dihalides.

A number of stereoselective methods of dehydroxylation, the Corey–Winter method being the most prominent, are based on *syn* elimination from cyclic derivatives. The original Corey–Winter procedure,[495] involving the desulphurization of a thionocarbonate with a trialkyl phosphite (equation 341) has been used in several notable syntheses. The reaction is envisaged as involving cyclofragmentation of the carbene (**201**), although this has been questioned.[496] Other reagents used to effect desulphurization are (**202**), which is

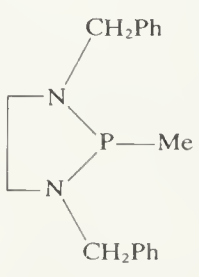


(63%) (341)

i, (**184b**), toluene, reflux, 1 h; ii, $(Bu^nO)_3P$, 115–120 °C, 44 h.



(**201**)



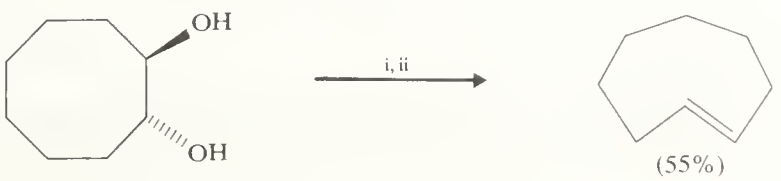
(**202**)

active at room temperature,[495] iron(0) pentacarbonyl,[497a] and the biscyclo-octa-1,5-diene complex of nickel(0).[497b] Stereoselectivity is lost in the desulphurization of some thionocarbonates with the zerovalent metal reagents. Another non-stereoselective use of thionocarbonates for dehydroxylation consists of ring-opening with MeI or Pr^iI, followed by reductive elimination from the iodohydrin thiocarbonate (equation 342).[498]

$$\underset{\textit{erythro/threo}}{PhCH(OH)CH(OH)Ph} \xrightarrow{\text{i, ii, iii}} \underset{(83\text{–}85\%)[95\%\ (E)]}{PhCH{=}CHPh} \qquad (342)$$

i, (**184b**), toluene, reflux; ii, MeI, glyme, 90 °C; iii, Mg/Hg, THF, room temperature.

Whitham's method of dehydroxylation[499] involves the treatment of a 2-phenyl-1,3-dioxolan with Bu^nLi (equation 343). Although the reaction is stereoselective and is recommended for the synthesis shown, its scope is uncertain. Little or no cycloelimination occurred[499] with the derivatives of *erythro*-hydrobenzoin, *trans*-cyclohexane-1,2-diol, and pinacol, but the reaction was apparently successful with some di-tertiary diol derivatives.[500]



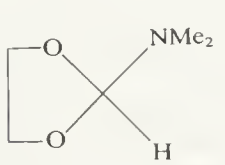
(343)

i, PhCHO, H_2SO_4 (catalytic amount), toluene, reflux;
ii, Bu^nLi, hexane, 20 °C, 14 h.

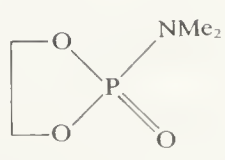
Eastwood's method,[501] which involves the acid-catalysed thermal elimination reaction of a cyclic orthoester, has greater generality. Yields are frequently high (equation 344) and — as with the Corey–Winter and Whitham methods[500] — *syn* elimination holds even for the derivatives of di-tertiary diols. Orthoesters are also considered to be intermediates in the formation of alkenes by reductive elimination from diol monoesters with zinc in acetic acid.[502] Similar eliminations can be induced by heating the cyclic acetals of DMF (**203**) with Ac_2O[503] and by reducing the cyclic phosphoramide esters of di-tertiary diols (**204**) with Li–NH_3 (equation 345).[504] Another type of derivative that undergoes thermal cycloelimination is the salt (**205**) of a carbonate tosylhydrazone, which is prepared[496a] *via*

$$\underset{\textit{threo}}{PhMeC(OH)C(OH)MePh} \xrightarrow{\text{i, ii}} \underset{(E)(83\%)}{PhMeC{=}CMePh} \qquad (344)$$

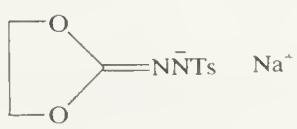
i, $HC(OEt)_3$, BzOH (catalytic amount), 100 °C, 2 h; ii, BzOH, 170–190 °C, 2 h.



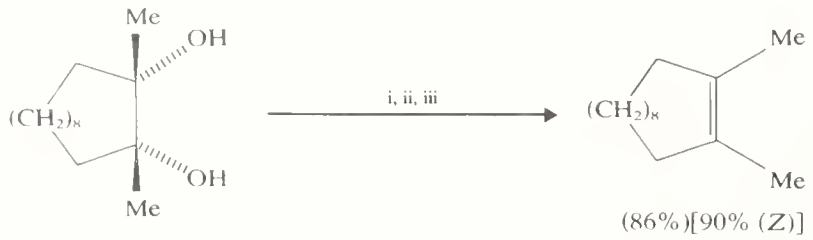
(**203**)



(**204**)



(**205**)

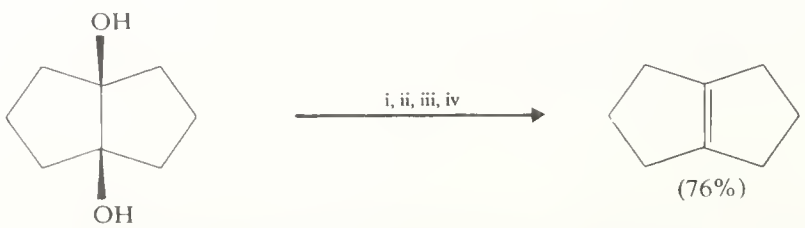


(345)

(86%)[90% (*Z*)]

i, MeLi, Et_2O, THF; ii, $(Me_2N)POCl_2$, THF; iii, Li, NH_3, THF.

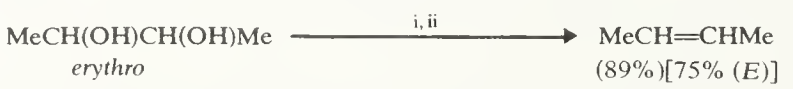
the immonium salt (**197**) as indicated by equation (346). The cyclic carbene (**201**) proposed as the intermediate in several of these eliminations is apparently also formed by the interaction of 1,2-diols with dichlorocarbene,[505] but the reaction is unlikely to constitute a preparatively useful method of dehydroxylation.



(346)

i, (**194**), CH_2Cl_2, reflux; ii, NH_2NHTs, Et_3N, THF, reflux; iii, NaH; iv, 300 °C, *in vacuo*.

Where stereoselectivity is not a requirement, more direct methods of dehydroxylation can be considered. Alkenes are obtained in moderate yield, predominantly by *syn* elimination, by the prolonged heating of dialkoxides with a tungsten(IV) reagent.[506] They can also be prepared by heating 1,2-diols with low- or zero-valent titanium reagents.[507]



(347)

i, MsCl, pyridine, 0 °C; ii, sodium naphthalenide, THF, −50 °C.

The cleavage of dimesylate esters with a radical anion[508] (equation 347) is an attractively simple method, though limitations are imposed by the absence of stereoselectivity and the possible reduction of other functional groups.

References

1. J. A. Monick, 'Alcohols. Their Chemistry, Properties and Manufacture', Reinhold, New York, 1968.
2. 'The Chemistry of the Hydroxyl Group', ed. S. Patai, Interscience, London, 1971.
3. D. R. Truax and H. Wieser, *Chem. Soc. Rev.*, 1976, **5,** 411.
4. S. Hoogasian, C. H. Bushweller, W. G. Anderson, and G. Kingsley, *J. Phys. Chem.*, 1976, **80,** 643.
5. 'Hard and Soft Acids and Bases', ed. R. G. Pearson, Dowden, Hutchinson and Ross, Stroudsburg, Pa., 1973.
6. S. Takahashi, L. A. Cohen, H. K. Miller, and E. G. Peake, *J. Org. Chem.*, 1971, **36,** 1205.
7. J. I. Brauman and L. K. Blair, *J. Amer. Chem. Soc.*, 1970, **92,** 5986; E. M. Arnett, L. E. Small, R. T. McIver, and J. S. Miller, *ibid.*, 1974, **96,** 5638; L. Radom, *Austral. J. Chem.*, 1975, **28,** 1; D. W. Davis and D. A. Shirley, *J. Amer. Chem. Soc.*, 1976, **98,** 7898.
8. R. F. Hudson, O. Eisenstein, and N. T. Anh, *Tetrahedron*, 1975, **31,** 751.
9. E. M. Arnett, R. P. Quirk, and J. J. Burke, *J. Amer. Chem. Soc.*, 1970, **92,** 1260.
10. J. Long and B. Munson, *J. Amer. Chem. Soc.*, 1973, **95,** 2427.
11. M. R. J. Dack, in 'Techniques of Chemistry. Vol. VIII. Solutions and Solubilities', ed. M. R. J. Dack, Wiley-Interscience, New York, 1976, part II, chapter XI.
12. S. Siggia, J. G. Hanna, and T. R. Stengle, in Ref. 2, chapter 6; S. Veibel, 'The Determination of Hydroxyl Groups', Academic, London, 1972.

13. L. J. Bellamy, 'Advances in Infrared Group Frequencies', Methuen, London, 1968; J. H. van der Maas and E. T. G. Lutz, *Spectrochim. Acta*, 1974, **30A,** 2005.
14. R. K. Sehgal, R. U. Koeningsberger, and T. J. Howard, *Tetrahedron Letters*, 1974, 4173.
15. A. F. Cockerill, G. L. O. Davies, R. C. Harden, and D. M. Rackham, *Chem. Rev.*, 1973, **73,** 553.
16. J. D. Roberts, F. J. Weigert, J. I. Kroschwitz, and H. J. Reich, *J. Amer. Chem. Soc.*, 1970, **92,** 1338.
17. N. K. Wilson and J. B. Stothers, *Topics Stereochem.*, 1974, **8,** 1; H. Eggert, C. L. VanAntwerp, N. S. Bhacca, and C. Djerassi, *J. Org. Chem.*, 1976, **41,** 71.
18. D. G. I. Kingston, B. W. Hobrock, M. M. Bursey, and J. T. Bursey, *Chem. Rev.*, 1975, **75,** 693; M. M. Green, *Topics Stereochem.*, 1976, **9,** 35.
19. S. H. Wilen, *Topics Stereochem.*, 1971, **6,** 107; B. A. Klyashchitskii and V. I. Shvets, *Russ. Chem. Rev.*, 1972, **41,** 592.
20. J. Dillon and K. Nakanishi, *J. Amer. Chem. Soc.*, 1974, **96,** 4055.
21. A. Horeau, 'Determination of the Configuration of Secondary Alcohols by Partial Resolution', Thieme-Verlag, Stuttgart, 1976.
22. G. R. Sullivan, J. A. Dale, and H. S. Mosher, *J. Org. Chem.*, 1973, **38,** 2143; S. Yamaguchi, F. Yasuhara, and K. Kabuto, *Tetrahedron*, 1976, **32,** 1363.
23. G. R. Sullivan, D. Ciavarella, and H. S. Mosher, *J. Org. Chem.*, 1974, **39,** 2411.
24. C. A. Buehler and D. E. Pearson, 'Survey of Organic Syntheses', Wiley-Interscience, New York, 1970, 1977.
25. I. T. Harrison and S. Harrison, 'Compendium of Organic Synthetic Methods', Wiley-Interscience, New York, 1971, 1974.
26. W. Charney and H. L. Herzog, 'Microbial Transformations of Steroids', Academic, New York, 1967; K. Kieslich, 'Microbial Transformations of Non-Steroid Cyclic Compounds', Georg Thieme Verlag, Stuttgart, 1976; G. S. Fonken and R. A. Johnson, 'Chemical Oxidations with Microorganisms', Dekker, New York, 1972.
27. 'Molecular Mechanisms of Oxygen Activation', ed. O. Hayaishi, Academic, New York, 1974; H. Mimoun and I. Seree de Roch, *Tetrahedron*, 1975, **31,** 777.
28. R. A. Sheldon and J. K. Kochi, *Adv. Catalysis*, 1976, **25,** 272.
29. D. G. Lee, in Ref. 266(c), vol. I. chapter 1.
30. For example (a) N. C. Deno and D. G. Pohl, *J. Amer. Chem. Soc.*, 1974, **96,** 6680; (b) Y. Mazur, *Pure Appl. Chem.*, 1975, **41,** 145; (c) J. T. Groves and M. van der Puy, *J. Amer. Chem. Soc.*, 1976, **98,** 5290; (d) N. C. Deno and L. A. Messer, *J.C.S. Chem. Comm.*, 1976, 1051; (e) S. R. Jones and J. M. Mellor, *J.C.S. Perkin I*, 1976, 2576.
31. D. J. Rawlinson and G. Sosnovsky, *Synthesis*, 1972, 1.
32. D. J. Rawlinson and G. Sosnovsky, *Synthesis*, 1973, 567.
33. R. M. Moriarty, in 'Selective Organic Transformations', ed. B. S. Thyagarajan, Wiley-Interscience, New York, 1972, vol. 2, p. 183.
34. E. N. Trachtenberg, in Ref. 266(c), vol. I, chapter 3; R. A. Jerussi in 'Selective Organic Transformations', ed. B. S. Thyagarajan, Wiley-Interscience, New York, 1970, vol. 1, p. 301.
35. R. W. Denny and A. Nickon, *Org. Reactions*, 1973, **20,** 133; G. Ohloff, *Pure Appl. Chem.*, 1975, **43,** 481.
36. H. C. Brown and P. J. Geoghegan, *J. Org. Chem.*, 1970, **35,** 1844; 1972, **37,** 1937.
37. (a) H. C. Brown, P. J. Geoghegan, G. J. Lynch, and J. T. Kurek, *J. Org. Chem.*, 1972, **37,** 1941; (b) M. Bambagiotti A., F. F. Vincieri, and S. A. Coran, *ibid.*, 1974, **39,** 680.
38. (a) G. Zweifel and H. C. Brown, *Org. Reactions*, 1963, **13,** 1; (b) H. C. Brown, 'Organic Syntheses via Boranes', Wiley-Interscience, New York, 1975.
39. M. Orchin and W. Rupilius, *Catalysis Rev.*, 1972, **6,** 85.
40. F. E. Paulik, *Catalysis Rev.*, 1972, **6,** 49; R. Fowler, H. Connor and R. A. Baehl, *Chemtech*, 1976, **6,** 772.
41. A. Rosenthal, *Adv. Carbohydrate Chem.*, 1968, **23,** 59.
42. H. M. R. Hoffmann, *Angew. Chem. Internat. Edn.*, 1969, **8,** 556.
43. R. A. Jones, *Aldrichim. Acta*, 1976, **9,** 35.
44. A. McKillop and M. E. Ford, *Tetrahedron*, 1974, **30,** 2467.
45. T. Mukaiyama and K. Hojo, *Chem. Letters*, 1976, 893.
46. (a) J. San Filippo, C.-I, Chern, and J. S. Valentine, *J. Org. Chem.*, 1975, **40,** 1678; (b) E. J. Corey, K. C. Nicolaou, M. Shibasaki, Y. Machida, and C. S. Shiner, *Tetrahedron Letters*, 1975, 3183.
47. H. O. House, 'Modern Synthetic Reactions', Benjamin, Menlo Park, Calif., 2nd edn., 1972.
48. H. Imai, T. Nishiguchi, and K. Fukuzumi, *J. Org. Chem.*, 1976, **41,** 665.
49. I. Ojima, M. Nihonyanagi, T. Kogure, M. Kumagai, S. Horiuchi, and K. Nakatsugawa, *J. Organometallic Chem.*, 1975, **94,** 449.
50. D. N. Kursanov, Z. N. Parnes, and N. M. Loim, *Synthesis*, 1974, 633.
51. M. P. Doyle, D. J. DeBruyn, S. J. Donnelly, D. A. Kooistra, A. A. Odubela, C. T. West, and S. M. Zonnebelt, *J. Org. Chem.*, 1974, **39,** 2740; M. P. Doyle and C. T. West, *ibid.*, 1975, **40,** 3821, 3829, 3835.
52. H. Haubenstock, *J. Org. Chem.*, 1975, **40,** 926.
53. C. F. Lane, *Synthesis*, 1975, 135.
54. (a) G. W. Gribble and D. C. Ferguson, *J.C.S. Chem. Comm.*, 1975, 535; (b) Y. Maki, K. Kikuchi, H. Sugiyama, and S. Seto, *Tetrahedron Letters*, 1977, 263.
55. M. Cinquini, F. Montanari, and P. Tundo, *J.C.S. Chem. Comm.*, 1975, 393.
56. D. J. Raber and W. C. Guida, *J. Org. Chem.*, 1976, **41,** 690.

57. (a) N. M. Yoon, H. J. Lee, H. K. Kim, and J. Kang, *J. Korean Chem. Soc.*, 1976, **20,** 59; (b) J. M. Lalancette, A. Frêche, J. R. Brindle and M. Laliberté, *Synthesis*, 1972, 526; (c) Y. Kikugawa, *Chem. Pharm. Bull. (Japan)*, 1976, **24,** 1059; (d) Y. Maki, K. Kikuchi, H. Sugiyama, and S. Seto, *Tetrahedron Letters*, 1975, 3295.
58. S. Krishnamurthy, R. M. Schubert, and H. C. Brown, *J. Amer. Chem. Soc.*, 1973, **95,** 8486.
59. S. Krishnamurthy and H. C. Brown, *J. Amer. Chem. Soc.*, 1976, **98,** 3383 and references cited.
60. J. M. Fortunato and B. Ganem, *J. Org. Chem.*, 1976, **41,** 2194.
61. (a) C. F. Lane, *Chem. Rev.*, 1976, **76,** 773; (b) H. C. Brown, P. Heim, and N. M. Yoon, *J. Org. Chem.*, 1972, **37,** 2942; (c) H. C. Brown, D. B. Bigley, S. K. Arora, and N. M. Yoon, *J. Amer. Chem. Soc.*, 1970, **92,** 7161; (d) H. C. Brown, S. Krishnamurthy, and N. M. Yoon, *J. Org. Chem.*, 1976, **41,** 1778; (e) G. W. Kabalka, J. D. Baker, and G. W. Neal, *ibid.*, 1977, **42,** 512.
62. H. C. Brown and V. Varma, *J. Org. Chem.*, 1974, **39,** 1631.
63. E. Winterfeldt, *Synthesis*, 1975, 617.
64. (a) J. Lipowitz and S. A. Bowman, *J. Org. Chem.*, 1973, **38,** 162; (b) N. M. Weinshenker, G. A. Crosby, and J. Y. Wong, *ibid.*, 1975, **40,** 1966.
65. G. H. Posner and A. W. Runquist, *Tetrahedron Letters*, 1975, 3601.
66. Y. Yamamoto, H. Toi, A. Sonoda, and S.-I. Murahashi, *J. Amer. Chem. Soc.*, 1976, **98,** 1965; *J.C.S. Chem. Comm.*, 1976, 672.
67. 'New Applications of Organometallic Reagents in Organic Synthesis', ed. D. Seyferth, Elsevier, Amsterdam, 1976.
68. (a) M. S. Kharasch and O. Reinmuth, 'Grignard Reactions of Non-metallic Substances', Prentice-Hall, New York, 1954; (b) H. Normant, *Adv. Org. Chem.*, 1960, **11,** 1, and *Bull. Soc. chim. France*, 1972, 2161.
69. E. C. Ashby and J. T. Laemmle, *Chem. Rev.*, 1975, **75,** 521.
70. M. Chastrette and R. Amouroux, *Bull. Soc. chim. France*, 1970, 4348.
71. R. A. Benkeser, *Synthesis*, 1971, 347.
72. G. Courtois and L. Miginiac, *J. Organometallic Chem.*, 1974, **69,** 1.
73. G. Deleris, J. Dunoguès, and R. Calas, *Tetrahedron Letters*, 1976, 2449.
74. C. Blomberg and F. A. Hartog, *Synthesis*, 1977, 18.
75. J. F. Ruppert and J. D. White, *J. Org. Chem.*, 1976, **41,** 550.
76. P. J. Pearce, D. H. Richards, and N. F. Scilly, *J.C.S. Perkin I*, 1972, 1655.
77. J. D. Buhler, *J. Org. Chem.*, 1973, **38,** 904; B. J. Wakefield, 'The Chemistry of Organolithium Compounds', Pergamon, Oxford, 1974.
78. L. Brandsma, 'Preparative Acetylenic Chemistry', Elsevier, Amsterdam, 1971.
79. G. Boireau, D. Abenhaim, J. L. Namy, and E. Henry-Basch, *J. Org. Chem. (U.S.S.R.)*, 1976, **12,** 1805.
80. T. Mole and E. A. Jeffery, 'Organoaluminium Compounds', Elsevier, Amsterdam, 1972; E. Negishi in Ref. 67, p. 93.
81. D. Abenhaim, G. Boireau, C. Bernardon, A. Deberly, and C. Germain, *Tetrahedron Letters*, 1976, 993, and references cited.
82. (a) C. R. Johnson, R. W. Herr, and D. M. Wieland, *J. Org. Chem.*, 1973, **38,** 4263; (b) P. Vermeer, J. Meijer, C. de Graaf, and H. Schreurs, *Rec. Trav. chim.*, 1974, **93,** 46.
83. E. Barreiro, J. L. Luche, J. Zweig, and P. Crabbé, *Tetrahedron Letters*, 1975, 2353.
84. (a) W. C. Still and T. L. Macdonald, *Tetrahedron Letters*, 1976, 2659; (b) G. Palmisano and R. Pellegata, *J.C.S. Chem. Comm.*, 1975, 892.
85. K. Smith, *Chem. Soc. Rev.*, 1974, **3,** 443; H. C. Brown, *Pure Appl. Chem.*, 1976, **47,** 49; E. Negishi, *J. Organometallic Chem.*, 1976, **108,** 281.
86. H. C. Brown, 'Boranes in Organic Chemistry', Cornell University Press, Ithaca, New York, 1972; G. M. L. Cragg, 'Organoboranes in Organic Synthesis', Dekker, New York, 1973; T. Onak, 'Organoborane Chemistry', Academic, London, 1975.
87. B. M. Mikhailov, *Organometallic Chem. Rev. (A)*, 1972, **8,** 1.
88. P. Jacob and H. C. Brown, *J. Org. Chem.*, 1977, **42,** 579.
89. H. C. Brown, *Accounts Chem. Res.*, 1969, **2,** 65.
90. A. Pelter, M. G. Hutchings, K. Rowe, and K. Smith, *J.C.S. Perkin I*, 1975, 138.
91. H. C. Brown, J.-J. Katz and B. A. Carlson, *J. Org. Chem.*, 1973, **38,** 3968.
92. R. J. Hughes, S. Ncube, A. Pelter, K. Smith, E. Negishi, and T. Yoshida, *J.C.S. Perkin I*, 1977, 1172.
93. Y. Yamamoto, K. Kondo, and I. Moritani, *J. Org. Chem.*, 1975, **40,** 3644.
94. M. M. Midland and H. C. Brown, *J. Org. Chem.*, 1975, **40,** 2845.
95. G. Zweifel and R. P. Fisher, *Synthesis*, 1974, 339.
96. A. B. Levy and S. J. Schwartz, *Tetrahedron Letters*, 1976, 2201.
97. M. Naruse, K. Utimoto, and H. Nozaki, *Tetrahedron*, 1974, **30,** 3037; K. Utimoto, T. Furubayashi, and H. Nozaki, *Chem. Letters*, 1975, 397.
98. H. C. Brown and Y. Yamamoto, *Synthesis*, 1972, 699; Y. Yamamoto and H. C. Brown, *J. Org. Chem.*, 1974, **39,** 861.
99. (a) J. K. Crandall and L.-H. Chang, *J. Org. Chem.*, 1967, **32,** 435; (b) R. P. Thummel and B. Rickborn, *ibid.*, 1972, **37,** 4250, and references cited.
100. A. Yasuda, S. Tanaka, K. Oshima, H. Yamamoto, and H. Nozaki, *J. Amer. Chem. Soc.*, 1974, **96,** 6513.
101. (a) K. B. Sharpless and R. F. Lauer, *J. Amer. Chem. Soc.*, 1973, **95,** 2697; (b) A. M. Leonard-Coppens and A. Krief, *Tetrahedron Letters*, 1976, 3227, and references cited; (c) H. J. Reich and S. K. Shah, *J. Amer. Chem. Soc.*, 1975, **97,** 3250.

102. (a) D. A. Evans and G. C. Andrews, *Accounts Chem. Res.*, 1974, **7,** 147; (b) H. J. Reich, *J. Org. Chem.*, 1975, **40,** 2570.
103. M. Schlosser and D. Coffinet, *Synthesis*, 1972, 575.
104. M. Huché, *Bull. Soc. chim. France*, 1975, 2369.
105. L.-I. Olsson, A. Claesson and C. Bogentoft, *Acta Chem. Scand.*, 1974, **28B,** 765.
106. A. Rosowsky, in 'Heterocyclic Compounds with Three- and Four-Membered Rings', ed. A. Weissberger, Interscience, New York, 1964, part I, chapter I.
107. (a) J. W. Cornforth and D. T. Green, *J. Chem. Soc.* (*C*), 1970, 846; (b) R. C. Cambie, W. I. Noall, G. J. Potter, P. S. Rutledge, and P. D. Woodgate, *J.C.S. Perkin I*, 1977, 226; (c) R. G. S. Ritchie and W. A. Szarek, *Canad. J. Chem.*, 1972, **50,** 507.
108. J. Kagan, B. E. Firth, N. Y. Shih, and C. G. Boyajian, *J. Org. Chem.*, 1977, **42,** 343.
109. (a) T. D. Inch, *Synthesis*, 1970, 466; J. W. Scott and D. Valentine, *Science*, 1974, **184,** 943; (b) J. D. Morrison and H. S. Mosher, 'Asymmetric Organic Reactions', Prentice-Hall, Englewood Cliffs, N.J., 1971.
110. R. M. Carlson and A. H. Funk, *Tetrahedron Letters*, 1971, 3661; T. Sugita, Y. Yamasaki, O. Itoh, and K. Ichikawa, *Bull. Chem. Soc. Japan*, 1974, **47,** 1945.
111. J. Balcells, S. Colonna, and R. Fornasier, *Synthesis*, 1976, 266; J. P. Massé and E. R. Parayre, *J.C.S. Chem. Comm.*, 1976, 438.
112. M. F. Grundon, D. G. McCleery, and J. W. Wilson, *Tetrahedron Letters*, 1976, 295.
113. A. J. Irwin and J. B. Jones, *J. Amer. Chem. Soc.*, 1976, **98,** 8476, and references cited.
114. Y. Izumi, *Angew. Chem. Internat. Edn.*, 1971, **10,** 871.
115. J. D. Morrison, W. F. Masler, and M. K. Neuberg, *Adv. Catalysis*, 1976, **25,** 81.
116. B. Heil, S. Törös, S. Vastag, and L. Markó, *J. Organometallic Chem.*, 1975, **94,** C47; T. Hayashi, M. Tanaka, and I. Ogata, *Tetrahedron Letters*, 1977, 295.
117. (a) I. Ojima, T. Kogure, M. Kumagai, S. Horiuchi, and T. Sato, *J. Organometallic Chem.*, 1976, **122,** 83; (b) R. J. P. Corriu and J. J. E. Moreau, *J. Organometallic Chem.*, 1975, **85,** 19; (c) H. B. Kagan, *Pure Appl. Chem.*, 1975, **43,** 401; (d) T. Hayashi, K. Yamamoto, K. Kasuga, H. Omizu, and M. Kumuda, *J. Organometallic Chem.*, 1976, **113,** 127; (e) J. Beneš and J. Hetflejš, *Coll. Czech. Chem. Comm.*, 1976, **41,** 2264.
118. T. Hayashi, K. Yamamoto, and M. Kumada, *J. Organometallic Chem.*, 1976, **112,** 253.
119. I. Ojima, T. Kogure, and Y. Nagai, *Chem. Letters*, 1975, 985.
120. A. I. Meyers and M. E. Ford, *Tetrahedron Letters*, 1974, 1341.
121. G. Boireau, D. Abenhaim, J. Bourdais, and E. Henry-Basch, *Tetrahedron Letters*, 1976, 4781.
122. T. Ogawa and M. Matsui, *Carbohydrate Res.*, 1976, **51,** C13, and references cited.
123. (a) S. Kobayashi, M. Tsutsui, and T. Mukaiyama, *Chem. Letters*, 1976, 373; (b) K. Hojo and T. Mukaiyama, *ibid.*, 1976, 619.
124. H. Loibner and E. Zbiral, *Helv. Chim. Acta*, 1977, **60,** 417, and references cited.
125. R. Appel, *Angew. Chem. Internat. Edn.*, 1975, **14,** 801, and references cited.
126. (a) F. Schmidt in Houben-Weyl, 'Methoden der Organischen Chemie', Thieme, Stuttgart, 1963, vol. 6/2, p. 5; (b) N. Y. Turova and A. V. Novoselova, *Russ. Chem. Rev.*, 1965, **34,** 161.
127. C. A. Fyfe, Ref. 2, chapter 2.
128. C. A. Brown, *Synthesis*, 1974, 427.
129. D. E. Pearson and C. A. Buehler, *Chem. Rev.*, 1974, **74,** 45.
130. C. A. Brown, *J.C.S. Chem. Comm.*, 1974, 680.
131. G. M. Whitesides, J. S. Sadowski, and J. Lilburn, *J. Amer. Chem. Soc.*, 1974, **96,** 2829.
132. M. Anbar and D. Ginsburg, *Chem. Rev.*, 1954, **54,** 925; A. Hausweiler, in Houben-Weyl, 'Methoden der Organischen Chemie', Thieme, Stuttgart, 1963, vol. 6/2, p. 487.
133. (a) C. M. Sharts and W. A. Sheppard, *Org. Reactions*, 1974, **21,** 125; (b) P. Brun and B. Waegell, *Tetrahedron*, 1976, **32,** 517.
134. M. J. Mintz and C. Walling, *Org. Synth.*, 1969, **49,** 9.
135. (a) C. Walling, *Pure Appl. Chem.*, 1967, **15,** 69; (b) J. K. Kochi, in 'Free Radicals', ed. J. K. Kochi, Wiley, New York, 1973, vol. II, chapter 23.
136. (a) M. L. Poutsma, in 'Free Radicals', ed. J. K. Kochi, Wiley, New York, 1973, vol. II, chapter 15; (b) L. Fieser and M. Fieser, 'Reagents for Organic Synthesis', Wiley, New York, 1967, and succeeding volumes.
137. C. Walling and R. T. Clark, *J. Org. Chem.*, 1974, **39,** 1962.
138. H. Feuer and J. Hooz, in 'The Chemistry of the Ether Linkage', ed. S. Patai, Interscience, London, 1967, chapter 10.
139. R. G. Smith, A. Vanterpool, and H. J. Kulak, *Canad. J. Chem.*, 1969, **47,** 2015; Y. Leroux, M. Larchevêque, and J.-C. Combret, *Bull. Soc. chim. France*, 1971, 3258.
140. M. Chastrette and H. Gauthier-Countani, *Bull. Soc. chim. France*, 1973, 363.
141. H.-O, Kalinowski, D. Seebach, and G. Crass, *Angew. Chem. Internat. Edn.*, 1975, **14,** 762.
142. C. A. Brown, D. Barton, and S. Sivaram, *Synthesis*, 1974, 434.
143. H. Björndal, C. G. Hellerqvist, B. Lindberg, and S. Svensson, *Angew. Chem. Internat. Edn.*, 1970, **9,** 610.
144. (a) A. Merz, *Angew. Chem. Internat. Edn.*, 1973, **12,** 846; (b) H. H. Freedman and R. A. Dubois, *Tetrahedron Letters*, 1975, 3251.
145. G. A. Olah, Y. Halpern, and H. C. Lin, *Synthesis*, 1975, 315.
146. M. J. Diem, D. F. Burow, and J. L. Fry, *J. Org. Chem.*, 1977, **42,** 1801.
147. S. Bittner and Y. Assaf, *Chem. and Ind.* (*London*), 1975, 281; M. S. Manhas, W. H. Hoffman, B. Lal, and A. K. Bose, *J.C.S. Perkin I*, 1975, 461.

148. I. M. Downie, H. Heaney, and G. Kemp, *Angew. Chem. Internat. Edn.*, 1975, **14,** 370.
149. E. Vowinkel, *Chem. Ber.*, 1966, **99,** 1479; F. L. Bach, *J. Org. Chem.*, 1965, **30,** 1300.
150. R. Bolton in 'Comprehensive Chemical Kinetics', ed. C. H. Bamford and C. F. H. Tipper, Elsevier, Amsterdam, 1973, vol. 9, chapter 1; C. F. Bernasconi and W. J. Boyle, *J. Amer. Chem. Soc.*, 1974, **96,** 6070.
151. H. C. Brown and M.-H. Rei, *J. Amer. Chem. Soc.*, 1969, **91,** 5646.
152. G. L. Grady and S. K. Chokshi, *Synthesis*, 1972, 483.
153. J. A. Marshall, *Accounts Chem. Res.*, 1969, **2,** 33.
154. P. J. Kropp, E. J. Reardon, Z. L. F. Gaibel, K. F. Williard, and J. H. Hattaway, *J. Amer. Chem. Soc.*, 1973, **95,** 7058.
155. H.-D. Becker, in Ref. 2, chapter 16; S. S. Hixson, *Tetrahedron Letters*, 1973, 277; J. M. Hornback, *J. Amer. Chem. Soc.*, 1974, **96,** 6773.
156. S. R. Sandler and W. Karo, 'Organic Functional Group Preparations', Academic, New York, 1971, vol. II, chapter 2.
157. E. Schmitz and I. Eichorn, in 'The Chemistry of the Ether Linkage', ed. S. Patai, Interscience, London, 1967, chapter 7.
158. D. P. Roelofsen and H. van Bekkum, *Synthesis*, 1972, 419; V. I. Stenberg and D. A. Kubik, *J. Org. Chem.*, 1974, **39,** 2815.
159. E. K. Euranto, in 'The Chemistry of Carboxylic Acids and Esters', ed. S. Patai, Interscience, London, 1969, chapter 11.
160. (a) E. C. Blossey, L. M. Turner, and D. C. Neckers, *Tetrahedron Letters*, 1973, 1823; (b) J. Bertin, H. B. Kagan, J.-L. Luche, and R. Setton, *J. Amer. Chem. Soc.*, 1974, **96,** 8113.
161. H. A. Staab and W. Rohr, in 'Newer Methods of Preparative Organic Chemistry', ed. W. Foerst, Verlag Chemie, Weinheim, 1968, vol. V, p. 61.
162. T. Mukaiyama, M. Usui, E. Shimada, and K. Saigo, *Chem. Letters*, 1975, 1045.
163. T. Mukaiyama and K. Hojo, *Chem. Letters*, 1976, 267.
164. S. Masamune, S. Kamata, and W. Schilling, *J. Amer. Chem. Soc.*, 1975, **97,** 3515.
165. (a) E. J. Corey and K. C. Nicolaou, *J. Amer. Chem. Soc.*, 1974, **96,** 5614; (b) H. Gerlach and A. Thalmann, *Helv. Chim. Acta*, 1974, **57,** 2661.
166. E. J. Corey and D. J. Brunelle, *Tetrahedron Letters*, 1976, 3409.
167. S. Takimoto, J. Inanaga, T. Katsuki, and M. Yamaguchi, *Bull. Chem. Soc. Japan*, 1976, **49,** 2335.
168. E. M. Kaiser and R. A. Woodruff, *J. Org. Chem.*, 1970, **35,** 1198.
169. G. Höfle and W. Steglich, *Synthesis*, 1972, 619.
170. T. Katsuki, *Bull. Chem. Soc. Japan*, 1976, **49,** 2019.
171. K. C. Nicolaou, *Tetrahedron*, 1977, **33,** 683.
172. (a) J. H. Brewster and C. J. Ciotti, *J. Amer. Chem. Soc.*, 1955, **77,** 6214; (b) R. C. Parish and L. M. Stock, *J. Org. Chem.*, 1965, **30,** 927.
173. O. Mitsunobu and M. Yamada, *Bull. Chem. Soc. Japan*, 1967, **40,** 2380.
174. G. Grynkiewicz and H. Burzyńska, *Tetrahedron*, 1976, **32,** 2109.
175. R. Aneja, A. P. Davies, A. Harkes, and J. A. Knaggs, *J.C.S. Chem. Comm.*, 1974, 963.
176. S. Bittner, Z. Barneis, and S. Felix, *Tetrahedron Letters*, 1975, 3871.
177. G. Grynkiewicz, J. Jurczak, and A. Zamojski, *Tetrahedron*, 1975, **31,** 1411; Z. Barneis, Y. Broeir, and S. Bittner, *Chem. and Ind. (London)*, 1976, 526.
178. R. K. Crossland and K. L. Servis, *J. Org. Chem.*, 1970, **35,** 3195.
179. J. F. King and J. R. du Manoir, *J. Amer. Chem. Soc.*, 1975, **97,** 2566.
180. R. M. Coates and J. P. Chen, *Tetrahedron Letters*, 1969, 2705.
181. S. R. Sandler and W. Karo, 'Organic Functional Group Preparations', Academic, New York, 1971, vol. II, (a) chapter 10, (b) chapter 11.
182. D. P. N. Satchell and R. S. Satchell, *Chem. Soc. Rev.*, 1975, **4,** 231.
183. S. Ozaki, *Chem. Rev.*, 1972, **72,** 457.
184. T. Francis and M. P. Thorne, *Canad. J. Chem.*, 1976, **54,** 24.
185. S. P. McManus, H. S. Bruner, H. D. Coble, and G. Choudhary, *J.C.S. Chem. Comm.*, 1974, 253.
186. E. W. Garbisch, *Chem. Comm.*, 1967, 806.
187. S. Mitsui, S. Imaizumi, and Y. Esashi, *Bull. Chem. Soc. Japan*, 1970, **43,** 2143; A. P. G. Kieboom, J. F. de Kreuk, and H. van Bekkum, *J. Catalysis*, 1971, **20,** 58.
188. Z. N. Parnes, G. D. Kolomnikova, M. I. Kalinkin, and D. N. Kursanov, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1975, 1911.
189. M. G. Adlington, M. Orfanopoulos, and J. L. Fry, *Tetrahedron Letters*, 1976, 2955.
190. J. H. Brewster and H. O. Bayer, *J. Org. Chem.*, 1964, **29,** 116, and other papers in the series.
191. Y. Fujimoto and N. Ikekawa, *Chem. Pharm. Bull. (Japan)*, 1976, **24,** 825.
192. E. M. Kaiser, *Synthesis*, 1972, 391; A. J. Birch and G. Subba Rao, *Adv. Org. Chem.*, 1972, **8,** 1.
193. G. H. Small, A. E. Minnella, and S. S. Hall, *J. Org. Chem.*, 1975, **40,** 3151.
194. I. Elphimoff-Felkin and P. Sarda, *Org. Synth.*, 1977, **56,** 101; *Tetrahedron*, 1977, **33,** 511.
195. H. Lund, H. Doupeux, M. A. Michel, G. Mousset, and J. Simonet, *Electrochim. Acta*, 1974, **19,** 629.
196. H. Felkin and G. Swierczewski, *Tetrahedron*, 1975, **31,** 2735.
197. S. Krishnamurthy and H. C. Brown, *J. Org. Chem.*, 1976, **41,** 3064.
198. R. O. Hutchins, D. Kandasamy, C. A. Maryanoff, D. Masilamani, and B. E. Maryanoff, *J. Org. Chem.*, 1977, **42,** 82, and references cited.

199. Y. Fujimoto and T. Tatsuno, *Tetrahedron Letters*, 1976, 3325.
200. E. J. Corey and K. Achiwa, *J. Org. Chem.*, 1969, **34,** 3667.
201. (a) G. A. Olah and J. A. Olah in 'Carbonium Ions', ed. G. A. Olah and P. von R. Schleyer, Wiley-Interscience, New York, 1970, vol. II, chapter 17; (b) A. Schriesheim, in 'Friedel-Crafts and Related Reactions', ed. G. A. Olah, Interscience, New York, 1964, vol. II, chapter 18; (c) H. E. Fritz, D. W. Peck, M. A. Eccles, and K. E. Atkins, *J. Org. Chem.*, 1965, **30,** 2540.
202. D. W. Harney, A. Meisters, and T. Mole, *Austral. J. Chem.*, 1974, **27,** 1639.
203. J. Furukawa, K. Omura, O. Yamamoto, and K. Ishikawa, *J.C.S. Chem. Comm.*, 1974, 77.
204. Y. Tanigawa, H. Kanamaru, A. Sonoda, and S.-I. Murahashi, *J. Amer. Chem. Soc.*, 1977, **99,** 2361.
205. J. E. McMurry and M. Silvestri, *J. Org. Chem.*, 1975, **40,** 2687.
206. I. Pri-Bar, O. Buchman, and J. Blum, *Tetrahedron Letters*, 1977, 1443.
207. G. W. Brown, in Ref. 2, chapter 11.
208. R. Fuchs and L. L. Cole, *Canad. J. Chem.*, 1975, **53,** 3620.
209. D. Landini, F. Montanari, and F. Rolla, *Synthesis*, 1974, 37.
210. H. R. Hudson, *Synthesis*, 1969, 112.
211. G. A. Olah, M. Nojima, and I. Kerekes, *Synthesis*, 1973, 786.
212. W. A. Szarek, *Adv. Carbohydrate Chem. Biochem.*, 1973, **28,** 225.
213. H. R. Hudson and G. R. de Spinoza, *J.C.S. Perkin I*, 1976, 104.
214. T. G. Squires, W. W. Schmidt, and C. S. McCandlish, *J. Org. Chem.*, 1975, **40,** 134.
215. (a) D. Landini, S. Quici, and F. Rolla, *Synthesis*, 1975, 430; (b) J. San Filippo and L. J. Romano, *J. Org. Chem.*, 1975, **40,** 1514.
216. (a) G. Stork, P. A. Grieco, and M. Gregson, *Org. Synth.*, 1974, **54,** 68; (b) E. W. Collington and A. I. Meyers, *J. Org. Chem.*, 1971, **36,** 3044; (c) C. A. Bunton, D. L. Hachey, and J.-P. Leresche, *J. Org. Chem.*, 1972, **37,** 4036; (d) Y. Bensimon and E. Ucciani, *Compt. rend.*, 1973, **276C,** 683.
217. C. Georgoulis and G. Ville, *Bull. Soc. chim. France*, 1975, 607.
218. (a) E. J. Corey, C. U. Kim, and M. Takeda, *Tetrahedron Letters*, 1972, 4339; (b) N. Furukawa, T. Inoue, T. Aida, and S. Oae, *J.C.S. Chem. Comm.*, 1973, 212.
219. (a) J. Kollonitsch, S. Marburg, and L. M. Perkins, *J. Org. Chem.*, 1975, **40,** 3808; (b) W. J. Middleton, *ibid.*, 1975, **40,** 574.
220. G. A. Olah, M. Nojima, and I. Kerekes, *J. Amer. Chem. Soc.*, 1974, **96,** 925.
221. H. R. Hudson, *J. Chem. Soc.* (*B*), 1968, 664; R. A. Arain and M. K. Hargreaves, *J. Chem. Soc.* (*C*), 1970, 67.
222. R. O. Hutchins, D. Masilamani, and C. A. Maryanoff, *J. Org. Chem.*, 1976, **41,** 1071.
223. R. M. Carman and I. M. Shaw, *Austral. J. Chem.*, 1976, **29,** 133.
224. H. N. Rydon, *Org. Synth.*, 1971, **51,** 44.
225. (a) H. M. Relles and R. W. Schluenz, *J. Amer. Chem. Soc.*, 1974, **96,** 6469; (b) P. Hodge and G. Richardson, *J.C.S. Chem. Comm.*, 1975, 622; S. L. Regen and D. P. Lee, *J. Org. Chem.*, 1975, **40,** 1669.
226. J. G. Calzada and J. Hooz, *Org. Synth.*, 1974, **54,** 63.
227. B. Castro and C. Selve, *Bull. Soc. chim. France*, 1971, 2296; Y. Chapleur, B. Castro, and B. Gross, *Tetrahedron*, 1977, **33,** 1615, and intervening papers in the series.
228. R. Aneja, A. P. Davies, and J. A. Knaggs, *Tetrahedron Letters*, 1974, 67; I. Tömösközi, L. Gruber, and L. Radics, *Tetrahedron Letters*, 1975, 2473.
229. A. K. Bose and B. Lal, *Tetrahedron Letters*, 1973, 3937; S. Hanessian and P. Lavallee, *Methods Carbohydrate Chem.*, 1976, **VII,** 49.
230. B. Castro, Y. Chapleur, and B. Gross, *Tetrahedron Letters*, 1974, 2313.
231. D. R. Hepburn and H. R. Hudson, *J.C.S. Perkin I*, 1976, 754; A. G. Anderson, N. E. T. Owen, F. J. Freenor, and D. Erickson, *Synthesis*, 1976, 398.
232. S. Kobayashi, M. Tsutsui, and T. Mukaiyama, *Chem. Letters*, 1976, 373; K. Hojo and T. Mukaiyama, *ibid.*, 1976, 619.
233. R. Scheffold and E. Saladin, *Angew. Chem. Internat. Edn.*, 1972, **11,** 229.
234. Y. Kobayashi, I. Kumadaki, A. Ohsawa, M. Honda, and Y. Hanzawa, *Chem. Pharm. Bull.* (*Japan*), 1975, **23,** 196.
235. M. E. Jung and P. L. Ornstein, *Tetrahedron Letters*, 1977, 2659.
236. (a) I. Tabushi, Z.-I. Yoshida, and N. Takahashi, *K. Amer. Chem. Soc.*,1971, **93,** 1820; (b) D. L. J. Clive and C. V. Denyer, *Chem. Comm.*, 1971, 1112; (c) F. R. Jensen and T. I. Moder, *J. Amer. Chem. Soc.*, 1975, **97,** 2281; (d) A. G. Pinkus and W. H. Lin, *Synthesis*, 1974, 279; (e) D. H. R. Barton, R. V. Stick, and R. Subramanian, *J.C.S. Perkin I*, 1976, 2112.
237. B. Lal, B. N. Pramanik, M. S. Manhas, and A. K. Bose, *Tetrahedron Letters*, 1977, 1977.
238. O. Mitsunobu, M. Wada, and T. Sano, *J. Amer. Chem. Soc.*, 1972, **94,** 679.
239. B. Castro and C. Selve, *Bull. Soc. chim. France*, 1971, 4368.
240. Y. Tanigawa, S.-I. Murahashi, and I. Moritani, *Tetrahedron Letters*, 1975, 471.
241. E. M. White and C. A. Elliger, *J. Amer. Chem. Soc.*, 1965, **87,** 5261.
242. E. M. Burgess, H. R. Penton, E. A. Taylor, and W. M. Williams, *Org. Synth.*, 1977, **56,** 40.
243. J. B. Hendrickson and I. Joffee, *J. Amer. Chem. Soc.*, 1973, **95,** 4083.
244. L. I. Krimen and D. J. Cota, *Org. Reactions*, 1969, **17,** 213.
245. (a) D. H. R. Barton, P. D. Magnus, J. A. Garbarino, and R. N. Young, *J.C.S. Perkin I*, 1974, 2101; (b) K. Takeuchi, M. Nojima, and N. Tokura, *ibid.*, 1976, 2205.

246. Y. T. Eidus and K. V. Puzitskii, *Russ. Chem. Rev.*, 1964, **33,** 438; Y. T. Eidus, A. L. Lapidus, K. V. Puzitskii, and B. K. Nefedov, *ibid.*, 1973, **42,** 199.
247. Y. Souma and H. Sano, *Bull. Chem. Soc. Japan*, 1976, **49,** 3296; K. V. Puzitskii, S. D. Pirozhkov, T. N. Myshenkova, K. G. Ryabova, and Y. T. Eidus, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1975, 443.
248. (a) M. Yoshimura, M. Nojima, and N. Tokura, *Bull. Chem. Soc. Japan*, 1973, **46,** 2164; (b) K. V. Puzitskii, S. D. Pirozhkov, K. G. Ryabova, T. N. Myshenkova, and Y. T. Eidus, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1974, 202; (c) Y. Takahashi, N. Tomita, N. Yoneda and A. Suzuki, *Chem. Letters*, 1975, 997.
249. J. F. Roth, J. H. Craddock, A. Hershman, and F. E. Paulik, *Chemtech*, 1971, **1,** 600.
250. W. J. Hickinbottom, 'Reactions of Organic Compounds', Longmans, London, 1957, 3rd edn., p. 136.
251. (a) H. Knözinger, in Ref. 2, chapter 12; (b) A. F. Cockerill, in 'Comprehensive Chemical Kinetics', ed. C. H. Bamford and C. F. H. Tipper, Elsevier, Amsterdam, 1973, vol. 9, chapter 3; (c) W. H. Saunders and A. F. Cockerill, 'Mechanisms of Elimination Reactions', Wiley-Interscience, New York, 1973, chapter VI.
252. D. Dautzenberg and H. Knözinger, *J. Catalysis*, 1974, **33,** 142.
253. H. Pines and J. Manassen, *Adv. Catalysis*, 1966, **16,** 49.
254 (a) A. J. Lundeen and R. van Hoozer, *J. Org. Chem.*, 1967, **32,** 3386;(b) P. Canesson and M. Blanchard, *J. Catalysis*, 1976, **42,** 205.
255. T. M. Santosusso and D. Swern, *J. Org. Chem.*, 1976, **41,** 2762.
256. S. Arimatsu, R. Yamaguchi, and M. Kawanisi, *Bull. Chem. Soc. Japan*, 1974, **47,** 1693; J. Lomas and J.-E. Dubois, *J. Org. Chem.*, 1974, **39,** 1776.
257. R. J. Arhart and J. C. Martin, *J. Amer. Chem. Soc.*, 1972, **94,** 5003.
258. R. O. Hutchins, M. G. Hutchins, and C. A. Milewski, *J. Org. Chem.*, 1972, **37,** 4190.
259. R. Appel and H.-D. Wihler, *Chem. Ber.*, 1976, **109,** 3446.
260. C. H. DePuy and R. W. King, *Chem. Rev.*, 1960, **60,** 431; G. G. Smith and F. W. Kelly, *Progr. Phys. Org. Chem.*, 1971, **8,** 75; S. de Burgh Norfolk and R. Taylor, *J.C.S. Perkin II*, 1976, 280; D. H. Wertz and N. L. Allinger, *J. Org. Chem.*, 1977, **42,** 698.
261. H. R. Nace, *Org. Reactions*, 1962, **12,** 57.
262. H. Gerlach, T. T. Huong, and W. Müller, *J.C.S. Chem. Comm.*, 1972, 1215.
263. E. M. Burgess, H. R. Penton, and E. A. Taylor, *J. Org. Chem.*, 1973, **38,** 26.
264. (a) G. H. Schmid and A. W. Wolkoff, *Canad. J. Chem.*, 1972, **50,** 1181; (b) R. Scheffold and U. Mareis, *Chimia*, 1975, **29,** 520.
265. D. H. R. Barton, M. Bolton, P. D. Magnus, K. G. Marathe, G. A. Poulton, and P. J. West, *J.C.S. Perkin I*, 1973, 1574.
266. (a) 'Oxidation in Organic Chemistry', ed. K. B. Wiberg (part A) and W. S. Trahanovsky (part B), Academic, New York, 1965 (part A) and 1973 (part B); (b) C. F. Cullis and A. Fish, in 'The Chemistry of the Carbonyl Group', ed. S. Patai, Interscience, London, 1966, chapter 2; (c) 'Oxidation', ed. R. L. Augustine (vol. 1 and 2) and D. J. Trecker (vol. 2), Dekker, New York, 1969 (vol. 1) and 1971 (vol. 2); (d) L. J. Chinn, 'Selection of Oxidants in Synthesis: Oxidation at the Carbon Atom', Dekker, New York, 1971.
267. Y. S. Rao and R. Filler, *J. Org. Chem.*, 1974, **39,** 3305.
268. K. E. Harding, L. M. May, and K. F. Dick, *J. Org. Chem.*, 1975, **40,** 1664.
269. G. Cainelli, G. Cardillo, M. Orena, and S. Sandri, *J. Amer. Chem. Soc.*, 1976, **98,** 6737.
270. (a) J.-M. Lalancette, G. Rollin, and P. Dumas, *Canad. J. Chem.*, 1972, **50,** 3058; (b) H. B. Kagan, *Chemtech*, 1976, **6,** 510.
271. D. G. Lee and U. A. Spitzer, *J. Org. Chem.*, 1970, **35,** 3589.
272. G. Cardillo, M. Orena, and S. Sandri, *Synthesis*, 1976, 394.
273. R. W. Ratcliffe, *Org. Synth.*, 1976, **55,** 84.
274. E. Piers and P. M. Worster, *Canad. J. Chem.*, 1977, **55,** 733.
275. (a) E. J. Corey and G. W. J. Fleet, *Tetrahedron Letters*, 1973, 4499; (b) E. J. Corey and J. W. Suggs, *Tetrahedron Letters*, 1975, 2647; (c) K. B. Sharpless and K. Akashi, *J. Amer. Chem. Soc.*, 1975, **97,** 5927.
276. W. G. Dauben and D. M. Michno, *J. Org. Chem.*, 1977, **42,** 682; P. Sundararaman and W. Herz, *ibid.*, 1977, **42,** 813.
277. M. Rahman and J. Roček, *J. Amer. Chem. Soc.*, 1971, **93,** 5462; F. Hasan and J. Roček, *ibid.*, 1976, **98,** 6574, and references cited.
278. K. B. Wiberg and S. K. Mukherjee, *J. Amer. Chem. Soc.*, 1974, **96,** 6647, and references cited.
279. *e.g.* R. Durand, P. Geneste, G. Lamaty, and J. P. Roque, *Rec. Trav. chim.*, 1975, **94,** 131; V. M. S. Ramanujam and N. Venkatasubramanian, *Indian J. Chem.*, 1975, **13,** 285; H. Kwart and J. H. Nickle, *J. Amer. Chem. Soc.*, 1976, **98,** 2881; P. Müller and J.-C. Perlberger, *ibid.*, 1976, **98,** 8407.
280. T.-Y. Peng and J. Roček, *J. Amer. Chem. Soc.*, 1976, **98,** 1026.
281. D. Benson, 'Mechanisms of Oxidation by Metal Ions', Elsevier, Amsterdam, 1976.
282. W. S. Trahanovsky, L. B. Young, and G. L. Brown, *J. Org. Chem.*, 1967, **32,** 3865.
283. F. J. Kakis, M. Fétizon, N. Douchkine, M. Golfier, P. Mourgues, and T. Prange, *J. Org. Chem.*, 1974, **39,** 523.
284. A. J. Fatiadi, *Synthesis*, 1976, 65 and 133.
285. D. G. Lee and M. van den Engh, in Ref. 266a, part B, chapter IV.
286. M. V. George and K. S. Balachandran, *Chem. Rev.*, 1975, **75,** 491.
287. T.-L. Ho and T. W. Hall, *Synth. Comm.*, 1975, **5,** 309.
288. (a) R. Criegee, in Ref. 266a, part A, chapter V; (b) M. L. Mihailović and R. E. Partch, in 'Selective Organic Transformations', ed. B. S. Thyagarajan, Wiley-Interscience, New York, 1972, vol. 2, p. 97.

289. G. A. Lee and H. H. Freedman, *Tetrahedron Letters*, 1976, 1641.
290. R. Filler, *Chem. Rev.*, 1963, **63,** 21; J. S. Pizey, 'Synthetic Reagents', Ellis Horwood, Chichester, 1974, vol. II, chapter 1.
291. M. A. Neirabeyeh, J.-C. Ziegler, B. Gross, and P. Caubère, *Synthesis*, 1976, 811.
292. (a) Y. Ueno and M. Okawara, *Tetrahedron Letters*, 1976, 4597; (b) K. Saigo, A. Morikawa, and T. Mukaiyama, *Bull. Chem. Soc. Japan*, 1976, **49,** 1656; (c) T. Ogawa and M. Matsui, *J. Amer. Chem. Soc.*, 1976, **98,** 1629.
293. T. Mukaiyama, M. Tsunoda, and K. Saigo, *Chem. Letters*, 1975, 691.
294. J. Wicha, A. Zarecki, and M. Kočor, *Tetrahedron Letters*, 1973, 3635.
295. J. Wicha and A. Zarecki, *Tetrahedron Letters*, 1974, 3059.
296. E. J. Corey and C. U. Kim, *J. Amer. Chem. Soc.*, 1972, **94,** 7586; G. A. Crosby, N. M. Weinshenker, and H.-S. Uh, *ibid.*, 1975, **97,** 2232.
297. E. J. Corey and C. U. Kim, *Tetrahedron Letters*, 1973, 919.
298. J. G. Moffatt, in Ref. 266c, vol. 2, p. 1.
299. N. M. Weinshenker and C.-M. Shen, *Tetrahedron Letters*, 1972, 3285.
300. D. H. R. Barton and C. P. Forbes, *J.C.S. Perkin I*, 1975, 1614.
301. C. Djerassi, *Org. Reactions*, 1951, **VI,** 207.
302. D. Walker and J. D. Hiebert, *Chem. Rev.*, 1967, **67,** 153.
303. A. Dobson and S. D. Robinson, *Inorg. Chem.*, 1977, **16,** 137.
304. T. Nishiguchi, K. Tachi, and K. Fukuzumi, *J. Org. Chem.*, 1975, **40,** 237; Y. Sasson and J. Blum, *J. Org. Chem.*, 1975, **40,** 1887.
305. K. B. Sharpless, K. Akashi, and K. Oshima, *Tetrahedron Letters*, 1976, 2503.
306. G. A. Tolstikov, V. P. Yur'ev, and U. M. Dzhemilev, *Russ. Chem. Rev.*, 1975, **44,** 319.
307. K. Heyns, H. Paulsen, G. Rüdiger, and J. Weyer, *Fortschr. Chem. Forsch.*, 1969, **11,** 285.
308. (a) M. P. Doyle, D. J. DeBruyn, and D. J. Scholten, *J. Org. Chem.*, 1973, **38,** 625; (b) G. Casnati, G. P. Gardini, and G. Palla, *Gazzetta*, 1975, **105,** 447; (c) M. E. Jung, *J. Org. Chem.*, 1976, **41,** 1479.
309. G. A. Olah and T.-L. Ho, *Synthesis*, 1976, 609.
310. R. W. Binkley, *J. Org. Chem.*, 1976, **41,** 3030.
311. J. A. Cella, J. P. McGrath, and S. L. Regen, *Tetrahedron Letters*, 1975, 4115; B. Ganem, *J. Org. Chem.*, 1975, **40,** 1998.
312. (a) S. D. Ross, M. Finkelstein, and E. J. Rudd, 'Anodic Oxidation', Academic, New York, 1975; (b) A. J. Irwin and J. B. Jones, *J. Amer. Chem. Soc.*, 1977, **99,** 1625, and references cited.
313. J. Kalvoda and K. Heusler, *Synthesis*, 1971, 501.
314. M. P. Doyle, L. J. Zuidema, and T. R. Bade, *J. Org. Chem.*, 1975, **40,** 1454.
315. M. L. Mihailović, S. Gojković, and S. Konstantinović, *Tetrahedron*, 1973, **29,** 3675.
316. P. Brun and B. Waegell, *Tetrahedron*, 1976, **32,** 1137.
317. C. Walling and D. Bristol, *J. Org. Chem.*, 1972, **37,** 3514.
318. R. H. Hesse, *Adv. Free-Radical Chem.*, 1969, **3,** 83.
319. Ž. Čeković and M. M. Green, *J. Amer. Chem. Soc.*, 1974, **96,** 3000, and references cited.
320. Ž. Čeković and T. Srnić, *Tetrahedron Letters*, 1976, 561.
321. R. Breslow, R. J. Corcoran, B. B. Snider, R. J. Doll, P. L. Khanna, and R. Kaleya, *J. Amer. Chem. Soc.*, 1977, **99,** 905, and references cited.
322. N. C. Deno, W. E. Billups, R. Fishbein, C. Pierson, R. Whalen, and J. C. Wyckoff, *J. Amer. Chem. Soc.*, 1971, **93,** 438; N. C. Deno, K. A. Eisenhardt, D. G. Pohl, H. J. Spinnelli, and R. C. White, *J. Org. Chem.*, 1974, **39,** 520.
323. G. A. Olah, N. Yoneda, and R. Ohnishi, *J. Amer. Chem. Soc.*, 1976, **98,** 7341.
324. K. Mackenzie (chapter 7) and R. H. DeWolfe and W. G. Young (chapter 10), in 'The Chemistry of Alkenes', ed. S. Patai, Interscience, London, 1964.
325. (a) R. Gelin, S. Gelin, and M. Albrand, *Bull. Soc. chim. France*, 1972, 720; (b) L.-I. Olsson, A. Claesson, and C. Bogentoft, *Acta Chem. Scand.*, 1973, **27,** 1629.
326. S. Swaminathan and K. V. Narayanan, *Chem. Rev.*, 1971, **71,** 429.
327. H. Pauling, D. A. Andrews, and N. C. Hindley, *Helv. Chim. Acta*, 1976, **59,** 1233; M. B. Erman, I. S. Aul'chenko, L. A. Kheifits, V. G. Dulova, J. N. Novikov, and M. E. Vol'pin, *Tetrahedron Letters*, 1976, 2981.
328. L. A. Yanovskaya and K. Shakhidayatov, *Russ. Chem. Rev.*, 1970, **39,** 859.
329. Y. Sasson and G. L. Rempel, *Tetrahedron Letters*, 1974, 4133; M. Dedieu and Y.-L. Pascal, *Compt. rend.*, 1976, **282C,** 65.
330. S. J. Rhoads and N. R. Raulins, *Org. Reactions*, 1975, **22,** 1.
331. D. A. Evans and A. M. Golob, *J. Amer. Chem. Soc.*, 1975, **97,** 4765.
332. W. T. Borden, *J. Amer. Chem. Soc.*, 1970, **92,** 4898; B. Grant and C. Djerassi, *J. Org. Chem.*, 1974, **39,** 968.
333. A. Claesson and C. Bogentoft, *Synthesis*, 1973, 539.
334. J. S. Cowie, P. D. Landor, and S. R. Landor, *J.C.S. Perkin I*, 1973, 720; A. Claesson, L.-I. Olsson, and C. Bogentoft, *Acta Chem. Scand.*, 1973, **27,** 2941; E. Galantay, I. Basco, and R. V. Coombs, *Synthesis*, 1974, 344.
335. A. Claesson, *Acta Chem. Scand.*, 1974, **28B,** 993.
336. R. Baudouy and J. Gore, *Tetrahedron*, 1975, **31,** 383; A. Claesson, *Acta Chem. Scand.*, 1975, **29B,** 609.

337. H. G. Richey, C. W. Wilkins, B. S. Brown, and R. E. Moore, *Tetrahedron Letters*, 1976, 723, and references cited.
338. B. Jousseaume and J.-G. Duboudin, *J. Organometallic Chem.*, 1975, **91**, C1; A. Claesson, I. Tämnefors, and L.-I. Olsson, *Tetrahedron Letters*, 1975, 1509.
339. J. K. Crandall and A. C. Rojas, *Org. Synth.*, 1976, **55**, 1; L.-I. Olsson and A. Claesson, *Acta Chem. Scand.*, 1976, **30B**, 521, and references cited.
340. A. Yasuda, H. Yamamoto, and H. Nozaki, *Tetrahedron Letters*, 1976, 2621.
341. L. E. Overman, *J. Amer. Chem. Soc.*, 1976, **98**, 2901.
342. H. M. Flowers, in Ref. 2, chapter 18; C. B. Reese, in 'Protective Groups in Organic Chemistry', ed. J. F. W. McOmie, Plenum, London, 1973, chapter 3.
343. V. G. Mairanovsky, *Angew. Chem. Internat. Edn.*, 1976, **15**, 281.
344. D. G. Bartholomew and A. D. Broom, *J.C.S. Chem. Comm.*, 1975, 38.
345. Y. Mizuno, T. Endo and K. Ikeda, *J. Org. Chem.*, 1975, **40**, 1385.
346. W. E. Barnett, L. L. Needham, and R. W. Powell, *Tetrahedron*, 1972, **28**, 419.
347. R. L. Letsinger and J. L. Finnan, *J. Amer. Chem. Soc.*, 1975, **97**, 7197.
348. H. Köster and F. Cramer, *Annalen*, 1972, **766**, 6; J. M. J. Fréchet and K. E. Haque, *Tetrahedron Letters*, 1975, 3055.
349. (a) S. Hanessian and A. P. A. Staub, *Tetrahedron Letters*, 1973, 3555; (b) Y. V. Wozney and N. K. Kochetkov, *Carbohydrate Res.*, 1977, **54**, 300.
350. D. Buchnea, *Lipids*, 1974, **9**, 55.
351. E. J. Corey and J. W. Suggs, *J. Org. Chem.*, 1973, **38**, 3224; P. A. Gent and R. Gigg, *J.C.S. Chem. Comm.*, 1974, 277.
352. R. Boss and R. Scheffold, *Angew. Chem. Internat. Edn.*, 1976, **15**, 558.
353. T.-L. Ho and C. M. Wong, *Synth. Comm.*, 1974, **4**, 109.
354. T.-L. Ho and T. W. Hall, *Synth. Comm.*, 1975, **5**, 367.
355. E. J. Corey and A. Venkateswarlu, *J. Amer. Chem. Soc.*, 1972, **94**, 6190; K. K. Ogilvie, S. L. Beaucage, D. W. Entwistle, E. A. Thompson, M. A. Quilliam, and J. B. Westmore, *J. Carbohydrates, Nucleosides and Nucleotides*, 1976, **3**, 197.
356. S. Hanessian and P. Lavallee, *Canad. J. Chem.*, 1975, **53**, 2975.
357. J. H. van Boom, P. van Deursen, J. Meeuwse, and C. B. Reese, *J.C.S. Chem. Comm.*, 1972, 766.
358. K. Fuji, S. Nakano, and E. Fujita, *Synthesis*, 1975, 276.
359. E. J. Corey, J.-L. Gras, and P. Ulrich, *Tetrahedron Letters*, 1976, 809.
360. (a) E. J. Corey and M. G. Bock, *Tetrahedron Letters*, 1975, 3269; (b) K. Yamada, K. Kato, H. Nagase, and Y. Hirata, *ibid.*, 1976, 65; (c) P. M. Pojer and S. J. Angyal, *ibid.*, 1976, 3067.
361. C. G. Kruse, N. L. J. M. Broekhof, and A. van der Gen, *Tetrahedron Letters*, 1976, 1725.
362. Y. Y. Lin and J. B. Jones, *J. Org. Chem.*, 1973, **38**, 3575.
363. D. H. R. Barton, I. H. Coates, and P. G. Sammes, *J.C.S. Perkin I*, 1973, 599.
364. R. L. Letsinger and P. S. Miller, *J. Amer. Chem. Soc.*, 1969, **91**, 3356.
365. R. D. Guthrie, T. J. Lucas, and R. Khan, *Carbohydrate Res.*, 1974, **33**, 391; T.-L. Ho and C. M. Wong, *Synth. Comm.*, 1975, **5**, 91; J. H. van Boom and P. M. J. Burgers, *Tetrahedron Letters*, 1976, 4875.
366. R. Arentzen and C. B. Reese, *J.C.S. Chem. Comm.*, 1977, 270.
367. A. Hassner, G. Strand, M. Rubinstein, and A. Patchornik, *J. Amer. Chem. Soc.*, 1975, **97**, 1614.
368. E. J. Corey and J. W. Suggs, *J. Org. Chem.*, 1973, **38**, 3223.
369. Y. Kondo, K. Hosoyama, and T. Takemoto, *Chem. Pharm. Bull. (Japan)*, 1975, **23**, 2167.
370. (a) E. S. Waight and A. Nechvatal, in 'Rodd's Chemistry of Carbon Compounds', ed. S. Coffey (vol. 1D) and M. F. Ansell (supplement to vol. 1D), Elsevier, Amsterdam, 1965 and 1973, vol. 1D and its supplement, chapter 12; (b) P. W. Kent and K. R. Wood, in 'Rodd's Chemistry of Carbon Compounds', ed. S. Coffey, Elsevier, Amsterdam, 1976, vol. 1E, chapter 18; (c) J. E. G. Barnett and P. W. Kent, in 'Rodd's Chemistry of Carbon Compounds', ed. S. Coffey, Elsevier, Amsterdam, 1976, vol. 1G, chapter 25; L. Hough and A. C. Richardson, *ibid.*, 1967, vol. 1F, chapter 22; J. S. Brimacombe and J. M. Webber, in 'The Carbohydrates. Chemistry and Biochemistry', ed. W. Pigman and D. Horton, Academic, New York, 2nd edn., 1972, vol. 1A, chapter 14; (d) T. Posternak, 'The Cyclitols', Hermann, Paris, 1965; L. Anderson, in 'The Carbohydrates. Chemistry and Biochemistry', ed. W. Pigman and D. Horton, Academic, New York, 2nd. edn., 1972, vol. 1A, chapter 15.
371. *Biochem. J.*, 1967, **105**, 897.
372. *Biochem. J.*, 1971, **125**, 673.
373. *Biochem. J.*, 1976, **153**, 23.
374. A. N. Anikeeva, G. M. Zarubinskii, and S. N. Danilov, *Russ. Chem. Rev.*, 1976, **45**, 43.
375. M. D. Joeston and L. J. Schaad, 'Hydrogen Bonding', Dekker, New York, 1974; W. K. Busfield, M. P. Ennis, and I. J. McEwen, *Spectrochim. Acta*, 1973, **29A**, 1259.
376. G. A. Jeffrey and H. S. Kim, *Carbohydrate Res.*, 1970, **14**, 207.
377. S. J. Angyal, D. Greeves, and J. A. Mills, *Austral. J. Chem.*, 1974, **27**, 1447, and references cited.
378. A. P. G. Kieboom, T. Spoormaker, A. Sinnema, J. M. van der Toorn, and H. van Bekkum, *Rec. Trav. chim.*, 1975, **94**, 53.
379. S. J. Angyal, *Tetrahedron*, 1974, **30**, 1695; S. J. Angyal, D. Greeves, L. Littlemore, and V. A. Pickles, *Austral. J. Chem.*, 1976, **29**, 1231, and preceding papers in the series.
380. A. P. G Kieboom, A. Sinnema, J. M. van der Toorn, and H. van Bekkum, *Rec. Trav. chim.*, 1977, **96**, 35; J. Reuben, *J. Amer. Chem. Soc.*, 1977, **99**, 1765.

381. R. W. Goulding, *J. Chromatog.*, 1975, **103,** 229.
382. W. Voelter, H. Bauer, and G. Kuhfittig, *Chem. Ber.*, 1974, **107,** 3602; W. L. Nelson, J. E. Wennerstrom, and S. R. Sankar, *J. Org. Chem.*, 1977, **42,** 1006, and references cited.
383. (a) J. Dillon and K. Nakanishi, *J. Amer. Chem. Soc.*, 1975, **97,** 5409; (b) J. Dillon and K. Nakanishi, *ibid.*, p. 5417.
384. (a) A. I. Scott and A. D. Wrixon, *Chem. Comm.*, 1969, 1184; (b) A. H. Haines and C. S. P. Jenkins, *J. Chem. Soc.* (*C*), 1971, 1438; V. Usieli, A. Pilersdorf, S. Shor, J. Katzhendler, and S. Sarel, *J. Org. Chem.*, 1974, **39,** 2073; (c) N. Harada, S. L. Chen, and K. Nakanishi, *J. Amer. Chem. Soc.*, 1975, **97,** 5345.
385. *e.g.* K. Nakanishi, D. A. Schooley, M. Koreeda, and I. Miura, *J. Amer. Chem. Soc.*, 1972, **94,** 2865; L. Cazaux and P. Maroni, *Bull. Soc. chim. France*, 1972, 773, and following papers; A. Krief, L. Hevesi, J. B. Nagy, and E. G. Derouane, *Angew. Chem. Internat. Edn.*, 1977, **16,** 100.
386. F. D. Gunstone, *Adv. Org. Chem.*, 1960, **1,** 103.
387. (a) L. T. Eremenko and A. M. Korolev, *Izv. Akad. Nauk S.S.S.R., Ser. khim.*, 1970, 147; (b) W. P. Weber and J. P. Shepherd, *Tetrahedron Letters*, 1972, 4907.
388. W. D. Lloyd, B. J. Navarette, and M. F. Shaw, *Synthesis*, 1972, 610.
389. (a) K. B. Sharpless and K. Akashi, *J. Amer. Chem. Soc.*, 1976, **98,** 1986; (b) V. VanRheenen, R. C. Kelly, and D. Y. Cha, *Tetrahedron Letters*, 1976, 1973.
390. M. Parrilli, V. Dovinola, and L. Mangoni, *Gazzetta*, 1974, **104,** 829; R. C. Cambie, G. J. Potter, P. S. Rutledge, and P. D. Woodgate, *J.C.S. Perkin I*, 1977, 530.
391. (a) R. C. Cambie, R. C. Hayward, J. L. Roberts, and P. S. Rutledge, *J.C.S. Perkin I*, 1974, 1858; (b) L. Mangoni, M. Adinolfi, G. Barone, and M. Parrilli, *Gazzetta*, 1975, **105,** 377; (c) M. Adinolfi, M. Parrilli, G. Barone, G. Laonigro, and L. Mangoni, *Tetrahedron Letters*, 1976, 3661.
392. D. Jasserand, J. P. Girard, J. C. Rossi, and R. Granger, *Tetrahedron Letters*, 1976, 1581.
393. (a) E. Glotter and A. Schwartz, *J.C.S. Perkin I*, 1976, 1660; (b) C. Freppel, R. Favier, J.-C. Richer, and M. Zador, *Canad. J. Chem.*, 1971, **49,** 2586.
394. J. Buddrus, *Angew. Chem. Internat. Edn.*, 1973, **12,** 163.
395. (a) J. M. Bachhawat and N. K. Mathur, *Tetrahedron Letters*, 1971, 691; (b) C. Wilkins, *Synthesis*, 1973, 156.
396. M. A. Khuddus and D. Swern, *Tetrahedron Letters*, 1971, 411.
397. J. G. Buchanan and H. Z. Sable, in 'Selective Organic Transformations', ed. B. S. Thyagarajan, Wiley-Interscience, New York, 1972, vol. 2, p. 1.
398. J. Klein, R. Levene, and E. Dunkelblum, *Tetrahedron Letters*, 1972, 2845; G. L. Larson, D. Hernandez, and A. Hernandez, *J. Organometallic Chem.*, 1974, **76,** 9; H. Kono and Y. Nagai, *Org. Prep. Proced. Internat.*, 1974, **6,** 19.
399. H. C. Brown, P. J. Geoghegan, J. T. Kurek, and G. J. Lynch, *Organometallics Chem. Synth.*, 1970/1971, **1,** 7.
400. L. E. Overman and C. B. Campbell, *J. Org. Chem.*, 1974, **39,** 1474.
401. A. A. P. Schreibmann, *Tetrahedron Letters*, 1970, 4271.
402. T. Mukaiyama, T. Sato, and J. Hanna, *Chem. Letters*, 1973, 1041; E. J. Corey, R. L. Danheiser, and S. Chandrasekaran, *J. Org. Chem.*, 1976, **41,** 260, and references cited.
403. E. H. Axelrod, *Chem. Comm.*, 1970, 451.
404. T. H. Chan and E. Vinokur, *Tetrahedron Letters*, 1972, 75.
405. L. G. Feoktistov and H. Lund, in 'Organic Electrochemistry', ed. M. M. Baizer, Dekker, New York, 1973, chapter VIII.
406. J. N. Pitts and J. K. S. Wan, in 'The Chemistry of the Carbonyl Group', ed. S. Patai, Interscience, London, 1966, chapter 16; A. Schönberg, 'Preparative Organic Photochemistry', Springer-Verlag, Berlin, 1968, p. 203.
407. (a) R. Le Goaller and J.-L. Pierre, *Canad. J. Chem.*, 1977, **55,** 757; (b) J.-P. Barnier and J.-M. Conia, *Bull. Soc. chim. France*, 1976, 281.
408. D. H. R. Barton, R. K. Haynes, G. Leclerc, P. D. Magnus, and I. D. Menzies, *J.C.S. Perkin I*, 1975, 2055.
409. H. C. Brown and E. Negishi, *Tetrahedron*, 1977, **33,** 2331.
410. A. Suzuki, N. Miyaura, and M. Itoh, *Tetrahedron*, 1971, **27,** 2775.
411. (a) K. Utimoto, K. Uchida, M. Yamaya, and H. Nozaki, *Tetrahedron*, 1977, **33,** 1945; (b) K. Utimoto, K. Uchida, and H. Nozaki, *Tetrahedron*, 1977, **33,** 1949.
412. G. Casnati, A. Pochini, G. Salerno, and R. Ungaro, *J.C.S. Perkin I*, 1975, 1527; A. Pochini, G. Salerno, and R. Ungaro, *Synthesis*, 1975, 164.
413. C. W. Roberts, in 'Friedel–Crafts and Related Reactions', ed. G. A. Olah, Interscience, New York, 1964, vol. II, chapter 27; D. R. Adams and S. P. Bhatnagar, *Synthesis*, 1977, 661.
414. V. I. Shvets, *Russ. Chem. Rev.*, 1974, **43,** 488.
415. Kirk–Othmer 'Encyclopedia of Chemical Technology', ed. S. Standen, Interscience, New York, 1970, 2nd edn., vol. 10, p. 638; G. G. Hawley, 'The Condensed Chemical Dictionary', Van Nostrand Reinhold, New York, 1977, 9th edn.
416. (a) G. W. Gokel and H. D. Durst, *Synthesis*, 1976, 168, and references cited; (b) D. J. Cram, R. C. Helgeson, L. R. Sousa, J. M. Timko, M. Newcomb, P. Moreau, F. de Jong, G. W. Gokel, D. H. Hoffman, L. A. Domeier, S. C. Peacock, K. Madan, and L. Kaplan, *Pure Appl. Chem.*, 1975, **43,** 327; (c) W. D. Curtis, D. A. Laidler, J. F. Stoddart, and G. H. Jones, *J.C.S. Perkin I*, 1977, 1756.
417. (a) N. H. Anderson and H.-S. Uh, *Synth. Comm.*, 1973, **3,** 125; (b) J. Egyed, P. Demerseman, and R. Royer, *Bull. Soc. chim. France*, 1972, 2287.

418. M. Anteunis and C. Becu, *Synthesis*, 1974, 23.
419. G. L. Larson and A. Hernandez, *J. Org. Chem.*, 1973, **38,** 3935.
420. S. Hanessian, G. Yang-Chung, P. Lavallee, and A. G. Pernet, *J. Amer. Chem. Soc.*, 1972, **94,** 8929.
421. R. M. Munavu and H. H. Szmant, *Tetrahedron Letters*, 1975, 4543.
422. H. J. E. Loewenthal, in 'Protective Groups in Organic Chemistry', ed. J. F. W. McOmie, Plenum, London, 1973, chapter 9.
423. (a) E. J. Corey and R. A. Ruden, *J. Org. Chem.*, 1973, **38,** 834; (b) J. Hébert and D. Gravel, *Canad. J. Chem.*, 1974, **52,** 187.
424. (a) E. J. Corey and J. W. Suggs, *Tetrahedron Letters*, 1975, 3775; (b) E. J. Corey, E. J. Trybulski and J. W. Suggs, *Tetrahedron Letters*, 1976, 4577; (c) C. C. Leznoff and S. Greenberg, *Canad. J. Chem.*, 1976, **54,** 3824.
425. S. Hanessian, T. Ogawa, Y. Guindon, J. L. Kamennof, and R. Roy, *Carbohydrate Res.*, 1974, **38,** C15; J. M. J. Fréchet and G. Pellé, *J.C.S. Chem. Comm.*, 1975, 225.
426. A. B. Foster, in 'The Carbohydrates. Chemistry and Biochemistry', ed. W. Pigman and D. Horton, Academic, New York, 2nd edn., 1972, vol. 1A, chapter 11; J. F. Stoddart, 'Stereochemistry of Carbohydrates', Wiley, New York, 1971.
427. S. Hanessian and E. Moralioglu, *Canad. J. Chem.*, 1972, **50,** 233.
428. R. H. De Wolfe, 'Carboxylic Ortho Acid Derivatives', Academic, New York, 1970; V. V. Mezheritskii, E. P. Olekhnovich, and G. N. Dorofeenko, *Russ. Chem. Rev.*, 1973, **42,** 392.
429. C. U. Pittman, S. P. McManus, and J. W. Larsen, *Chem. Rev.*, 1972, **72,** 357.
430. H. Paulsen, *Pure Appl. Chem.*, 1975, **41,** 69; *Adv. Carbohydrate Chem. Biochem.*, 1971, **26,** 127.
431. G. Wulff and G. Röhle, *Angew. Chem. Internat. Edn.*, 1974, **13,** 157.
432. J. P. Kutney and A. H. Ratcliffe, *Synth. Comm.*, 1975, **5,** 47.
433. S. Sakai, Y. Kiyohara, K. Itoh, and Y. Ishii, *J. Org. Chem.*, 1970, **35,** 2347; E. I. Stout, B. S. Shasha, D. Trimnell, and C. R. Russell, *Carbohydrate Res.*, 1974, **36,** 311.
434. A. A. Vegnere, E. M. Shvarts, and A. F. Ievin'sh, *J. Gen. Chem.* (*U.S.S.R.*), 1974, **44,** 2172; S. J. Angyal, J. E. Klavins, and J. A. Mills, *Austral. J. Chem.*, 1974, **27,** 1075, and references cited.
435. H. Bauer and W. Voelter, *Chromatographia*, 1976, **9,** 433; K. Larsson and O. Samuelson, *Carbohydrate Res.*, 1976, **50,** 1.
436. E. J. Bourne, I. R. McKinley, and H. Weigel, *Carbohydrate Res.*, 1974, **35,** 141; W. V. Dahlhoff and R. Köster, *J. Org. Chem.*, 1976, **41,** 2316.
437. I. R. McKinley and H. Weigel, *Carbohydrate Res.*, 1973, **31,** 17.
438. R. J. Ferrier, *Methods Carbohydrate Chem.*, 1972, **VI,** 419.
439. (a) E. Seymour and J. M. J. Fréchet, *Tetrahedron Letters*, 1976, 1149; (b) E. Seymour and J. M. J. Fréchet, *ibid.*, 1976, 3669; (c) A. M. Yurkevich, I. I. Kolodkina, E. A. Ivanova and E. I. Pichuzhkina, *Carbohydrate Res.*, 1975, **43,** 215.
440. F. Eisenberg, *Carbohydrate Res.*, 1971, **19,** 135; P. J. Wood and I. R. Siddiqui, *ibid.*, 1971, **19,** 283; S. G. Batrakov, A. G. Panosyan, A. N. Ushakov, B. V. Rozynov and L. D. Bergel'son, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1974, 1738.
441. P. J. Garegg and K. Lindström, *Acta Chem. Scand.*, 1971, **25,** 1559.
442. A. H. Haines, *Adv. Carbohydrate Chem. Biochem.*, 1976, **33,** 11.
443. O. Mitsunobu, J. Kimura, K. Iizumi, and N. Yanagida, *Bull. Chem. Soc. Japan*, 1976, **49,** 510.
444. E.-F. Fuchs and J. Lehmann, *Chem. Ber.*, 1974, **107,** 721.
445. S. A. Bone and S. Trippett, *J.C.S. Perkin I*, 1976, 156; R. Boigegrain and B. Castro, *Tetrahedron*, 1976, **32,** 1283.
446. B. Castro and C. Selve, *Bull. Soc. chim. France*, 1974, 3004, 3009; R. Boigegrain, B. Castro, and C. Selve, *Tetrahedron Letters*, 1975, 2529.
447. P. J. Garegg, T. Iversen, and S. Oscarson, *Carbohydrate Res.*, 1976, **50,** C12; *ibid.*, 1977, **53,** C5.
448. (a) J. M. J. Fréchet and L. J. Nuyens, *Canad. J. Chem.*, 1976, **54,** 926; T. M. Fyles and C. C. Leznoff, *Canad. J. Chem.*, 1976, **54,** 935, and references cited; (b) C. C. Leznoff, T. M. Fyles, and J. Weatherston, *Canad. J. Chem.*, 1977, **55,** 1143.
449. M. E. Jung and L. M. Speltz, *J. Amer. Chem. Soc.*, 1976, **98,** 7882.
450. D. H. R. Barton, P. D. Magnus, G. Smith, G. Streckert, and D. Zurr, *J.C.S. Perkin I*, 1972, 542.
451. (a) E. J. Corey and C. U. Kim, *Tetrahedron Letters*, 1974, 287; (b) J. Bastard, M. Fétizon, and J. C. Gramain, *Tetrahedron*, 1973, **29,** 2867; (c) S. L. T. Thuan and P. Maitte, *Tetrahedron Letters*, 1975, 2027.
452. (a) M. Fétizon, M. Golfier, and J.-M. Louis, *Chem. Comm.*, 1969, 1102; (b) M. Fétizon, M. Golfier, and J.-M. Louis, *Tetrahedron*, 1975, **31,** 171.
453. R. K. Boeckman and B. Ganem, *Tetrahedron Letters*, 1974, 913.
454. J. H. Exner, *Tetrahedron Letters*, 1975, 1197, and references cited.
455. B. T. Golding, D. R. Hall, and S. Sakrikar, *J.C.S. Perkin I*, 1973, 1214; G. Schneider and I. Weisz-Vincze, *Tetrahedron Letters*, 1975, 2115.
456. (a) A. A. Akhrem, V. V. Zharkov, G. V. Zaitseva, and I. A. Mikhailopulo, *Tetrahedron Letters*, 1973, 1475; (b) A. A. Akhrem, G. V. Zaitseva, and I. A. Mikhailopulo, *Carbohydrate Res.*, 1976, **50,** 143.
457. C. Rüchardt and S. Rochlitz, *Annalen*, 1974, 15.
458. M. S. Newman and C. H. Chen, *J. Org. Chem.*, 1973, **38,** 1173.
459. (a) M. S. Newman and C. H. Chen, *J. Amer. Chem. Soc.*, 1973, **95,** 278; O. Itoh, Y. Ichikawa, H. Katano, and K. Ichikawa, *Bull. Chem. Soc. Japan*, 1976, **49,** 1353; (b) M. S. Newman and D. R. Olson, *J. Org.*

Chem., 1973, **38,** 4203; M. W. Logue, *Carbohydrate Res.*, 1975, **40,** C9; (c) M. J. Robins, R. Mengel, R. A. Jones, and Y. Fouron, *J. Amer. Chem. Soc.*, 1976, **98,** 8204.
460. (a) S. Hanessian, *Methods Carbohydrate Chem.*, 1972, **VI,** 183; D. A. Secley and J. McElwee, *J. Org. Chem.*, 1973, **38,** 1691; (b) T. P. Culbertson, *J. Org. Chem.*, 1973, **38,** 3624; (c) D. H. R. Barton and R. V. Stick, *J.C.S. Perkin I*, 1975, 1773.
461. (a) R. Marumoto and M. Honjo, *Chem. Pharm. Bull. (Japan)*, 1974, **22,** 128; (b) S. Greenberg and J. G. Moffatt, *J. Amer. Chem. Soc.*, 1973, **95,** 4016; (c) Z. Janousek and H. G. Viehe, *Adv. Org. Chem.*, 1976, **9,** 343; A. Klemer, R. Lemmes, and G. Nicolaus, *Annalen*, 1977, 177; (d) T. G. Back, D. H. R. Barton, and B. L. Rao, *J.C.S. Perkin I*, 1977, 1715.
462. D. H. R. Barton and R. Subramanian, *J.C.S. Perkin I*, 1977, 1718.
463. S. Hanessian and A. P. A. Staub, *Tetrahedron Letters*, 1973, 3551.
464. P. Deslongchamps and C. Moreau, *Canad. J. Chem.*, 1971, **49,** 2465.
465. T. Ogawa and M. Matsui, *Carbohydrate Res.*, 1977, **56,** C1.
466. D. Wagner, J. P. H. Verheyden and J. G. Moffatt, *J. Org. Chem.*, 1974, **39,** 24; S. David, *Compt. rend.*, 1974, **278C,** 1051; C. Augé, S. David and A. Veyrières, *J.C.S. Chem. Comm.*, 1976, 375; R. M. Munavu and H. H. Azmant, *J. Org. Chem.*, 1976, **41,** 1832; M. A. Nashed and L. Anderson, *Tetrahedron Letters*, 1976, 3503; *Carbohydrate Res.*, 1977, **56,** 419.
467. D. Dauzonne, P. Demerseman, J. Egyed, C. Lang, N. Platzer, and R. Royer, *Tetrahedron*, 1977, **33,** 19.
468. H. von Brachel and U. Bahr, in Houben-Weyl, 'Methoden der Organischen Chemie', Thieme, Stuttgart, 1970, vol. 5/1c, p. 214.
469. W. J. Hickinbottom, 'Reactions of Organic Compounds', Longmans, London, 1957, p. 143; D. Dieterich, in Houben-Weyl, 'Methoden der Organischen Chemie', Thieme, Stuttgart, 1973, vol. 7/2a, p. 927.
470. C. J. Collins, *Quart. Rev.*, 1960, **14,** 357.
471. (a) T. Yvernault and M. Mazet, *Bull. Soc. chim. France*, 1971, 2652, and references cited; (b) M. Mazet and M. Desmaison-Brut, *ibid.*, 1971, 2656.
472. P. Demerseman, J. Egyed, and R. Royer, *Bull. Soc. chim. France*, 1974, 1364.
473. K. Kaneda, M. Wayaku, T. Imanaka, and S. Teranishi, *Chem. Letters*, 1976, 231.
474. V. Z. Sharf, L. K. Freidlin, and A. A. Nazaryan, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1970, 597, and reference 1 cited; M. Jaubert, M. Mazet and T. Yvernault, *Bull. Soc. chim. France*, 1974, 595.
475. (a) H. Kröper, in Houben-Weyl, 'Methoden der Organischen Chemie', Thieme, Stuttgart, 1965, vol. 6/3, p. 528; (b) B. T. Gillis and P. E. Beck, *J. Org. Chem.*, 1963, **28,** 1388; (c) J. Egyed, P. Demerseman, and R. Royer, *Bull. Soc. chim. France*, 1973, 3014; (d) L. T. Scott and J. O. Naples, *Synthesis*, 1973, 209.
476. M. L. Mihailović, S. Gojković, and Ž. Čeković, *J.C.S. Perkin I*, 1972, 2460; G. Dana and J.-P. Girault, *Bull. Soc. chim. France*, 1972, 1650; J. Jacobus, *J. Org. Chem.*, 1973, **38,** 402; H. Neudeck and K. Schlögl, *Monatsh.*, 1975, **106,** 229.
477. B. G. Hudson and R. Barker, *J. Org. Chem.*, 1967, **32,** 3650; R. Barker, *J. Org. Chem.*, 1970, **35,** 461.
478. S. Soltzberg, *Adv. Carbohydrate Chem. Biochem.*, 1970, **25,** 229.
479. S. Holand and R. Epsztein, *Synthesis*, 1977, 706.
480. A. Balsamo, G. Ceccarelli, P. Crotti, and F. Macchia, *J. Org. Chem.*, 1975, **40,** 473.
481. P. Picard, D. Leclercq, and J. Moulines, *Tetrahedron Letters*, 1975, 2731.
482. B. Delmond, J.-C. Pommier, and J. Valade, *J. Organometallic Chem.*, 1973, **50,** 121, and references cited; J. Biggs, *Tetrahedron Letters*, 1975, 4285.
483. J. C. Martin, J. A. Franz, and R. J. Arhart, *J. Amer. Chem. Soc.*, 1974, **96,** 4604.
484. T. E. Nalesnik and N. L. Holy, *J. Org. Chem.*, 1977, **42,** 372.
485. C. A. Bunton, in Ref. 266a, part A, chapter VI; A. S. Perlin, in Ref. 266c, vol. 1, chapter 4.
486. A. K. Qureshi and B. Sklarz, *J. Chem. Soc.* (*C*), 1966, 412; E. Espinassou, C. le Reste, and M. Guernet, *Analusis*, 1975, **3,** 19.
487. E. S. Huyser and L. G. Rose, *J. Org. Chem.*, 1972, **37,** 851.
488. W. H. Trahanovsky, J. R. Gilmore, and P. C. Heaton, *J. Org. Chem.*, 1973, **38,** 760.
489. R. Konaka and K. Kuruma, *J. Org. Chem.*, 1971, **36,** 1703.
490. A. Goosen and H. A. H. Laue, *J. Chem. Soc.* (*C*), 1969, 383.
491. A. McKillop, R. A. Raphael, and E. C. Taylor, *J. Org. Chem.*, 1972, **37,** 4204.
492. G. Ohloff and W. Giersch, *Angew. Chem. Internat. Edn.*, 1973, **12,** 401.
493. G. de Vries and A. Schors, *Tetrahedron Letters*, 1968, 5689.
494. T. Shono, Y. Matsumura, T. Hashimoto, K. Hibino, H. Hamaguchi, and T. Aoki, *J. Amer. Chem. Soc.*, 1975, **97,** 2546.
495. E. J. Corey, *Pure Appl. Chem.*, 1967, **14,** 19.
496. (a) W. T. Borden, P. W. Concannon, and D. I. Phillips, *Tetrahedron Letters*, 1973, 3161; (b) J. I. G. Cadogan and R. K. Mackie, *Chem. Soc. Rev.*, 1974, **3,** 87.
497. (a) J. Daub, V. Trautz, and U. Erhardt, *Tetrahedron Letters*, 1972, 4435; (b) M. F. Semmelhack and R. D. Stauffer, *ibid.*, 1973, 2267.
498. E. Vedejs and E. S. C. Wu, *J. Org. Chem.*, 1974, **39,** 3641.
499. J. N. Hines, M. J. Peagram, E. J. Thomas, and G. H. Whitham, *J.C.S. Perkin I*, 1973, 2332.
500. M. Guisnet, I. Plouzennec, and R. Maurel, *Compt. rend.*, 1972, **274C,** 2102.
501. G. Crank and F. W. Eastwood, *Austral. J. Chem.*, 1964, **17,** 1392; J. S. Josan and F. W. Eastwood, *ibid.*, 1968, **21,** 2013; T. Hiyama and H. Nozaki, *Bull. Chem. Soc. Japan*, 1973, **46,** 2248.
502. G. Goto, *Bull. Chem. Soc. Japan*, 1977, **50,** 186.

503. F. W. Eastwood, K. J. Harrington, J. S. Josan, and J. L. Pura, *Tetrahedron Letters*, 1970, 5223.
504. J. A. Marshall and M. E. Llewellyn, *Synth. Comm.*, 1975, **5,** 293.
505. P. Stromquist, M. Radcliffe, and W. P. Weber, *Tetrahedron Letters*, 1973, 4523.
506. K. B. Sharpless and T. C. Flood, *J.C.S. Chem. Comm.*, 1972, 370.
507. J. E. McMurry and M. P. Fleming, *J. Org. Chem.*, 1976, **41,** 896, and references cited.
508. J. C. Carnahan and W. D. Closson, *Tetrahedron Letters*, 1972, 3447; S. Bank and M. Platz, *ibid.*, 1973, 2097.

4.2

Phenols

D. A. WHITING
University of Nottingham

4.2.1 THE PHENOLS: INTRODUCTION AND GENERAL PROPERTIES 707
4.2.1.1 Introduction 707
4.2.1.2 Physical properties 709
4.2.1.3 General chemical properties 713
4.2.2 SYNTHETIC METHODS FOR PHENOLS 717
4.2.2.1 Methods involving displacement by hydroxide anion 717
4.2.2.2 Oxidative methods 717
4.2.2.3 Synthesis from aliphatic precursors 721
4.2.3 THE CHEMISTRY OF MONOHYDRIC PHENOLS 730
4.2.3.1 Reactions of the hydroxy group 731
4.2.3.2 The oxidation of phenols 739
4.2.3.3 Reactions of the aromatic ring 754
4.2.3.4 Hydroxypolynuclear hydrocarbons 776
4.2.4 DI-, TRI-, AND POLY-HYDRIC PHENOLS 778
4.2.4.1 Catechol and relatives 778
4.2.4.2 Resorcinol and relatives 780
4.2.4.3 Hydroquinone and relatives 787
4.2.4.4 Polyhydroxybenzenes 787

4.2.1 THE PHENOLS: INTRODUCTION AND GENERAL PROPERTIES

4.2.1.1 Introduction

The term 'phenol', specifically signifying the monohydroxy derivative of benzene, is applied generally to all derivatives of benzene and its relatives having nuclear hydroxy groups. According to the number of hydroxy groups present, the compounds are termed mono-, di-, tri-hydric phenols, *etc.* The salts of phenols are called phenolates or phenoxides; the latter term is preferred by the IUPAC.

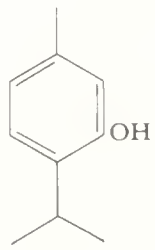
(i) Sources

Crude phenol was first isolated from coal tar by Runge in 1834 as 'carbolic acid'. Substantial quantities of the *o*-, *m*-, and *p*-cresols (hydroxytoluenes) are found in the same source. Currently, little phenol is obtained from coal tar, most of the supply being

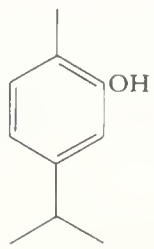
manufactured by cumene oxidation (the Rashig and Dow process) and by sulphonation. The last preparation was discovered by Wurtz and by Kekule (1867); an earlier synthesis was recorded by Hunt (1849). Phenol, cresols, and xylenols (hydroxy-xylenes) are also formed during petroleum cracking; the mixture extracted with alkali is termed 'creosote' and is a useful source of cresols. Phenols are important starting materials in the manufacture of fine chemicals, plastics, dyestuffs, insecticides, and herbicides; they find uses as antioxidants, fungicides (wood preparation), and bactericides. Lister first made use of phenol itself as a germicide in 1867. Higher homologues are generally less toxic.

(ii) Natural occurrence

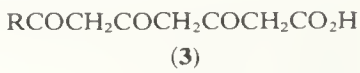
Complex phenols are widespread in Nature but the simple ones are relatively uncommon. Phenol itself is found in mammalian urine, pine needles, and the essential oil of tobacco leaves; *p*-cresol, *p*-allylphenol, thymol (**1**), and carvacrol (**2**) have been detected in other essential oils. Natural phenols are listed in various valuable compendia, *e.g.* those of Karrer,[1a] Devon and Scott,[1b] and Miller.[1c] Phenolic compounds in Nature arise in three important ways, briefly summarized here.



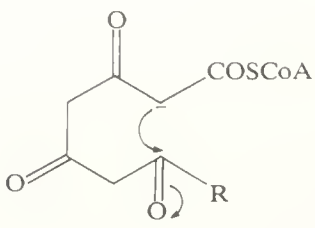
(**1**)



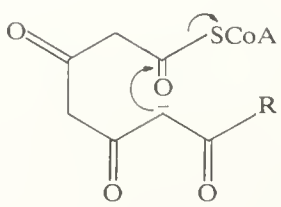
(**2**)



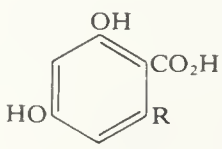
(**3**)



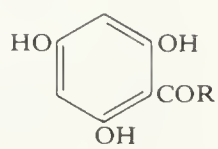
(**4**)



(**5**)

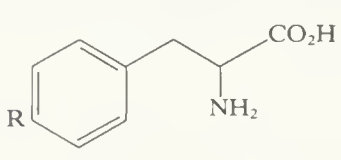


(**6**)

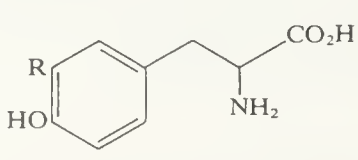


(**7**)

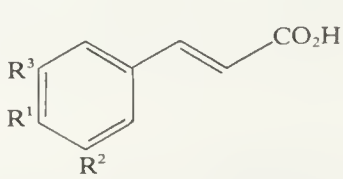
(*a*) Poly-β-ketones (polyketides), *e.g.* (**3**), derived from a 'starter acid' RCO_2H and three malonate units, are intermediates (enzyme-bound) in phenol biosynthesis. Cyclization can be envisaged in manners analogous to the aldol reaction (see **4**) or the Claisen condensation (see **5**), yielding respectively phenolic acids (*e.g.* **6**; with R = Me, orsellinic acid) or phenolic ketones (*e.g.* **7**; with R = Me, phloracetophenone) after enolization of the carbonyl functions. Modification processes may ensue or intervene; thus reduction of a carbonyl to secondary alcohol, away from the cyclization site, may afford a phenol with one less hydroxyl. However, this mode of biogenesis (for reviews see Rickards,[2a] Neish,[2b] and Birch[2c]) leads to phenols with *meta* disposed hydroxyls. This character may be diagnostic of the origin.



(**8**)

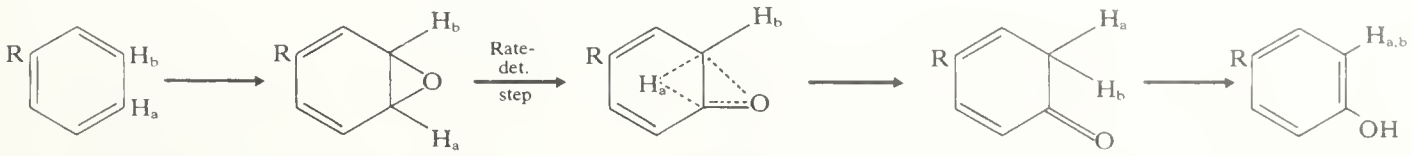


(**9**)



(**10**) $R^1 = R^2 = R^3 = H$
(**11**) $R^1 = OH$, $R^2 = R^3 = H$
(**12**) $R^1 = R^2 = OH$, $R^3 = H$
(**13**) $R^1 = R^2 = R^3 = OH$

(*b*) Aromatic rings may be hydroxylated *in vivo* by mono-oxygenases. Such reactions are often encountered in aromatics derived from the shikimate–prephenate pathway.[3] Thus phenylalanine (**8**; R = H) is *p*-hydroxylated to tyrosine (**9**; R = OH) by phenylalanine mono-oxygenase using molecular oxygen, and cinnamic acid (**10**) can be hydroxylated to *p*-hydroxycinnamic acid (**11**), and on to di- and tri-hydroxy acids, *e.g.* caffeic (**12**) and gallic (**13**) acids, with adjacent hydroxy functions. A useful list of micro–organisms and higher plant mono-oxygenases and phenolases is available.[4] Hydroxylations such as (**8**) → (**9**) may be accompanied by proton rearrangements; thus (**8**; R = D) → (**9**; R = D), the 'National Institute of Health (NIH)' shift. The mechanism[5] is outlined in Scheme 1. Related 'NIH' shifts have been observed *in vitro* for various synthetic arene oxides and in oxidation of aromatics by permanganate and by chromyl compounds,[5c] *e.g.* CrO_2Cl_2, $CrO_2(OAc)_2$.



SCHEME 1

(*c*) Alicyclic rings with oxygen functions may be dehydrogenated to phenols; thus (**1**) and (**2**) are probably derived from monocyclic monoterpenes carrying a 3- or 2-oxygen function, of which there are many examples in Nature. Similarly, phenolic steroids, *e.g.* estrone and equilenin, are likely to be derived in this manner; this route to phenolic products is relatively unstudied.

4.2.1.2 Physical properties

(*i*) *Acidity*

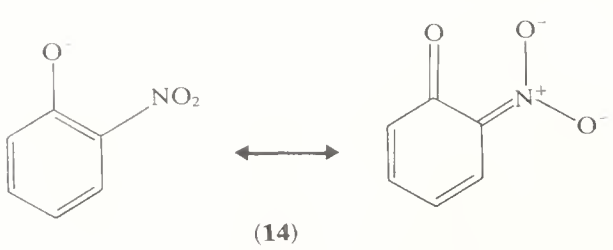
Phenol and its lower homologues are weak acids, generally soluble in aqueous alkali, but not in bicarbonate solutions, and thus easily distinguished from simple carboxylic acids: the pK_a values of phenol and benzoic acid are 9.94 and 4.18, respectively. Electron-withdrawing substituents, particularly in the *ortho* and/or *para* positions, enhance, and electron-donating groups suppress, the acid character of phenols. In general the acidity can be calculated for a substituted phenol from the relation:

$$pK_a = 9.94 - 2.26\Sigma\sigma$$

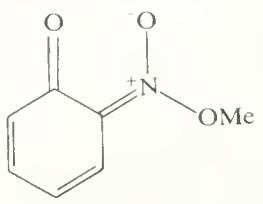
where $\Sigma\sigma$ is the sum of individual σ constants for the substituents. The expression gives a satisfactory answer only when electronic factors dominate the acidity; other factors may intervene. Thus steric factors may decrease acidity (steric inhibition of solvation); phenols with bulky *para* substituents are generally soluble only in hot concentrated alkali, while phenols with large *ortho* groups are insoluble in aqueous alkali. Some such phenols ('cryptophenols') may be dissolved in media of stronger basicity (*e.g.* Claisen's alkali, 35% potassium hydroxide in 20% aqueous methanol). Extremely large *ortho* substituents may render the deprotonation rate negligibly low, *e.g.* 2,4,6-tri-t-pentylphenol does not react with sodium in liquid ammonia. There is some evidence that phenols are more acidic in the electronically excited state.[6]

p-Fluoro-, *p*-chloro-, *p*-bromo-, and *p*-iodo-phenols have pK_a values of 9.95, 9.38, 9.36, and 9.31, respectively. Trichloro- and tribromo-phenols are sufficiently acidic to decompose alkali metal carbonates, and pentachlorophenol (pK_a 5.26) can be titrated with standard alkali and Thymol Blue. Pentafluorophenol (pK_a 5.5) is slightly less acidic than pentachlorophenol. Useful acid strength data are given by Albert and Serjeant.[7]

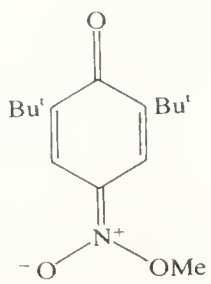
Nitrophenols are much stronger acids than alkylphenols; phenol, 2-nitrophenol, 2,4-dinitrophenol, and 2,4,6-trinitrophenol have pK_a values of 9.94, 7.23, 4.01, and 0.71, respectively. Salts of nitrophenols are more intensely coloured than the parent phenols, an effect usually attributed to resonance involving quinonoid forms, as in (**14**). In support, two series of ethers have been obtained from some nitrophenols, *e.g.* 2-nitrophenol affords the almost colourless *O*-methyl ether and the deep yellow, and unstable, azo-quinonoid ether (**15**); the *p*-azoquinonoid (**16**) has been obtained as an orange solid.[8a] The reasons why *m*-nitrophenols also yield coloured salts are less obvious.[8b]



(**14**)



(**15**)



(**16**)

Other functions with a $-M$ effect may have a similar acid-strengthening effect; thus *p*-hydroxyacetophenone or *p*-hydroxybenzaldehyde are more acidic than phenol. However, the *ortho* isomers, *e.g.* salicylaldehyde (*o*-hydroxybenzaldehyde), have functions engaged in hydrogen bonding: proton abstraction is thus relatively slow. Although salicylaldehyde forms a stable yellow sodium salt, it is only slowly extracted from ether by aqueous sodium hydroxide.

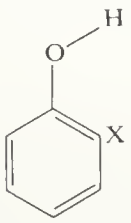
Methoxy and amino groups decrease phenol acidity; *p*-methoxyphenol has a pK_a of 10.21 and *p*-aminophenol has a pK_a of 10.3. The aminophenols behave as weak bases (*p*-aminophenol has a pK_b of 5.5), giving salts with mineral acids. Dihydric phenols are slightly more acidic than phenol; 1,2-, 1,3-, and 1,4-dihydroxybenzenes have pK_a values of 9.25, 9.20, and 9.91 (first dissociation), respectively. Stabilization of the anions by hydrogen bonding contributes to this effect.

(*ii*) *Spectroscopic data*

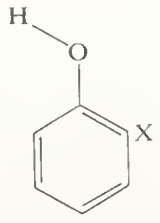
Introduction of a hydroxy group into the benzene nucleus shifts the u.v. absorption bands to longer wavelength and intensifies them; phenol absorbs at 210.5 (ε 6200) and 270 (1450) nm. The effect of substituents and solvents on these maxima has been discussed.[9a] A bathochromic shift is observed when phenolic solutions are made basic; such a shift can be useful in diagnosis of phenol structure and has been employed in analysis.[9b] Various reactions of phenols have been utilized to yield products absorbing visible light; these can be used for qualitative detection of phenols and sometimes for quantitative analysis. Thus neutral ferric chloride solution gives a green-blue colour with phenols (red-violet with *ortho*-carbonyl containing phenols) and red with nitrous acid–mercuric nitrate (Millon's test). Gibbs' reagent (2,6-dichloroquinone-4-chloroimine) tests for phenols with a free *para* position. Diazonium coupling and the antipyrine reaction have been used for quantitative purposes: see the standard works of Feigl[10a] and Zweig[10b] for fuller accounts.

Infrared absorptions of phenols are chiefly of interest in connection with hydrogen bonding; this topic has been reviewed.[11] Phenol itself in carbon tetrachloride shows monomer phenol ν_{OH} at 3611 cm^{-1} and various intermolecular H-bonded vibrations: Ph—O(H)$\cdots$ at 3599 cm^{-1}, Ph—O—H$\cdots$ at 3481 cm^{-1}, and Ph—O(H)$\cdots$ at 3393 cm^{-1}. The ν_{OH} values for phenols as H-bond donors to various acceptors have been measured and $K_{association}$ and ν_{OH} can be correlated. The π-electrons of an aromatic ring[12a] may serve as an acceptor, *e.g.* in 2-hydroxybiphenyl, as may the π-electrons of an olefinic linkage.[12b]

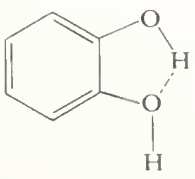
2-Substituted phenols exist as *s-cis* (**17**) or *s-trans* (**18**) isomers.[13a] With bulky 2-substituents the *s-trans* conformation becomes preferred. Even for 2,6-di-t-butylphenol the hydroxy function is coplanar with the aryl ring. If a substituent is an H-bond acceptor, then intramolecular H-bonding leads to a preference for the *s-cis* conformation: catechol (**19**) shows two absorptions, of about equal intensity, at 3618 cm^{-1} (OH with O as H-bond acceptor) and 3570 cm^{-1} (OH as donor). The 1,2,3-triol pyrogallol (**20**) exists mainly in the conformation shown, with two intramolecular H-bonds. The out-of-plane deformation, γ_{OH}, of the OH function occurs in the 300–860 cm^{-1} region:[13b] the stronger H-bonds resonate at higher γ_{OH}. There is no general correlation between OH · · · X and OD · · · X intramolecular H-bond strengths; the latter may be weaker or stronger depending on the particular geometry.



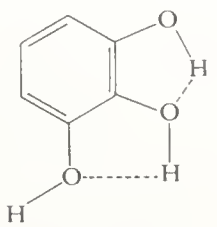
(**17**)



(**18**)

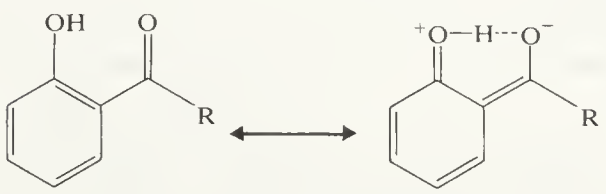


(**19**)

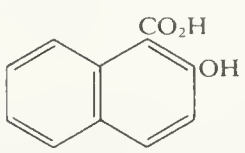


(**20**)

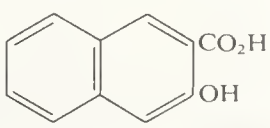
Strong H-bonds occur when an *ortho* carbonyl function is present in a phenol; the ν_{OH} absorption is moved substantially, *ca.* 350–500 cm^{-1} (to lower wavenumber) and becomes very broad. A six-membered 'chelate' ring is formed; the strength of the H-bond is confirmed by measurement of enthalpies of formation, *e.g.* −20.9 kJ mol^{-1} for *o*-hydroxybenzoic acid. The contribution of resonance forms such as (**21**) is implied. In these cases the strength of the H-bond is dependent on the the bond order in the C-1—C-2 π-bond. This is apparent from chemical evidence but is also shown in, for example, the enthalpies of formation of the H-bonds in the hydroxynaphthoic acids (**22**) and (**23**), which are −30.8 and −20.4 kJ mol^{-1}, respectively. A degree of bond fixation is recognized in naphthalene derivatives in the sense shown; (**22**) with more C-1—C-2 π-character forms a significantly stronger H-bond.



(**21**)



(**22**)

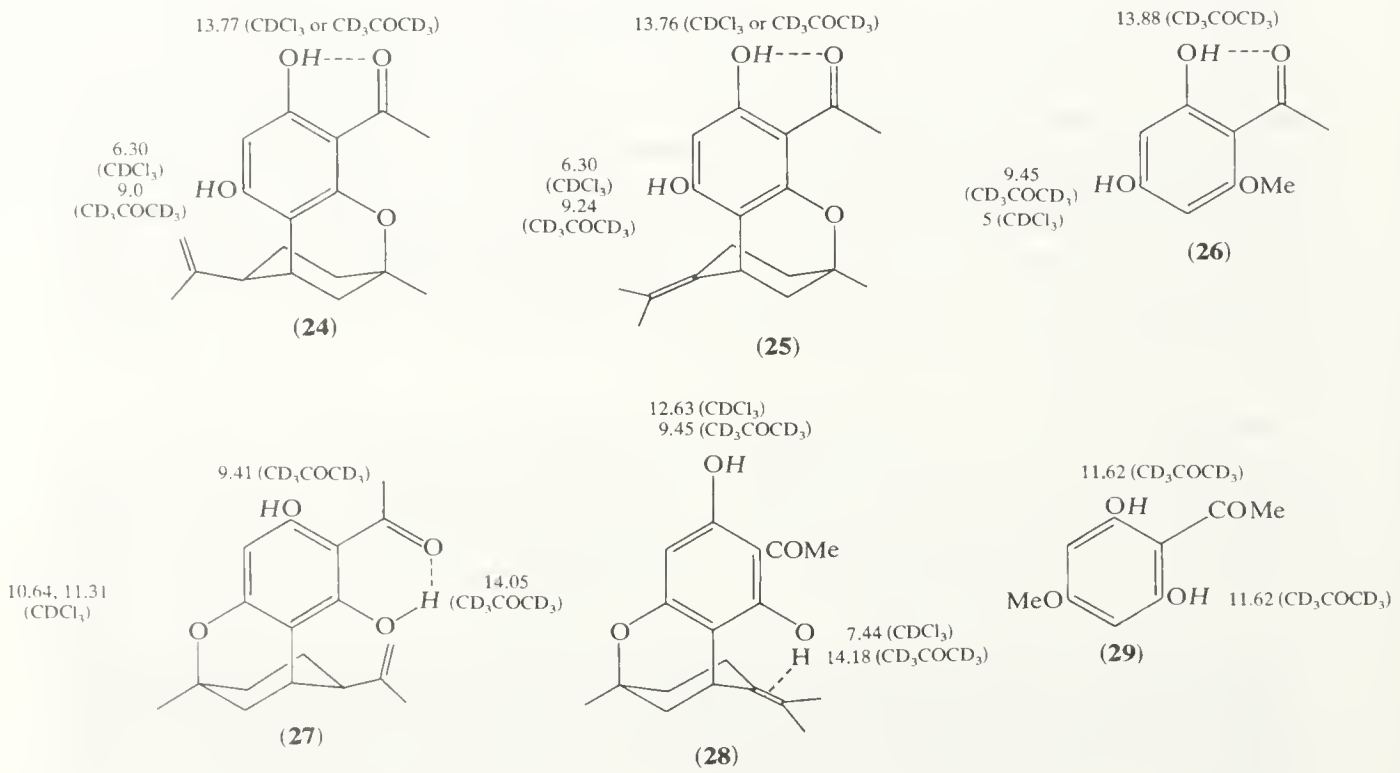


(**23**)

Substituents at the 3-position in 1-hydroxy-2-carbonyl arenes increase the H-bond strength by forcing the carbonyl function closer to the hydroxyl. Such buttressing, however, with large substituents may force the carbonyl out of plane and reduce H-bonding.

In ^1H n.m.r. spectroscopy the chemical shifts of aromatic protons are well documented in many texts devoted to spectroscopic methods. In simple phenols and their derivatives, such shifts may generally be understood in terms of the electronic effects of substituents. Thus hydroxy or alkoxy substitution into benzene causes marked upfield shifts of *ortho* and *para* protons: for OH, Δ_o, Δ_m, Δ_p (in p.p.m. from benzene at δ7.27 in deuteriochloroform) are −0.49, −0.13, and −0.20, respectively. The corresponding shifts for the methoxy group are −0.46, −0.10, and −0.41. Acylation reduces electron release into the ring; for OCOR the $\Delta_{o,m,p}$ parameters are about −0.2, +0.1, and −0.2. Acetylation of a phenolic hydroxyl will thus induce downfield shift (0.2–0.5 p.p.m.) of the *ortho* proton.[14]

Esterification of hydroxyls may, through spatial anisotropy effects, alter chemical shifts in other structural units in a complex phenol. Thus the difficult problems of orientation in phenolic chromens can sometimes be solved from such data.[15] Solvent-induced shifts are also of value in structural work,[16a] *e.g.* methoxy protons, *ortho* to an aromatic hydrogen, shift upfield (*ca.* 0.3–0.5 p.p.m.) on changing from chloroform to benzene as solvent and when the methoxy group is the major solvation site. Solvent-induced changes in chemical shift have been observed and usefully rationalized for various proton groups in a number of cases.[16] Small spin–spin couplings (five bond) have been observed between methoxy and *ortho* aromatic protons; couplings (<1 Hz) have also been recorded between aromatic protons and methyl or methylene groups attached to the ring.[17] Significant n.O.e. can be observed between methoxy and *ortho* aromatic protons,[18a] and between hydroxy and *ortho* aromatic protons.[18b] Phenols with a single hydroxy group provide an unambiguous site for binding of lanthanide ions and the induced chemical shifts have been analysed.[19] The hydroxy proton appears in ^{1}H n.m.r. spectra over a wide range and shifts vary widely with temperature, concentration, pH, and solvent; signals are often broad, which can lead to difficulty in location. In deuteriochloroform, hydroxyls not engaged in strong hydrogen bonding congregate in the range δ 4.5–7.5, while those involved in chelation appear at lower field — down to *ca.* 14.5 p.p.m. Signals of the latter type are generally sharp. In deuterioacetone or deuteriodimethyl sulphoxide, hydrogen bonding to the solvent produces sharper signals in a narrower range. The ramifications that can arise in complex phenols are nicely illustrated by the O*H* shift data for the dihydric phenols (**24**)–(**29**).[20]



The 2,4-dihydroxy examples (**24**)–(**26**) show the chelated C-2 hydroxy group near δ 13.8 in either deuteriochloroform or deuterioacetone, the intramolecular H-bond with the carbonyl group being stronger than that with the solvent. The C-4 hydroxy group resonates near δ 6.3 in deuteriochloroform but is shifted to *ca.* δ 9 in the ketonic solvent by intermolecular bonding. In the isomeric series, (**29**) shows equivalent hydroxy protons with relatively fast rotation of the acetyl group between equivalent conformations. In deuteriochloroform, (**27**) shows two signals at intermediate shift values, as a result of equilibrium between the two non-equivalent conformations involving acetyl rotation; however, in deuterioacetone, hydrogen bonding is maximized by the adoption of one

conformation only; the shift data are thus close to those of isomer (**24**). Data for (**28**) are similar in deuterioacetone to those for (**27**), but in deuteriochloroform the spectra suggest the intervention of a weak H-bond between the C-6 hydroxy group and the adjacent trisubstituted π-bond; the C-2 hydroxy group is occupied with the carbonyl group and conformational freedom is again restricted.

^{13}C N.m.r. spectroscopic data for phenolic compounds have also become abundantly available in recent years and several invaluable compilations have been made, *e.g.* by Stothers[21a] and by Levy and Nelson.[21b] Substituent shifts for benzene derivatives have been extracted; for OH, $\Delta_{o,m,p}$ are −12.7, +1.4, and −7.3, respectively, while for OMe the corresponding shifts are −14.4, +1.0, and −7.7. These shifts are additive and provide a surprisingly good guide to the interpretation of the ^{13}C n.m.r. spectra of complex phenolic molecules, *e.g.* Ref. 21c and refs. therein. Relatively little data on ^{13}C relaxation times have been published, but such measurements promise to be of value. ^{13}C–^{1}H coupling, involving the protons of chelated hydroxyls, has been observed.[22]

4.2.1.3 General chemical properties

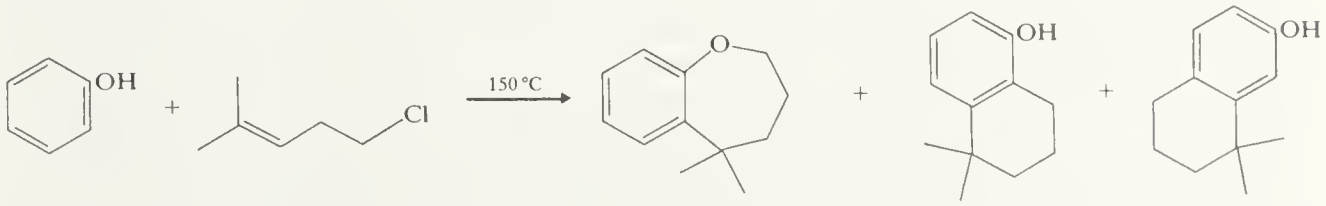
In Section 4.2.3 the chemistry of phenols is discussed in detail; at this point, only the general scope of reactivity of the group will be mentioned. Phenol chemistry is dominated by the nucleophilicity of the system and its propensity for varied reactions with a wide range of electrophiles. Both neutral and ionized phenols are ambident nucleophiles and may react at O or C centres with neutral or positively charged electrophiles.

The ambident phenoxide ion has received substantial attention. ^{1}H N.m.r. spectroscopic data show that simple sodium phenoxides in methanol carry at least 10% of the negative charge at the *ortho* and *para* carbons. In the ^{1}H n.m.r. spectra, protons at *para* carbons are markedly shifted upfield in these conditions; the effect at the *ortho* protons is partly counteracted by the deshielding of the counter-ion and/or H-bonded solvent molecules. The addition of dimethyl sulphoxide decreases these counteracting effects and large upfield shifts of *ortho* protons result.[23] The alkylation of bidentate phenoxide ions has been reviewed[24a] and many of the factors involved have been investigated.[24] These factors are related to those involved in the alkylation and acylation of β-dicarbonyl compounds. *C*-Alkylation is generally favoured when the aryloxide is heavily solvated, *e.g.* in water or fluoroalkanols, by tight ion pairs, and by alkylation with soft electrophiles; solvation of the leaving group may be important. *O*-Alkylation is favoured with the aryloxide unsolvated, but with the counter-ion solvated, or by loose ion pairs. Solvents such as DMSO and DMF, hard electrophiles, and complexations of metal counter-ions by crown ethers all promote *O*-alkylation.

Sodium β-naphthoxide displays a more even balance between *C*- and *O*-alkylation than sodium phenoxide: benzylation of the former with benzyl bromide proceeds to 95% *O*-benzyl ether in DMSO, but to 85% *C*-benzyl ether in 2,2,2-trifluoroethanol. These generalizations may not apply to heterogeneous alkylations.

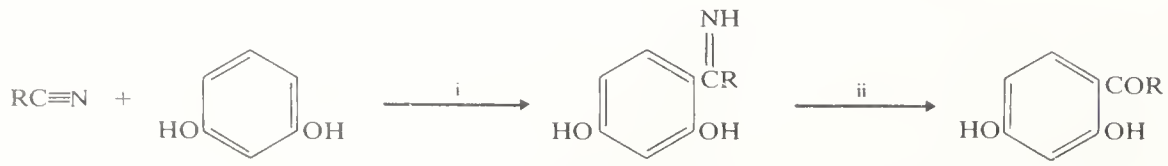
Neutral phenol molecules may also exhibit ambident nucleophilicity: Scheme 2 shows the reaction of phenol with 5-chloro-2-methylpent-2-ene at 150 °C, giving products stemming from both *C*- and *O*-alkylation.[25]

The general mesomeric enhancement by the hydroxy group to electrophilic substitution in the aromatic ring (*ortho*/*para* directing) leads to ready reaction with weak electrophiles, and this reactivity is even more pronounced in di- and poly-hydric phenols. Some classes



SCHEME 2

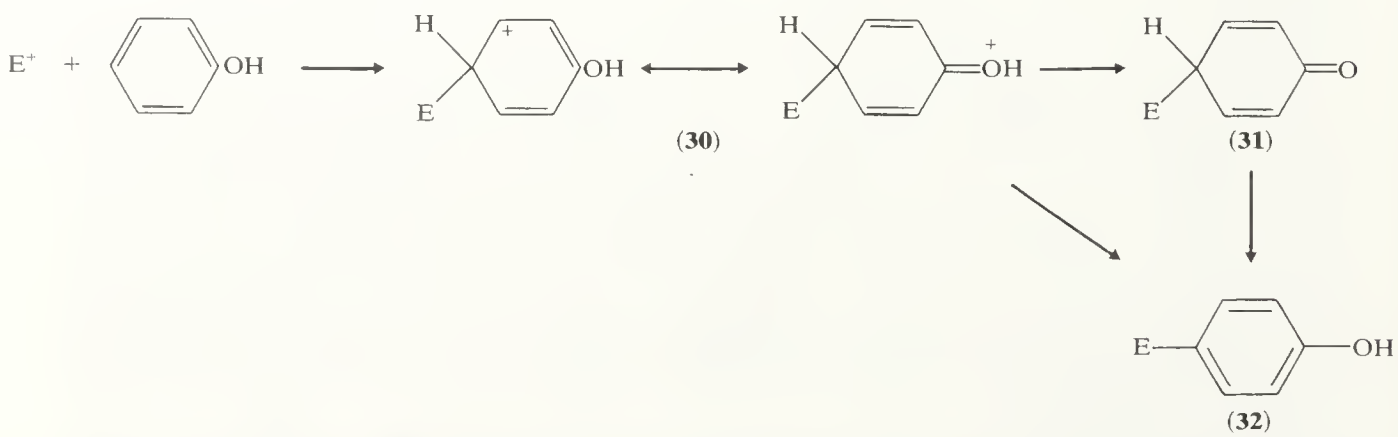
of electrophilic reaction are thus largely confined to phenolic substrates. For example, the Houben–Hoesch reaction (Scheme 3), involving the generation of electrophilic iminium ion from nitriles by acid catalysts, is a practical proposition only with reactive phenols. Also, resorcinols and phloroglucinols (1,3-di- and 1,3,5-tri-hydroxyphenols) can be substituted by electrophilic carbons in reactions with α,β-unsaturated aldehydes, and even acetals, under pyridine catalysis.



i, $ZnCl_2$, HCl; ii, H_3O^+.

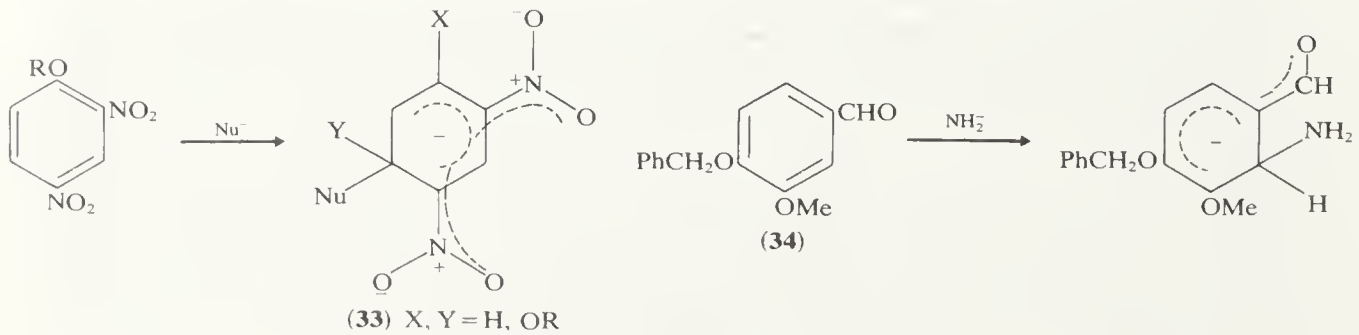
SCHEME 3

Two other features distinguish reactions in phenols from similar reactions in other aromatic compounds, apart from increased reactivity. Firstly, the *ortho/para* ratios are often high, *i.e. ortho* substitution products quite often predominate; this may reflect hydrogen-bonding and/or oxygen coordination with acid catalysts involved in the reaction. Secondly, the intermediate (**30**), formed by addition of electrophile (only *para* substitution shown) to the phenolic nucleus (Scheme 4), may lose a proton from carbon to form phenolic product (**32**) directly or it may lose a proton from oxygen to give a dienone (**31**) as a second intermediate; (**31**) can then tautomerize to (**32**). If tautomerism is blocked, dienone products can be isolated.



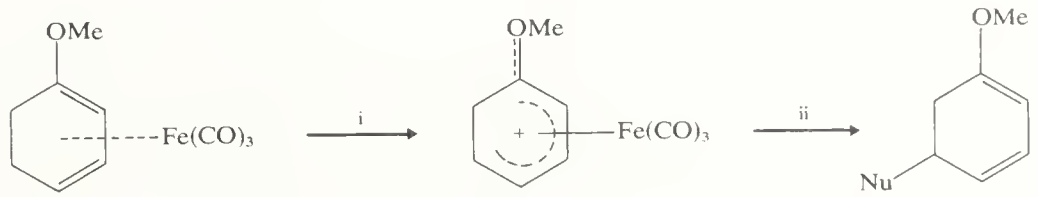
SCHEME 4

Nucleophilic substitution is not known in simple phenols but is a matter of importance in certain substituted derivatives. Thus nitrophenyl ethers are effective acceptors of nucleophiles as in (**33**); such compounds, called 'Meisenheimer complexes', are briefly described below under 'nitrophenols', although other phenolic compounds with $-M$ substituents may behave similarly, *e.g.* the aldehyde (**34**).



(**33**) X, Y = H, OR

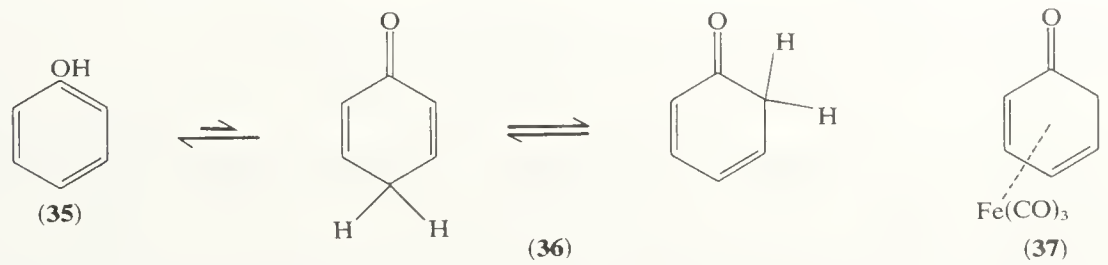
In an interesting reversal of reactivity, phenols can be made subject to nucleophilic attack in an indirect way through Birch reduction of their methyl ethers to methoxycyclohexa-1,4-dienes; iron tricarbonyl adducts of these can be oxidized by the triphenylmethyl cation to afford stabilized carbenium ions which may then trap added nucleophile. The products are substituted dihydrophenyl ethers with potential for aromatization. This sequence[26] is sketched in Scheme 5.



i, Ph_3C^+; ii, Nu^-.

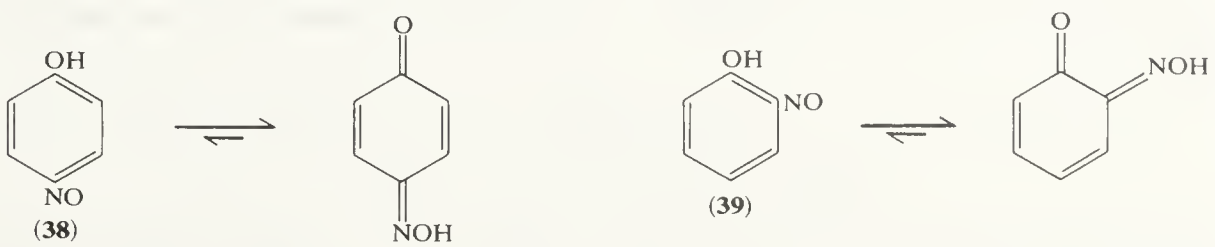
SCHEME 5

Simple phenols exist exclusively in the enolic form (**35**), tautomerism to ketonic forms (**36**) being accompanied by a decrease in resonance energy of about 146 kJ mol^{-1}. A dienone tautomer of phenol, trapped as its iron tricarbonyl complex (**37**), is known, and gives a 2,4-dinitrophenylhydrazone in acid solution. It is prepared by an indirect route from anisole.



(**35**) (**36**) (**37**)

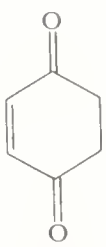
Certain phenols with strongly electron-withdrawing *ortho* or *para* groups do exist as an equilibrium mixture of tautomers, *e.g.* *p*-nitrosophenol (**38**) and *p*-benzoquinone oxime with *ca.* 80% as the quinonoid (from spectroscopic measurements[27]); the *ortho* isomer (**39**) prefers the phenol form.



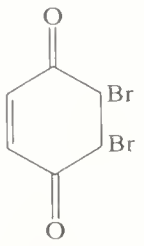
(**38**) (**39**)

Dihydric phenols should show a greater tendency to ketonize than phenol since the energy barriers between the forms are lower. There is no evidence for any great concentration of keto forms in solution for hydroquinones (1,4-dihydroxybenzenes), although the diketone (**40**) has been prepared; this is stable in the solid state at 0 °C for long periods. Rearrangement to hydroquinone is slow in aprotic solvents, but fast in protic media, and not reversible; the stability of (**40**) is due to kinetic and not thermodynamic factors.[28] The dibromodiketone (**41**) is available from addition of bromine to *p*-benzoquinone; enolization of (**41**) is also irreversible. There is abundant evidence for *m*-dihydric phenols to show that *oxo* forms, again not isolable, mediate in many reactions, especially in basic media: *e.g.* resorcinol has long been known to yield cyclohexane-1,4-dione (**42**) on hydrogenation in alkaline solution. 1,3,5-Trihydroxybenzene (phloroglucinol) exists in the enol form,[29] but its dianion (**43**) prefers the oxo form shown; its ^1H

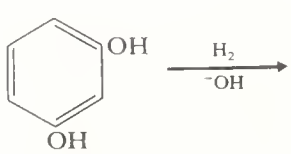
n.m.r. spectrum shows olefinic and methylene, but no aromatic, protons. This change in constitution produces a large increase in the second acid dissociation constant for phloroglucinol compared with other di- and tri-hydric phenols. Phloroglucinol, like resorcinol, exhibits many of the reactions of ketones.



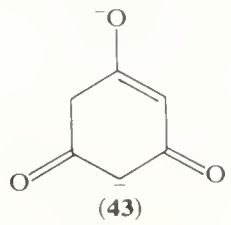
(40)



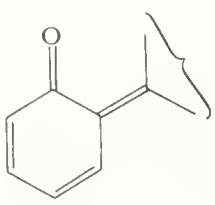
(41)



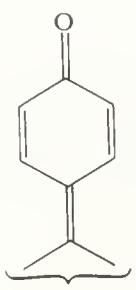
(42)



(43)



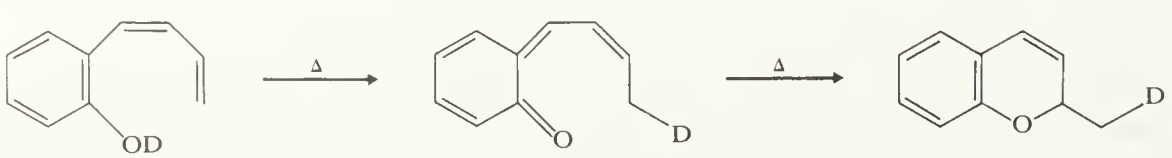
(44)



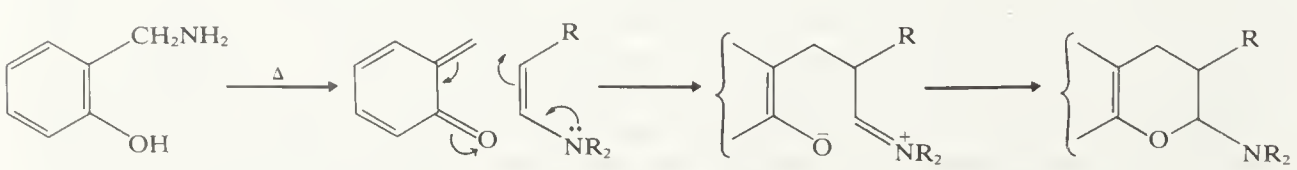
(45)

Most phenols can be induced to participate in ^{18}O isotope exchange processes,[30] and deuteriation/tritiation of *ortho* and *para* protons can be effected by base-catalysed exchange.[31]

One branch of phenol chemistry that warrants mention here is the formation of quinone methides from alkylphenols; *ortho* (**44**) and *para* (**45**) forms are known. These can be produced in varied reactions, including oxidation (see Section 4.2.3.2), prototropic shifts, and 1,4-eliminations. A full review cannot be made here, but some examples are (i) photoenolization[32] of *o*-acylphenols, (ii) thermally allowed prototropic shifts, *e.g.* the 1,7-shift in Scheme 6,[33] and (iii) elimination from phenolic Mannich bases[34] (Scheme 7); differing fates of the quinone methides are illustrated. Other examples appear later in this text.



SCHEME 6



SCHEME 7

4.2.2 SYNTHETIC METHODS FOR PHENOLS

4.2.2.1 Methods involving displacement by hydroxide anion

(i) From aryl halides

This is an important industrial method for the production of phenol. In the continuous process developed by Dow, chlorobenzene is hydrolysed by 10–20% aqueous sodium hydroxide at 350–400 °C under pressure.[35a] In the related Rashig method, phenol is produced by passing benzene, air, and hydrogen chloride through an aluminium–copper–iron hydroxide catalyst at about 200 °C. A two-step reaction ensues:

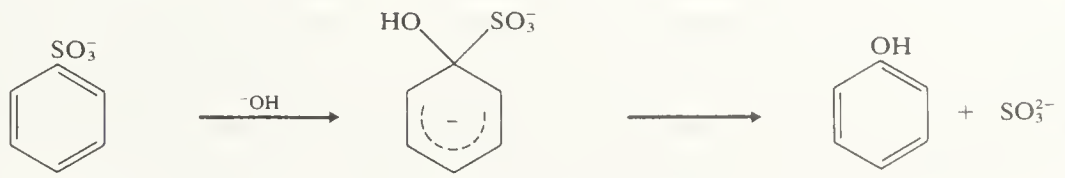
$$C_6H_6 + HCl + \tfrac{1}{2}O_2 \rightarrow C_6H_5Cl + H_2O$$
$$C_6H_5Cl + H_2O \rightarrow C_6H_5OH + HCl$$

Hydrogen chloride produced in the second step is recycled.[35b]

Aryl halides with *ortho* or *para* electron-withdrawing groups (notably NO_2) react relatively readily with hydroxide or alkoxide ions to give phenols or phenol ethers.[36]

(ii) From sulphonic acids

Fusion of an arenesulphonic acid with alkali at about 300 °C gives the corresponding phenol in good yield, generally. The reaction is a simple type of aromatic substitution,[37a] as shown in Scheme 8. A typical procedure is described by Hartman.[37b] Aryl sulphones behave similarly.[37c]



SCHEME 8

(iii) From diazonium salts

Hydrolysis of arene diazonium salts in acid solution is considered to be a rare example of an S_N1 reaction involving an aryl cation,[38] which combines rapidly with water:

$$ArN_2^+ X^- \longrightarrow Ar^+ + N_2 + X^- \xrightarrow{H_2O} ArOH + HX$$

Under alkaline conditions, the phenoxide formed condenses rapidly with unchanged diazonium salt. An intriguing rearrangement ($ArN^*{\equiv}N \rightarrow ArN{\equiv}N^{*+}$) accompanies hydrolysis.[38b]

4.2.2.2 Oxidative methods

(i) Direct oxidation of the aromatic nucleus

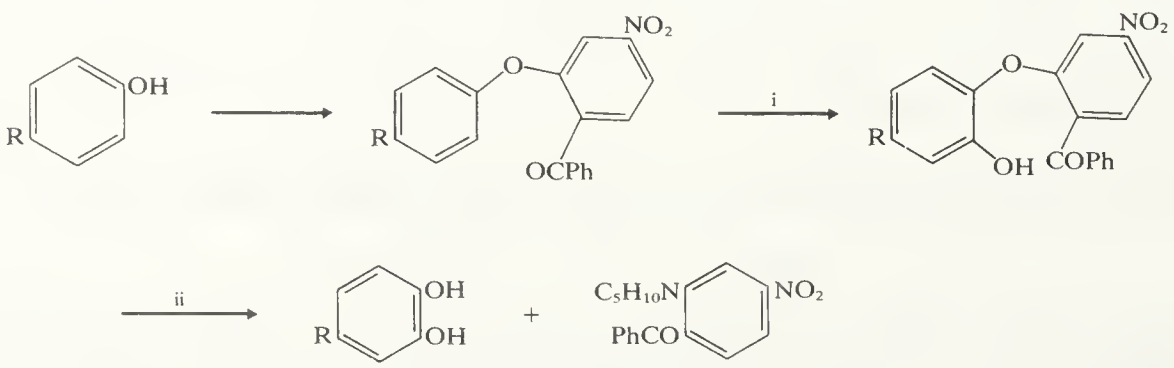
Oxygen, and a great variety of peroxy compounds, have been utilized to oxidize arenes to phenols. In the presence of acid catalysts these reagents may often function as electrophiles (heterolytic mode), or they may react homolytically, providing oxygen

radicals. Appropriate directive effects operate. Although many useful reactions of this type are known with relatively simple phenols, applications in the synthesis of complex molecules are not widespread, since an aromatic nucleus is often not the most readily oxidizable site in the substrate and because phenolic products are likely to be oxidized readily themselves.

(*a*) *With oxygen.* In the gaseous phase, benzene can be oxidized to phenol by air[39a] and fairly good yields (40–60%) may be obtained by using atomic oxygen and catalytic quantities of iodine or cyclohexane. Copper and iron salts efficiently catalyse aerial oxidation in the liquid phase. Thus phenol (~60%) is produced from mixtures of benzene and aqueous cupric sulphate.[39b] A more economic industrial route[40] can involve the sequence benzene → cyclohexane → cyclohexanol → phenol; the hydrogen from the dehydrogenation step can be utilized for the reduction stage.

(*b*) *Hydroxylation.* Free-radical hydroxylation of aromatic compounds is of great interest in relation to biological hydroxylation processes, and a variety of reagents have been used to mimic mixed-function oxidases. These are usually based either on hydrogen peroxide with a transition metal catalyst and a 'redox buffer', *e.g.* $Fe^{2+}+H_2O_2$ (Fenton's reagent), $Ti^{3+}+H_2O_2$, $Fe^{2+}+H_2O_2+$catechol (Hamilton's reagent), or on oxygen, *e.g.* $O_2+Fe^{2+}+$ ascorbic acid+EDTA (Udenfriend's reagent). Their general and physical organic chemistry has been reviewed.[41] Their synthetic value is limited, low yields of *ortho*/*para* products resulting. However, acetanilide has been *ortho* hydroxylated in 46% yield,[42] and phenol (57%) has been obtained from benzene with $H_2O_2+Fe^{2+}+Cu^{2+}$.[43]

Radical hydroxylation may also be achieved radiolytically.[41b] Benz[^{14}C]oic acid usefully provides the constitutionally isomeric hydroxybenz[^{14}C]oic acids; these isomers equilibrate under the reaction conditions, presumably *via* valence tautomerism. Photolytic hydroxylation is theoretically possible since water dissociates homolytically on irradiation with light below 240 nm, but there are no applications as yet, although hydrogen peroxide and light convert phenol to catechol and hydroquinone.[43] Electrophilic oxygenation using hydrogen peroxide with acid catalysts is also known; it has been employed for *ortho* hydroxylation (H-bonding control) of phenols, as shown in Scheme 9.[44]

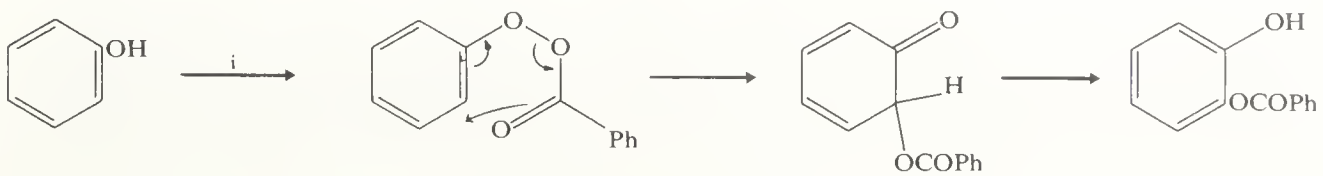


i, H_2O_2, H_2SO_4; ii, piperidine.

SCHEME 9

(*c*) *Peroxy compounds.* Aryl peroxides, aroyl peroxides, arenesulphonyl peroxides, peroxy acids, and peroxy esters have all been utilized for hydroxylation and acyloxylation. Di-isopropyl peroxydicarbonate ($Pr^iOCOO_2COOPr^i$) is one of the more useful reagents,[45] giving fair yields with little side reaction; it may be employed with aluminium chloride for electrophilic acyloxylation — toluene gives 52% of *ortho*/*para* (*ca.* 1 : 2) products while anisole affords 76% of *ortho*/*para* (1 : 4) products — or for radical substitution with cuprous chloride and heat or light for initiation; *ortho*/*para* substitution still predominates. *m*-Nitrobenzenesulphonyl peroxide decomposes thermally in aromatic solvents to give

good yields of esters (55–70%) from which the phenols are, of course, easily obtained: ionic intermediates are postulated.[46] Peroxy acid oxidation may be effective. In particular, trifluoroperacetic acid, alone or with boron trifluoride, gives reasonable yields of phenol trifluoroacetates,[47] *e.g.* mesitol (80%) from mesitylene. Mixtures of hydrogen peroxide and sulphuric acid may react similarly. However, in either case, rearrangements may be initiated by the strong acid conditions, *e.g.* 1,2,3,4-tetramethylbenzene gives 2,3,4,6-tetramethylphenol on treatment with trifluoroperacetic acid. Benzoyloxylation with benzoyl peroxide introduces a benzoyl unit mainly *ortho* to an existing hydroxyl, but *para* products can be formed by [3,3] migration of the acyloxy group around the ring periphery of the dienone intermediates.[48a] Other diacyl peroxides behave similarly. The mechanism of Scheme 10 has been proposed to rationalize the predominance of (initial) *ortho* substitution.[48b]



i, PhCO—OO—COPh.

SCHEME 10

(*d*) *Lead tetra-acetate.* Acyloxylation may also be carried out using lead(IV) salts, *e.g.* lead tetra-acetate or tetra(trifluoroacetate), with modest yields[49] (*cf.* Section 4.2.3.2).

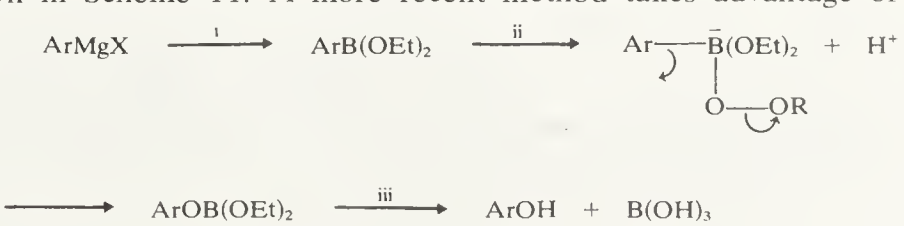
(*e*) *Elbs reaction.* Yet another oxidation which can be useful in the appropriate circumstances is the Elbs persulphate reaction,[50] which introduces a second hydroxyl into a phenol in the *para* position, or, if this is occupied, into the *ortho* site. Potassium persulphate in alkaline medium is employed, and kinetic studies have shown that a bimolecular reaction between phenoxide and persulphate anions takes place.[50c] Mixtures of potassium persulphate and palladium acetate will effect direct acetoxylation; in the presence of 2,2′-bipyridyl, *ca.* 60% of the *meta* acetoxy product was formed from each of chlorobenzene, toluene, and anisole.

(*ii*) *Oxidation* via *organometallic intermediates*

Autoxidation of an aryl Grignard reagent or aryl-lithium gives a mixture of products which includes the phenol in variable yield:[51]

$$ArLi + O_2 \longrightarrow ArOOLi \xrightarrow{ArLi} 2ArOLi \xrightarrow{H_2O} 2ArOH$$

More efficiently, Grignard reagents may be reacted with ethyl borate; the resulting aryl borinic ester can be oxidized to a phenol with hydrogen peroxide or t-butyl hydroperoxide,[52] as shown in Scheme 11. A more recent method takes advantage of the ready



i, $B(OEt)_3$; ii, HOOR; iii, H_2O.

SCHEME 11

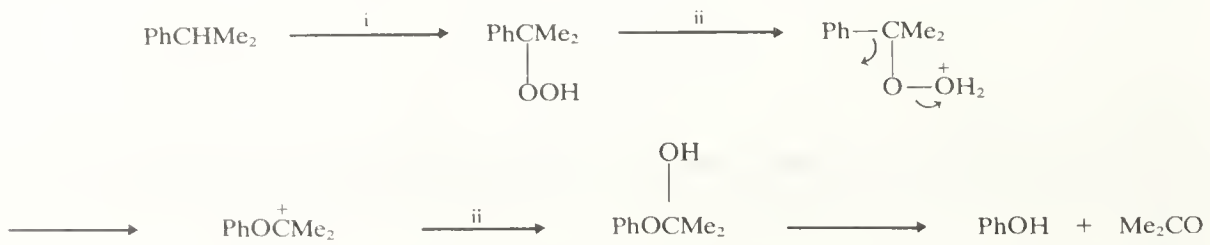
thallation of aromatics by thallium(III) trifluoroacetate;[53] the resulting arylthallium bis(trifluoroacetate) is successively treated with lead tetra-acetate and triphenyl phosphine to form the aryl trifluoroacetate (Scheme 12). *p*-Cresol can be obtained from toluene in 62% yield.

i, $Tl(OCOCF_3)_3$; ii, $Pb(OAc)_4$; iii, Ph_3P; iv, ^-OH.

SCHEME 12

(*iii*) *Reactions involving aryl migration to oxygen*

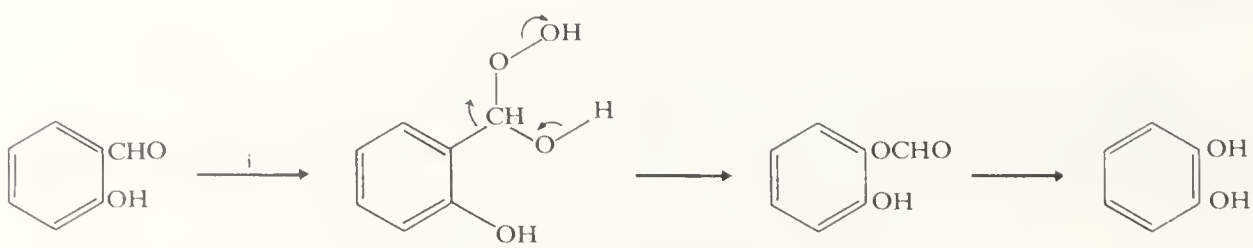
(*a*) *Hydroperoxide decomposition.* Decomposition with acid of benzylic hydroperoxides derived from alkylbenzenes gives good yields of phenols. Proton-induced rearrangement of cumyl hydroperoxide at *ca.* 50 °C is an economical commercial process of phenol production (*cf.* Section 4.6.1.1) with acetone as a useful by-product (Scheme 13).[54]



i, O_2; ii, H^+, H_2O.

SCHEME 13

(*b*) *Dakin reaction.* The oxidation of aromatic aldehydes with alkaline hydrogen peroxide leads *via* rearrangement to formyl esters of phenols. This reaction is effective for phenolic arylaldehydes (particularly salicylaldehyde, Scheme 14), but in other cases a high proportion of aryl carboxylic acid can result.



i, H_2O_2, ^-OH.

SCHEME 14

(*c*) *Baeyer–Villiger oxidation.* Peroxy acid oxidation of aromatic carbonyl compounds is a good method for preparing phenols.[55] Ketone oxidation is preferred, since the use of aldehydes is usually dogged by unwanted by-products. Combined with acylation, it provides a valuable method for introducing a hydroxy group into an aromatic ring; thus sesamol, 3,4-dimethoxyphenol, frequently required in natural product synthesis, can be prepared most conveniently from veratrole in this way.

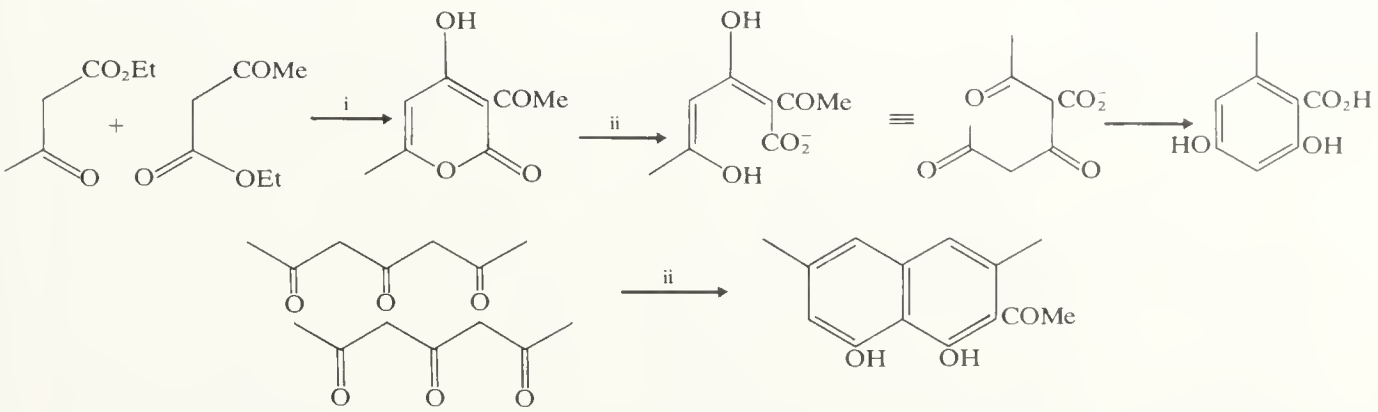
(*d*) *Oxidative decarboxylation.* The oxidative decarboxylation[56] of aromatic acids in the presence of cupric salts (at 200–350°C) yields phenols or their esters according to the solvent employed. This reaction is used in the manufacture of phenol from toluene *via*

benzoic acid. Basic cupric salts of toluic and benzoic acids at 200–220 °C yield the corresponding *o*-hydroxy-acid; at higher temperatures these decarboxylate rapidly.

4.2.2.3 Synthesis from aliphatic precursors

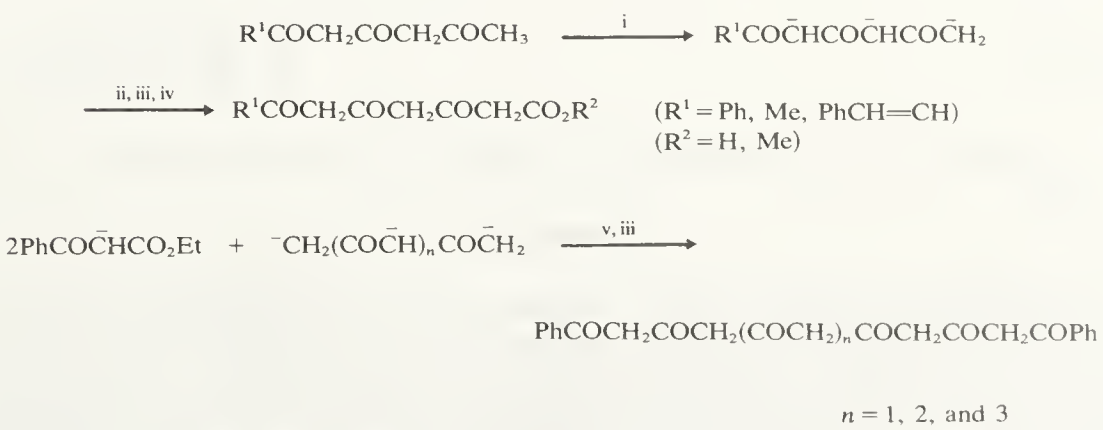
(i) Biomimetic poly-β-ketone cyclizations

The biosynthetic pathway briefly described in Section 4.2.1.1 was anticipated by the observations of Collie,[58] who discovered the cyclizations to aromatic products summarized in Scheme 15 while investigating reactions of polycarbonyl compounds. The accumulated evidence for the credibility of the poly-β-ketone biosynthetic road[2] to phenols has in turn prompted a spate of work on further *in vitro* analogies, which has been reviewed.[59] The preparation of free poly-β-ketones is a major hurdle in these investigations; the development of suitable methods is largely due to Harris[60] and some key reactions are outlined in Scheme 16. Poly-β-keto acids or esters may cyclize along various courses according to the number and type of functions present; some of the modes which have been demonstrated are shown in Scheme 17.[61] The difficulties of preparing and isolating poly-β-keto acids have induced some highly ingenious syntheses of masked poly-β-ketones, which may cyclize during the unmasking process. Chief among these are the pyrone–polypyrone systems devised by Money and Scott;[62] the construction, ring-opening, and re-cyclization of some examples of this type are illustrated in Schemes 18 and 19. Other approaches[63] to blocked polyketones have been devised; one of these[63a] using isoxazoles is shown in Scheme 20.



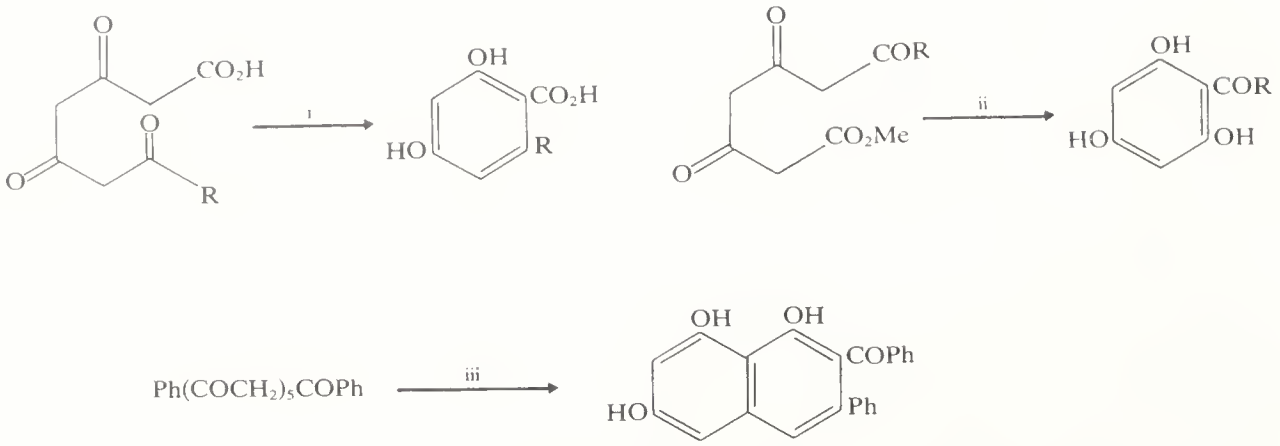
i, Δ; ii, ^-OH.

SCHEME 15



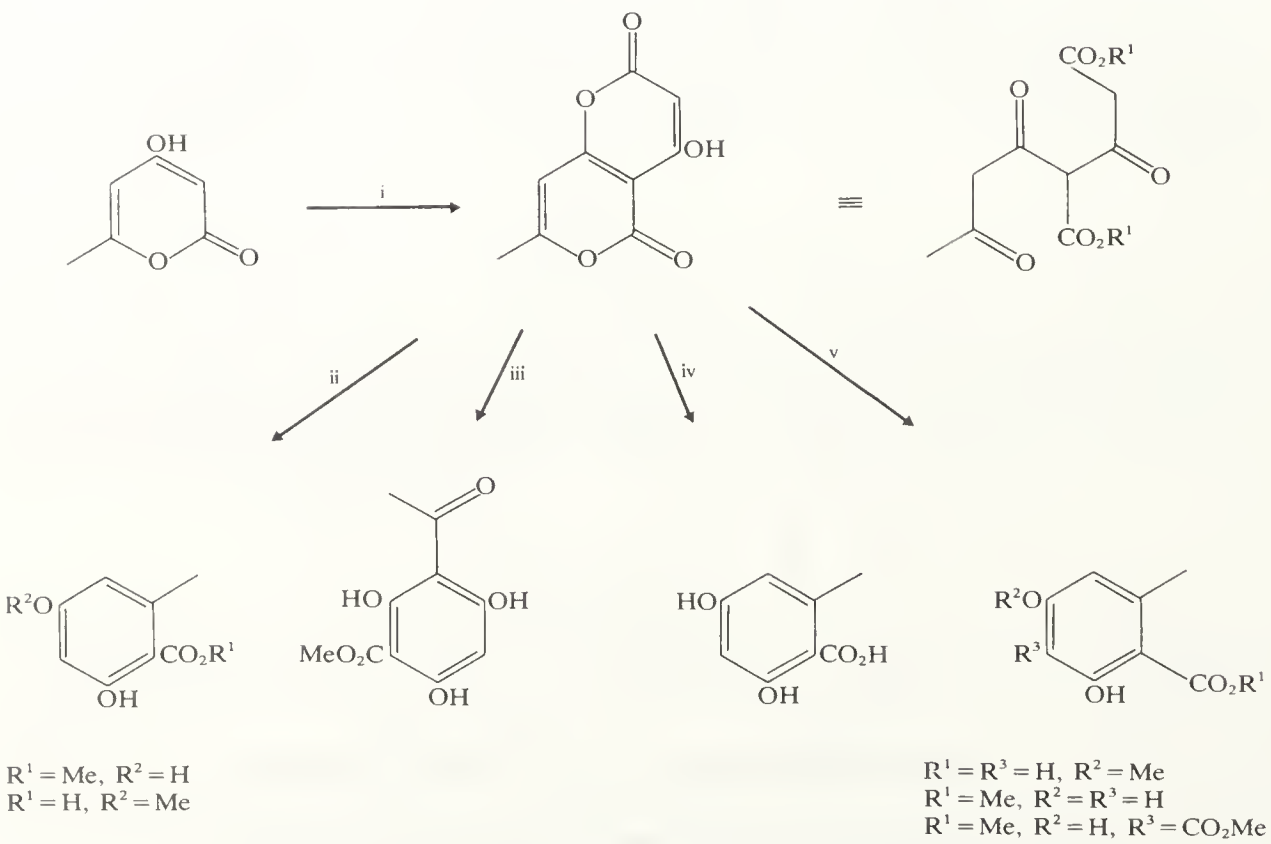
i, $^-NH_2$, NH_3; ii, CO_2; iii, H^+; iv, CH_2N_2; v, Bu^nLi.

SCHEME 16



i, buffer, pH 5; ii, $^-$OH; iii, pH 8.

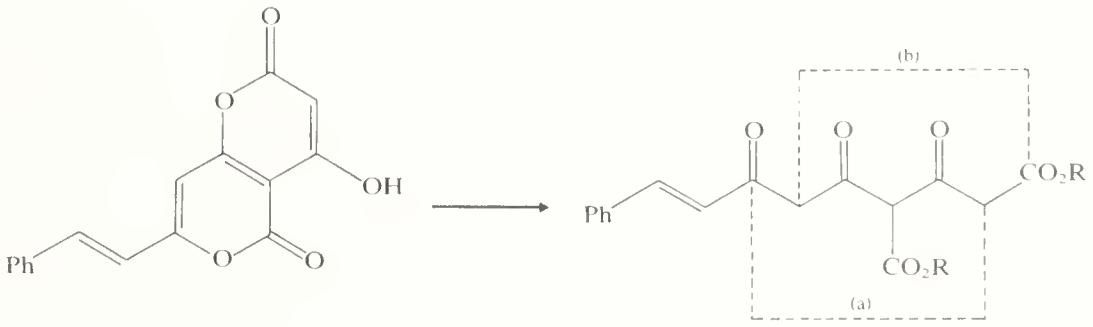
SCHEME 17

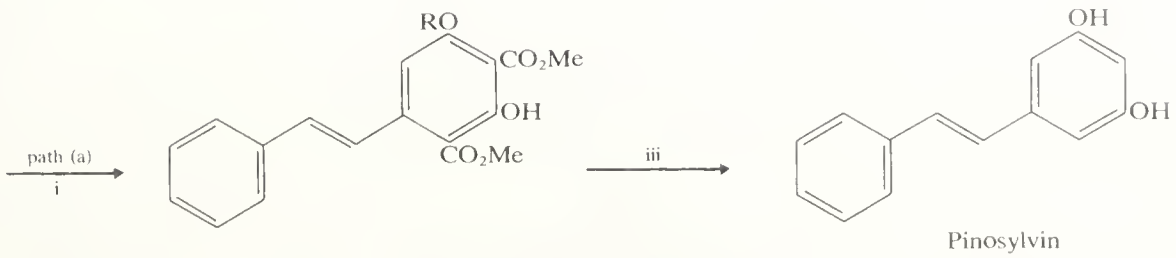


i, $CH_2(COCl)_2$, H^+; ii, KOH, 90% MeOH; iii, $Mg(OMe)_2$; iv, H_2O, KOH; v, MeOH, KOH.

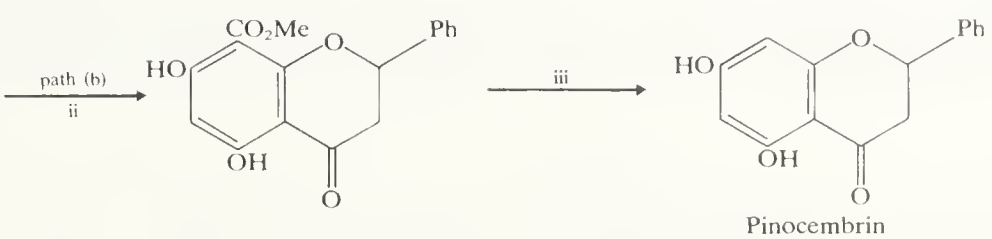
SCHEME 18

The aromatization of model systems is impressive, but not surprisingly they lack the degree of control exhibited in Nature. Various chemical controlling factors have been investigated. For example, metal chelation can exert a directive effect, as shown by the reactions of the pyrone (**46**) (dimethylxanthophanic enol) with excess of magnesium methoxide (Scheme 21).[64] Introduction of strategic *cis* double bonds into a cyclizing chain would also be expected to exert considerable control over cyclization, and a subtle





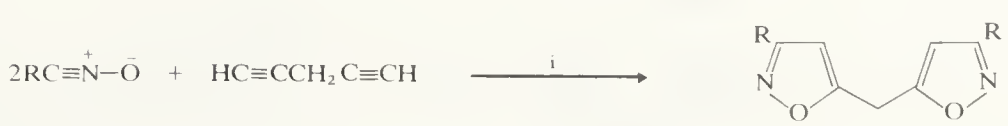
Pinosylvin

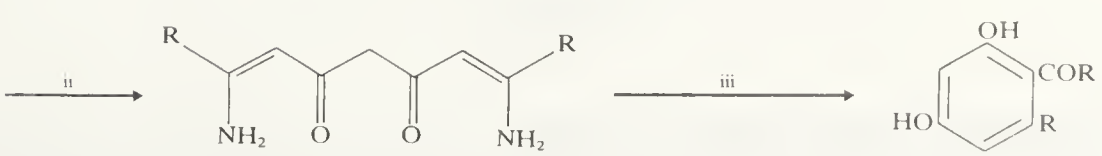


Pinocembrin

i, KOH, MeOH; ii, $Mg(OMe)_2$, MeOH; iii, acid or base.

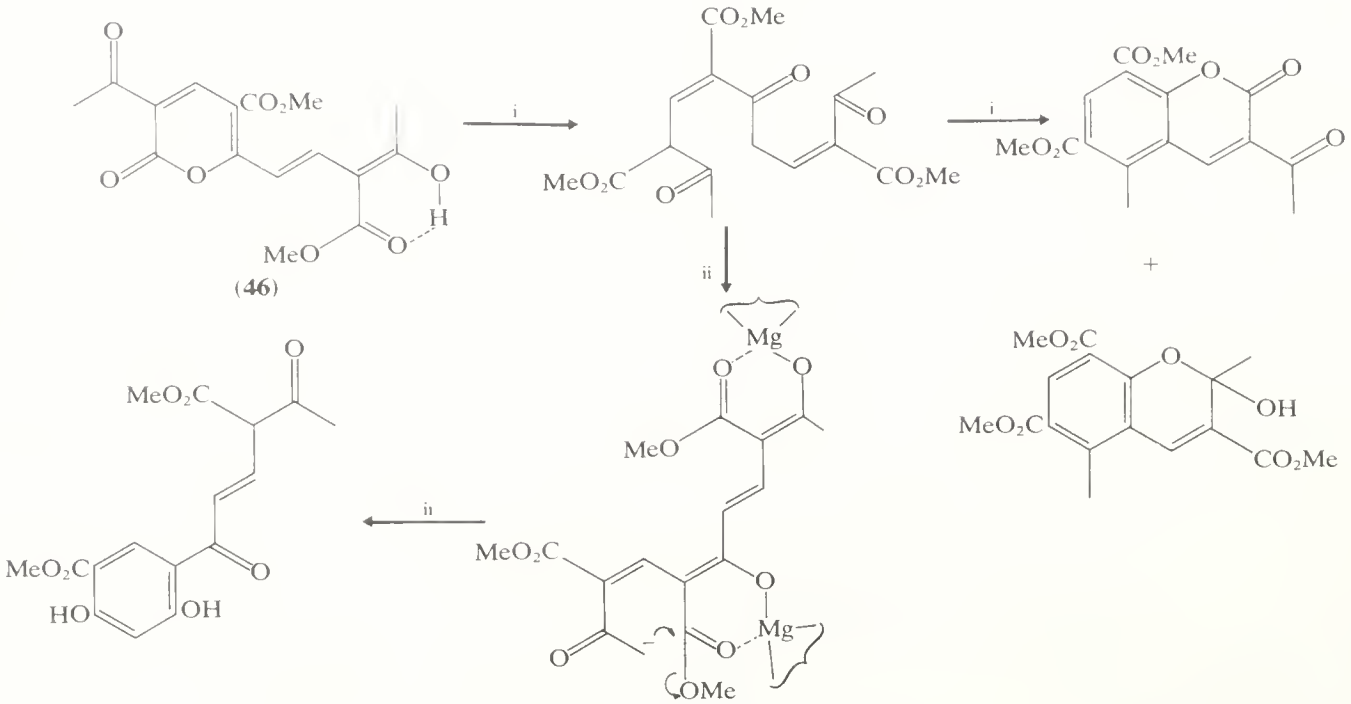
SCHEME 19





i, Δ; ii, Raney Ni; iii, H_3O^+.

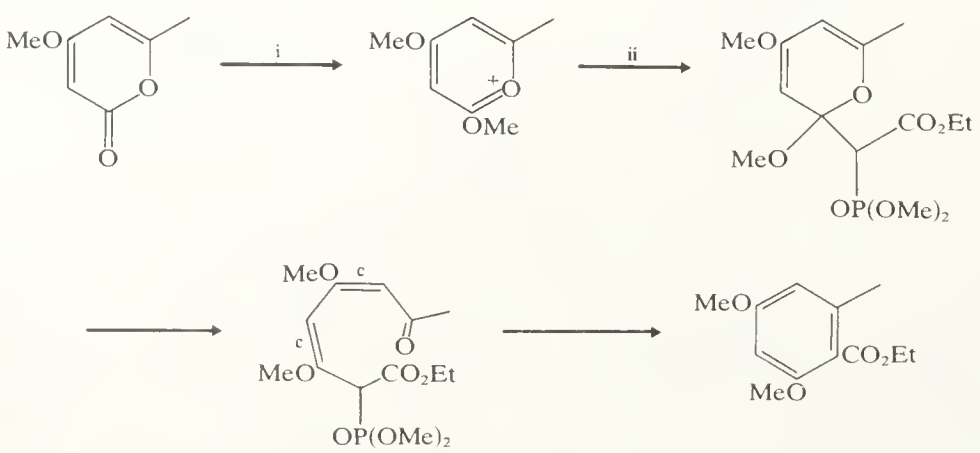
SCHEME 20



i, 2 mol $Mg(OMe)_2$; ii, 6 mol $Mg(OMe)_2$.

SCHEME 21

sequence developing carbonyl groups as *cis* enol ethers is shown in Scheme 22.[65] Application of these principles to longer chains should restrict the number of cyclization modes in an interesting way.



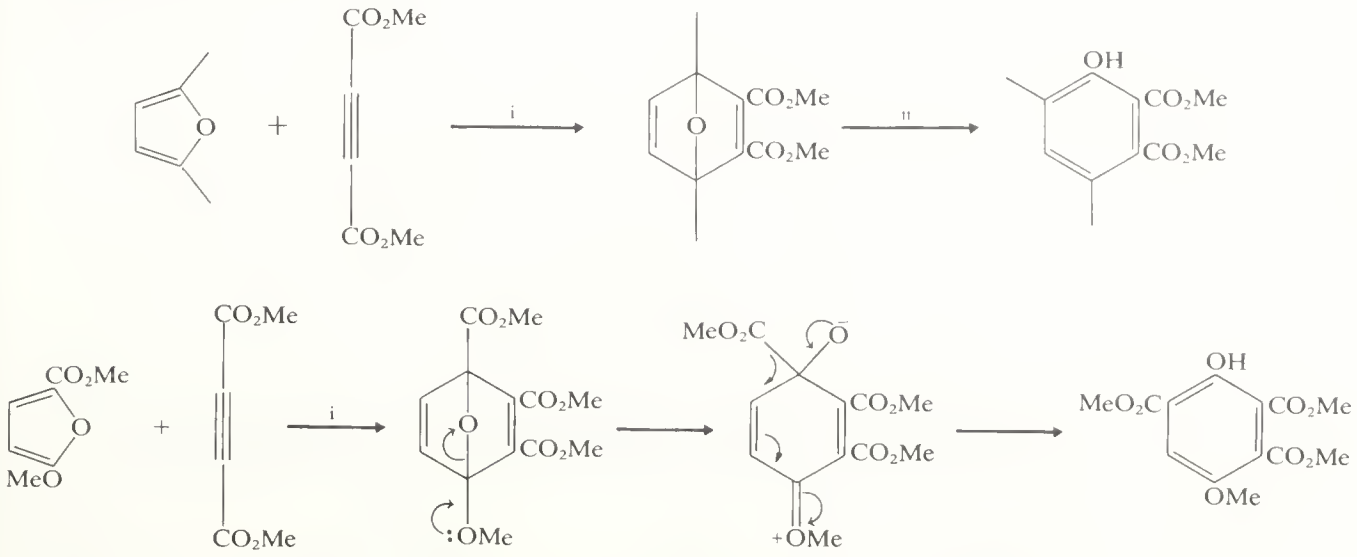
i, $MeOSO_2F$; ii, $EtO_2C\bar{C}HPO(OMe)_2$

SCHEME 22

(*ii*) *Construction of phenols from two sub-units*

The better-known methods of phenol synthesis have been described in Sections 4.2.2.1 and 4.2.2.2: they rely on manipulation *via* substitution and/or oxidation of a preformed aryl ring. Phenols of certain substitution patterns are not amenable to preparation by such methods and several alternative strategies have recently been devised for constructing aryl

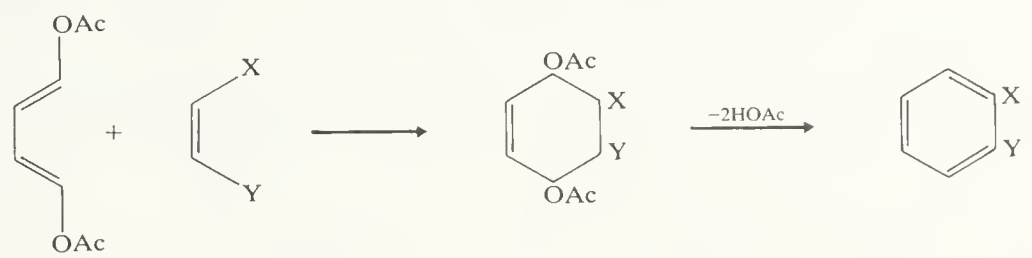
rings, with appropriate oxygen functions, from two non-benzenoid units. The Diels–Alder reaction is particularly useful in this respect and some typical sequences are shown in Scheme 23.[66]



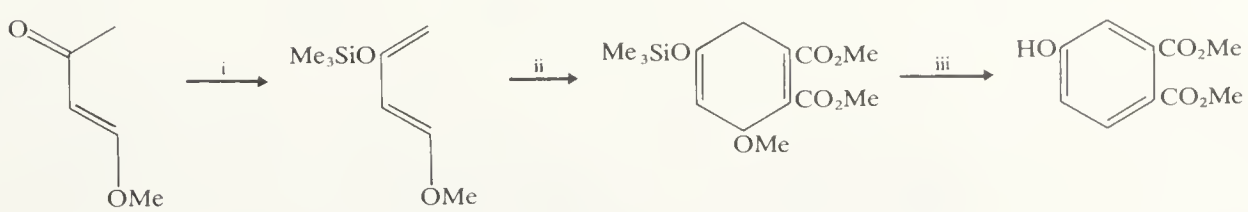
i, Δ; ii, $AlCl_3$.

SCHEME 23

The enolacetate of succindialdehyde reacts with varied dienophiles on heating. Acetic acid is eliminated from the product on pyrolysis to form the phenolic product (Scheme 24).[67] Different methods of aromatization to retain oxygen functions can be envisaged. Another substitution pattern is produced by the related reactions shown in Scheme 25.[68]



SCHEME 24

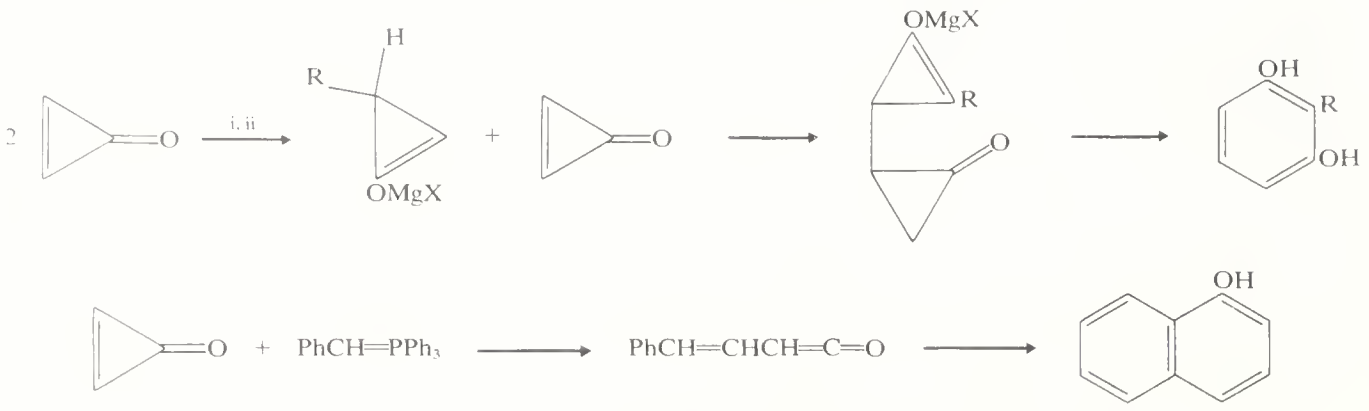


i, Me_3SiCl, $Et_3N.ZnCl_2$; ii, $MeO_2CC{\equiv}CCO_2Me$; iii, H^+.

SCHEME 25

More exotic routes have been explored based on cyclopropenone chemistry;[69] some possibilities appear in Scheme 26.

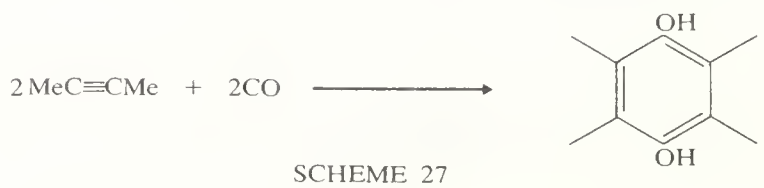
Reactions such as those described here may lend themselves to a particular requirement, *e.g.* the introduction of ^{13}C or ^{14}C labels into specific positions of an aromatic core for mechanistic or biosynthetic purposes. Many other syntheses are known, *e.g.* the



i, RMgX; ii, H_3O^+.

SCHEME 26

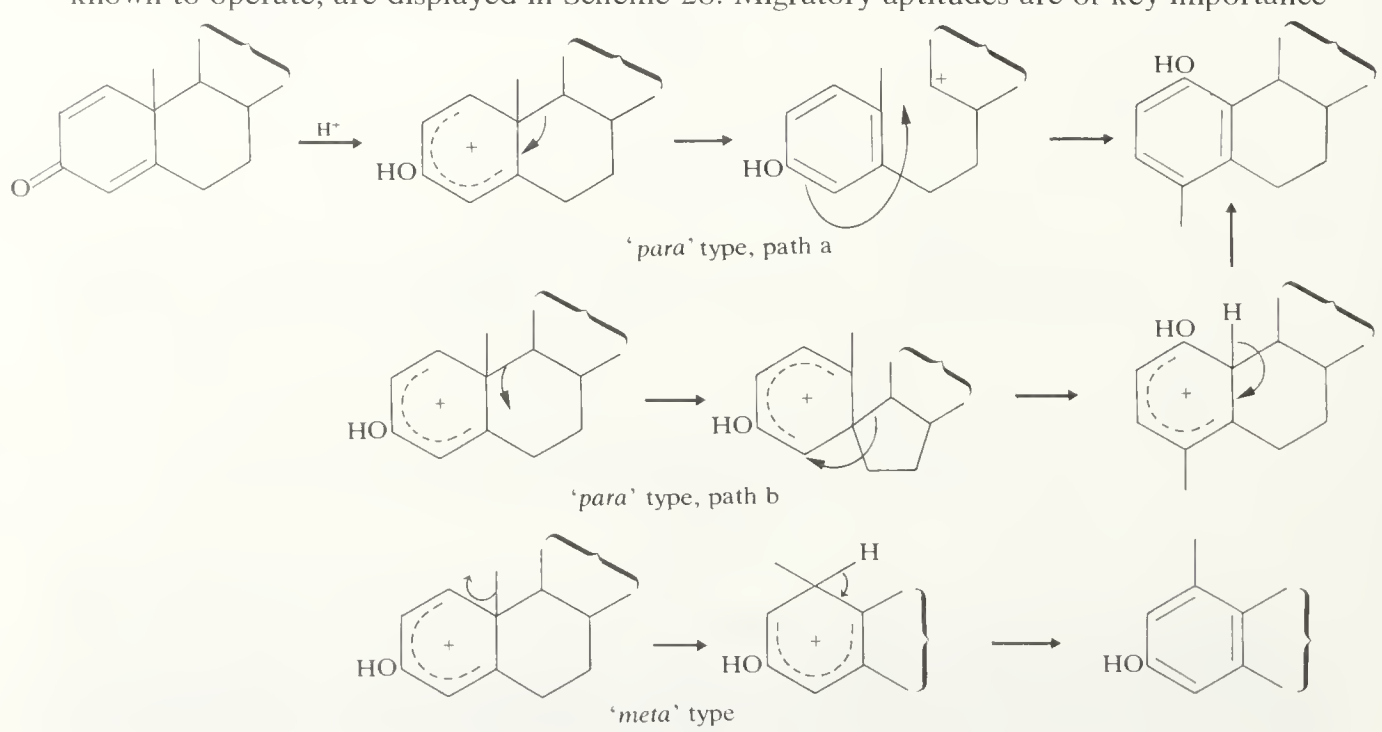
catalytic carbonylation of alkylacetylenes[70] to give hydroquinones (Scheme 27), and the self-condensation of biacetyl using sodium bisulphite to 2,5-dimethylhydroquinone.



SCHEME 27

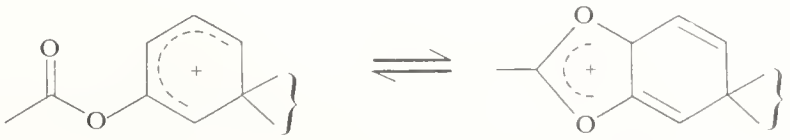
(iii) The dienone–phenol rearrangement

Cyclohexadienones prevented from aromatization by *gem*-disubstitution at a ring position can be prepared by functional manipulation of cyclohexanones and from phenols by *C*-substitution or oxidation. Aromatization of such dienones must involve migration of one of the *gem*-substituents; this reaction comprises the dienone–phenol rearrangement, and many examples are known, a number of them being of historical interest in steroid chemistry. Reviews are available.[71] The main types of reaction, and the main mechanisms known to operate, are displayed in Scheme 28. Migratory aptitudes are of key importance

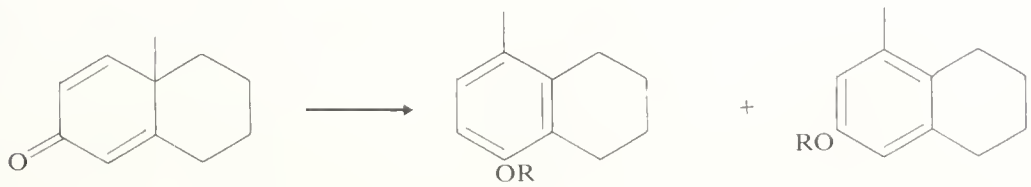


SCHEME 28

in deciding the pathway taken; these are often finely balanced and are catalyst- and solvent-dependent. For example, with acetic anhydride catalyst, the ability of acetate to participate in carbenium ion stabilization can be of decisive importance, as in (**47**) ⇌ (**48**) in equation (1). The balance between alternative pathways is nicely shown in the example drawn out in Scheme 29.



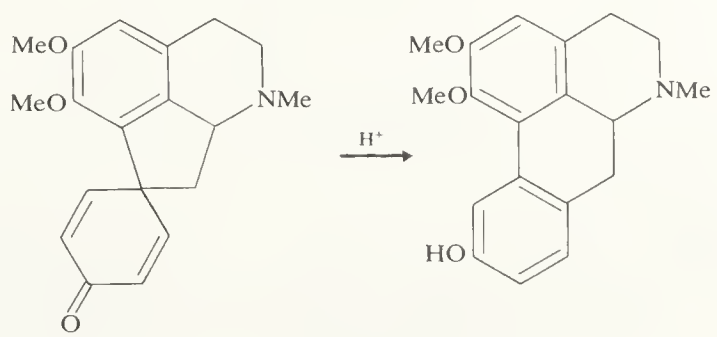
(**47**) (**48**) (1)



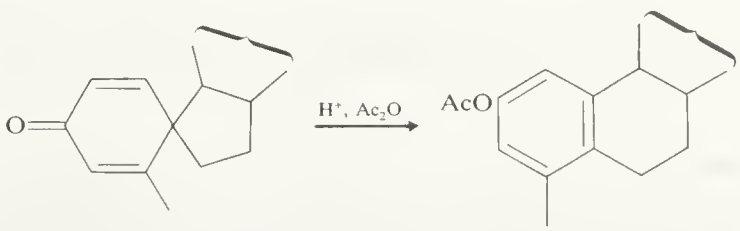
With Ac_2O, H_2SO_4	80%	20% (R = Ac)
With H_3O^+	20%	80% (R = H)

SCHEME 29

Aryl groups migrate more readily than alkyl, and more substituted alkyls more easily than less, as shown by the rearrangements of (**49**) and (**50**) in equations (2) and (3). The choice between migration of carbon and migration of nitrogen or oxygen is more difficult to predict. Scheme 30 shows examples of both *C*- and *O*-shifts.

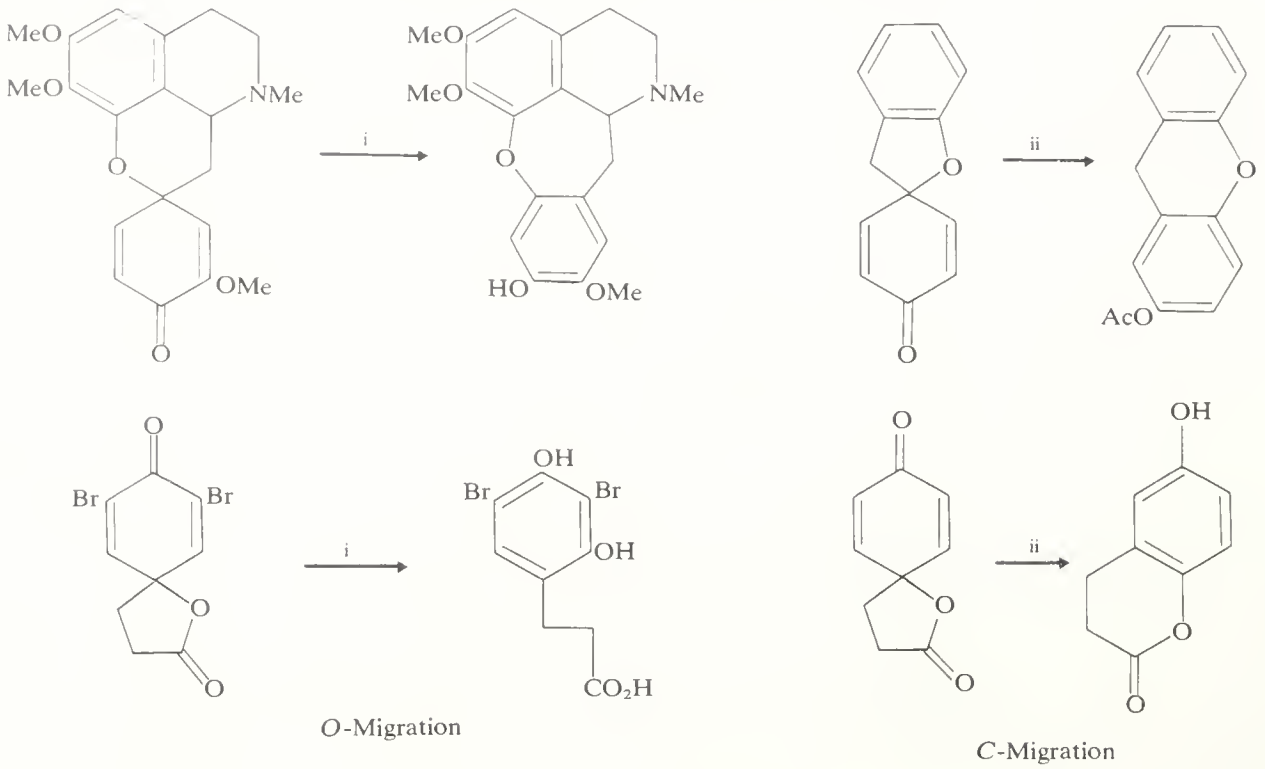


(**49**) (2)



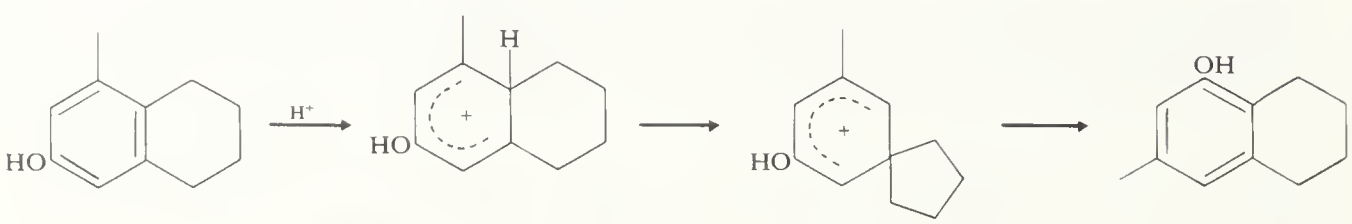
(**50**) (3)

A phenol–phenol migration is known, following a similar pathway (Scheme 31). The impression must not be given that all dienone–phenol rearrangements involve 1,2-shifts following the examples above. Scheme 32 shows the rearrangement of an *ortho* dienone (such cases are less well studied), with formal 3,4- and 1,5-shifts.[72]

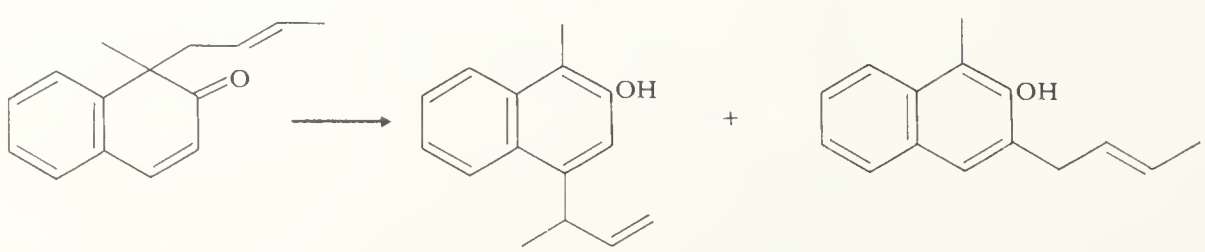


i, $H_3\overset{+}{O}$; ii, H^+, Ac_2O.

SCHEME 30



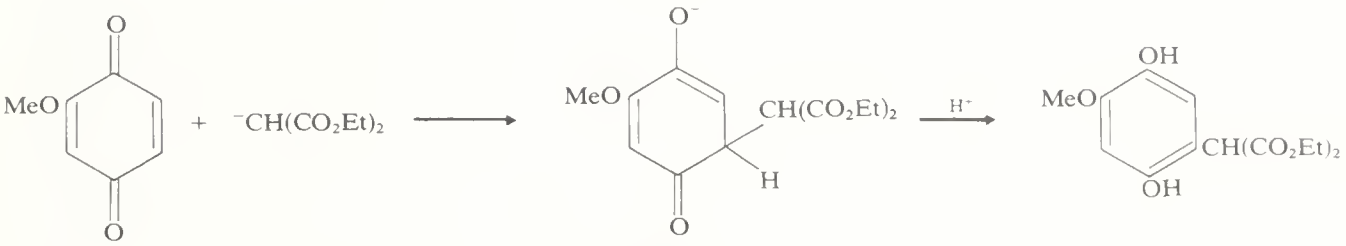
SCHEME 31



SCHEME 32

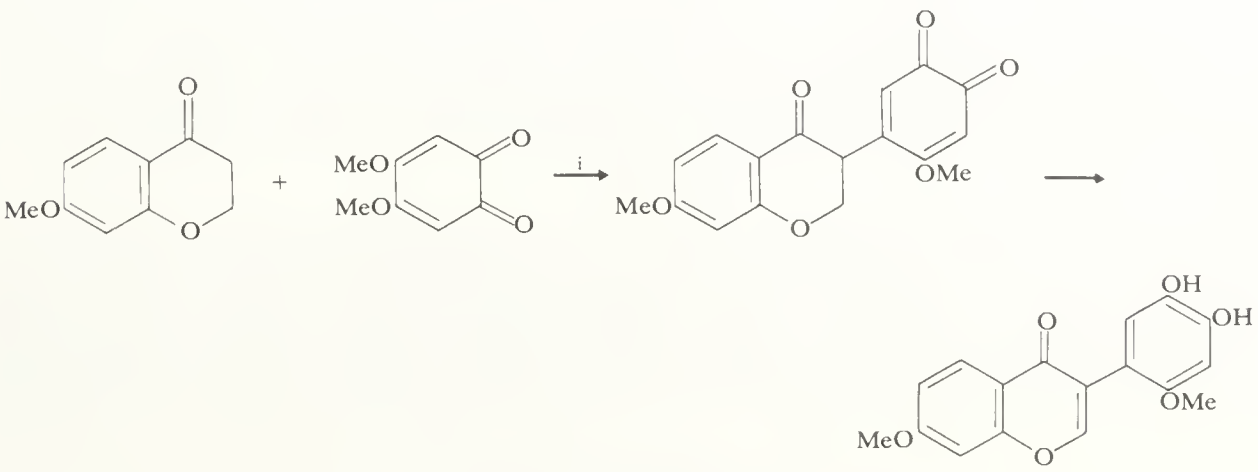
(*iv*) *Addition to quinones*

ortho- and *para*-quinones are highly susceptible to nucleophilic addition and suitably substituted products can subsequently aromatize. Good yields can be obtained with nitrogen, sulphur, and oxygen nucleophiles (*e.g.* Thiele acetylation) to yield correspondingly substituted phenols. More modest returns have been obtained from carbanion additions, *e.g.* with diethyl sodiomalonate and benzoquinone (Scheme 33).[73] Such reactions are of synthetic interest.



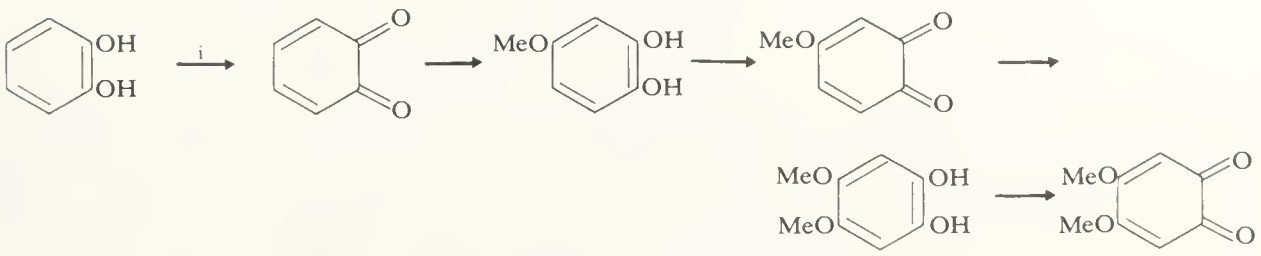
SCHEME 33

This type of reaction can be engineered so that a phenol is oxidized to quinone, and then reacts with a carbon nucleophile with consequent reversion to substituted phenol (reversal of reagent polarity with respect to usual electrophilic substitution). Such a strategy has been employed by Wanzlick and co-workers[74] for isoflavone synthesis, as shown in Scheme 34; the requisite quinone is prepared separately by the method of Scheme 35.[75]



i, $MeSOCH_2Na$, MeSOMe

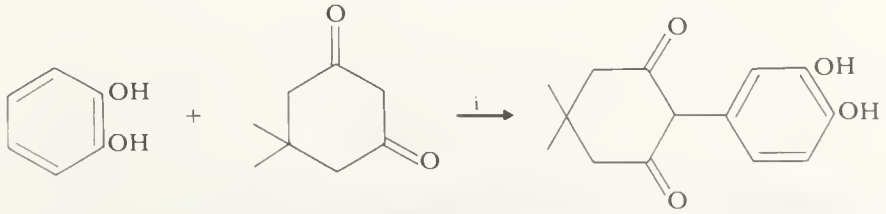
SCHEME 34



i, NaOMe, MeOH, PbO_2.

SCHEME 35

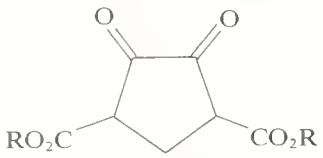
In an alternative procedure (Scheme 36) a phenol (*e.g.* catechol) may be oxidized in the presence of a carbanion-forming system (*e.g.* β-diketone and base); the quinone formed is



i, $NaHCO_3$, $K_3Fe(CN)_6$.

SCHEME 36

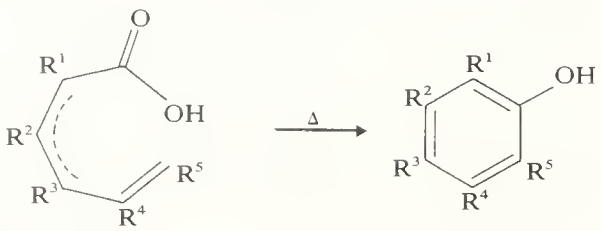
trapped by the carbanion (the 'nascent quinone' synthesis) without isolation.[76] More reactive carbon nucleophiles can react without the need for added base, *e.g.* indole or the diketo diester (**51**).



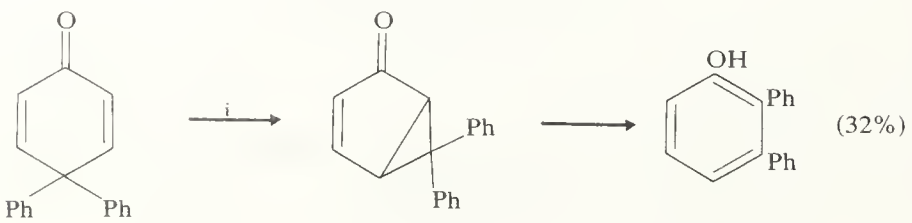
(**51**)

(*v*) *Other methods*

Any organic compound containing a six-carbon unit at the appropriate oxidation level, and with one or more oxygen functions, may if sufficiently activated find a pathway through to a more stable aromatic, *i.e.* phenolic, state. Thus, apart from the reactions highlighted above, phenols can be formed in variable yield in many reactions in which the chief interest is not that of phenol synthesis. However, it is conceivable that such reactions could be put to service for a particular purpose. Some examples are the pyrolysis of 2,5- or 3,5-dienoic acids[77] (**52**) (equation 4) with acid or base catalysts, the photolysis of bicyclic ketones[78] (Scheme 37), and the pyrolysis of tricyclic ketones[79] (Scheme 38).

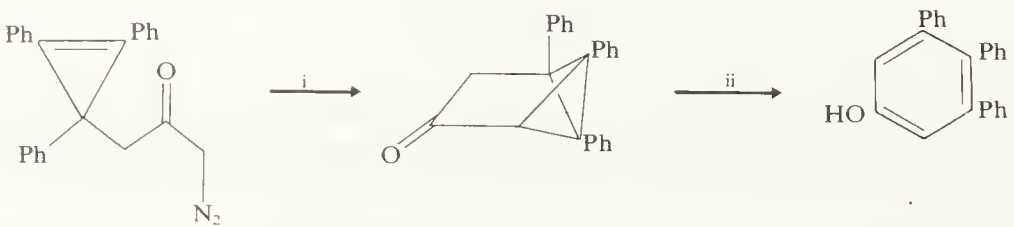


(**52**) (4)



i, $h\nu$, H_2O, dioxan.

SCHEME 37



i, Cu, C_6H_6; ii, Δ, 180 °C.

SCHEME 38

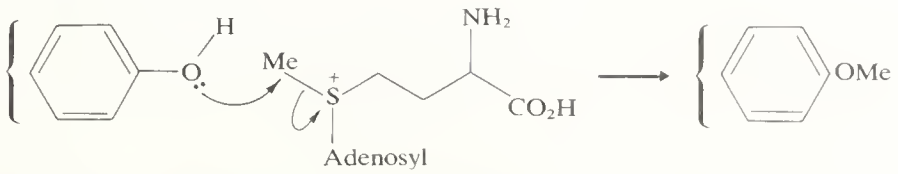
4.2.3 THE CHEMISTRY OF MONOHYDRIC PHENOLS

Most of the general reactions of phenols will be discussed in this section with specific variations for di- and tri-hydric phenols being dealt with in Section 4.2.4.

4.2.3.1 Reactions of the hydroxy group

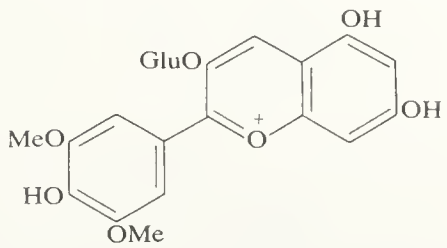
(i) O-Alkylation, acylation, and related reactions

(a) Ether and acetal formation. Ether formation warrants attention for several reasons. Phenols frequently occur in Nature as their methyl ethers; *O*-methylation *in vivo* is conducted by *S*-adenosylmethionine, and involves either preformed phenol or an intermediate *en route* to a phenol (Scheme 39). Phenols also occur in Nature as their glycosides, or other carbohydrate acetals; oenin (**53**), a pigment of black grapes, exhibits these structural variations. Thus methods for methylation and glucosylation are particularly important in natural product synthesis. Of equal consequence are methods for the protection and blocking of phenolic hydroxyls; ether functions are widely used for this purpose and are treated here.

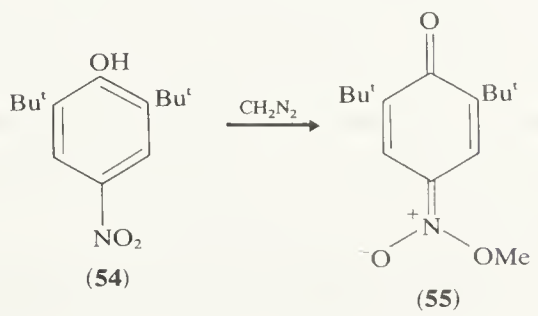


SCHEME 39

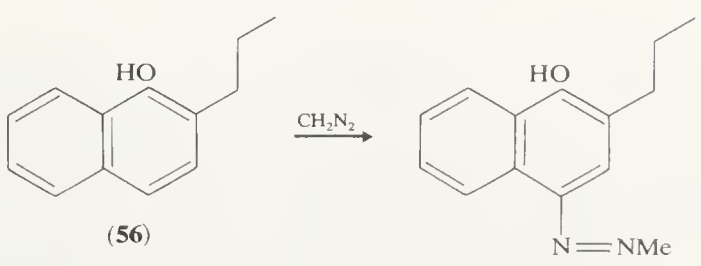
Methylation and other simple alkylations are readily conducted with dialkyl sulphates in those cases in which the phenols give water-soluble alkali metal salts; the hard electrophilic sulphates favour *O*-alkylation. Hindered or chelated phenols may be converted into sodium or lithium salts by sodium hydride or an alkyl-lithium, and alkylated with alkyl halide in an ether or dipolar aprotic solvent. Methyl sulphate–dry acetone–potassium carbonate also works well with chelated phenols.



(**53**)

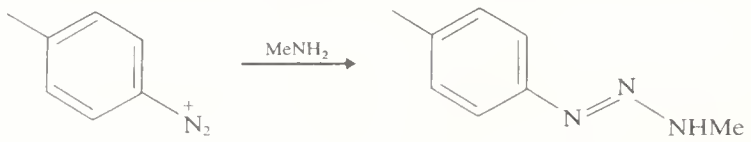


(**54**) (**55**) (5)



(**56**) (**57**) (6)

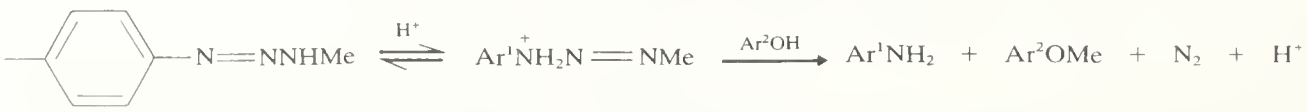
Diazomethane reacts relatively slowly with acidic phenols, the reaction being catalysed by methanol, by boron trifluoride, and by fluoroboric acid. *O*-Methylation is not the only possible reaction pathway:[80] the di-*o*-substituted *p*-nitrophenol (**54**) reacts at the nitro group oxygen to provide the nitronic acid (**55**) (equation 5) and the hindered naphthol (**56**) yields the *p*-azophenol (**57**) (equation 6). In the methylation of carboxylic acids, diazomethane may be conveniently replaced by *N*-methyltolyltriazine (**58**), easily prepared



(7)

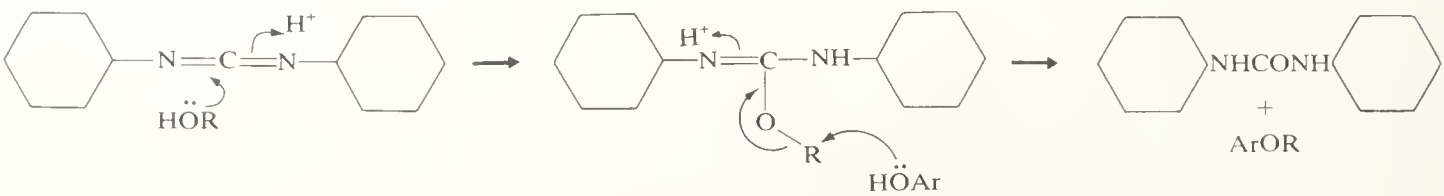
(**58**)

as indicated in equation (7). The triazines decompose in acid media to give carbenium ions (free or potential) which alkylate acidic oxygen functions[81] (Scheme 40). Most applications refer to carboxylic acids, but reactions with phenols have been described[81b] and are catalysed by aluminium alkoxides. The aromatic amine by-product is easily removed.



SCHEME 40

One other method for formation of simple alkyl ethers deserves mention, which uses *N,N*-dicyclohexylcarbodi-imide. This reagent, well known in peptide chemistry for carboxyl–amine coupling, also serves to drive other mechanistically related condensations, including phenol–alcohol reactions (Scheme 41); however, forcing conditions are required.[85]



SCHEME 41

'Magic methyl', methyl fluorosulphonate, is a potent methylating agent for nitrogen, sulphur, and ether oxygen nucleophiles. However, no reports have been made of useful *O*-methylation of phenols and it may be that *O*- and *C*-sulphonation intervene.

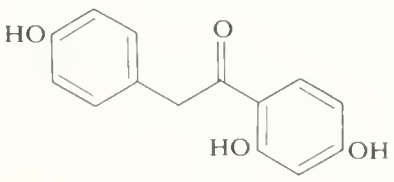
Methyl and other simple alkyl ethers require relatively harsh treatment (see Section 4.3.3.2) for their cleavage and are only used as protecting groups where this is acceptable. t-Butyl ethers can be prepared by treatment of phenols with isobutene:

$$ArOH + Me_2C{=}CH_2 \xrightarrow{H^+} ArOCMe_3$$

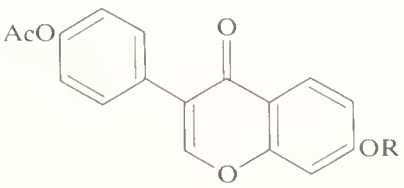
the reaction is reversible in the presence of acid and the use of t-butyl ethers as protecting groups has been reported. Protection of phenols in general is discussed in McOmie's useful book.[82]

Benzyl ethers can be prepared by refluxing the phenol in dry acetone with benzyl chloride and potassium iodide over potassium carbonate. Their cleavage can be accomplished by acid under moderate conditions — trifluoroacetic acid performs this function at ambient temperature[83] — or by hydrogenolysis over palladium catalysts. Benzyl and methoxymethyl ether functions are widely used for blocking phenolic hydroxy groups. Some degree of selectivity can often be achieved in polyhydric phenols: thus in a phenolic fragment such as (**59**), the hydroxy group *para* to the carbonyl group (most acidic) is the fastest to be alkylated, while the slowest reaction is with the chelated hydroxy function. An interesting way to perform such reactions involves formation of the peracetate of the

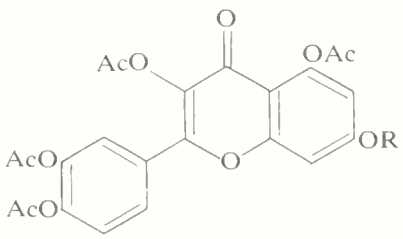
polyhydric phenol, which is reacted with benzyl chloride in the usual way. Deacetylation–benzylation at the most reactive site ensues:[84] thus daidzein diacetate (**60**) gives the monoacetate monobenzyl ether (**61**), and quercetin penta-acetate (**62**) gives the monoether tetra-acetates (**63**) and (**64**). This procedure, which incidentally helps to prevent loss of phenol by oxidation, or irreversible adsorption during chromatography, can also be applied to polyalcohols.



(**59**)

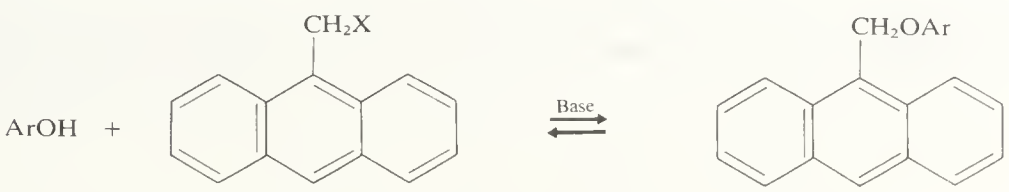


(**60**) R = Ac
(**61**) R = $PhCH_2$



(**62**) R = Ac
(**63**) R = Me
(**64**) R = $PhCH_2$

As an alternative to benzylation, 9-anthrylmethyl ethers (**65**) have been recommended as a blocking groups,[86] not only for phenols but also for acids, thiophenols, and thiols (see equation 8) for their formation. Such ethers are very readily cleaved by brief treatment at ambient temperature with sodium thiomethoxide in HMPT.



(**65**)

(8)

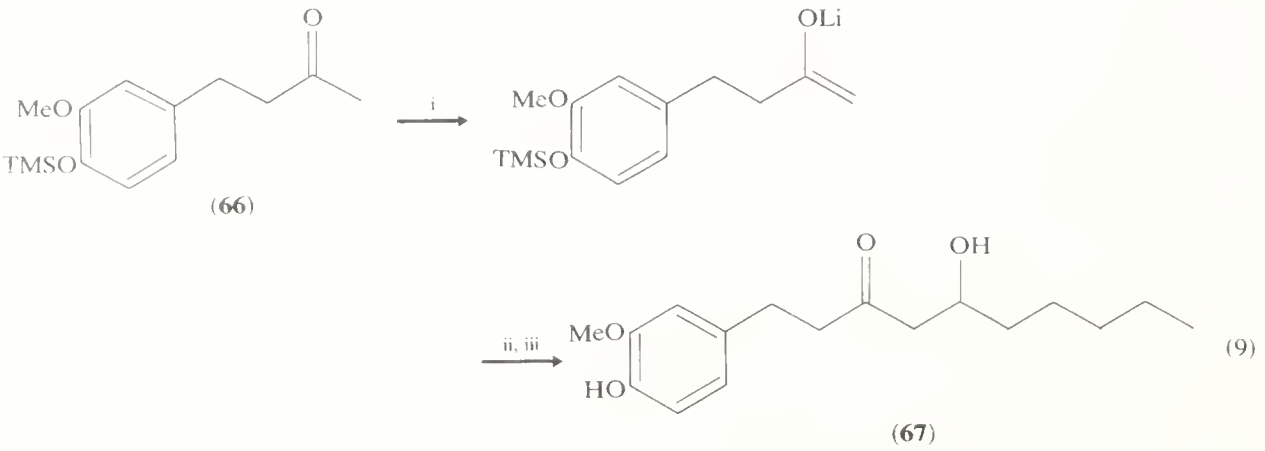
The silicon analogues of alkyl ethers have useful properties. Because of the ready availability of trimethylsilyl reagents, the trimethylsilyl ethers are commonly used, but others, *e.g.* butyldimethylsilyl, which are bulkier and slower to cleave on hydrolysis, can be used with advantage. Trimethylsilylation can be effected with trimethylsilyl chloride (tertiary amine catalysed), with hexamethyldisilazane, or with mixtures of the two in proportions to give only ammonium chloride as the by-product:

$$3ArOH + Me_3SiCl + Me_3SiNHSiMe_3 \rightarrow 3ArOSiMe_3 + NH_4Cl$$

Reaction is usually rapid, but if the phenol is reluctant to silylate, bis(trimethylsilyl)acetamide or bis(trimethylsilyl)trifluoroacetamide are more reactive reagents. The second of these affords only trifluoroacetamide as by-product and it is volatile and readily removed to afford a convenient, small-scale preparation:

$$2ArOH + CF_3CON(SiMe_3)_2 \rightarrow 2ArOSiMe_3 + CF_3CONH_2$$

Silyl ethers are popular derivatives of phenols for gas chromatography since they generally boil at reduced temperatures (lack of H-bonding) and reduce column tailing and irreversible adsorption. Although quickly hydrolysed and susceptible to nucleophilic attack, silyl ethers can resist various reagents used under anhydrous conditions, including certain strong bases. Thus trimethylsilylzingerone (**66**) can be deprotonated, under kinetic control, and the resulting anion trapped with hexaldehyde to give the trimethylsilyl ether of gingerol (**67**) (equation 9),[87] the pungent principle of ginger root. The silyl ether is cleaved by brief exposure to dilute acid without affecting the sensitive β-ketol unit.



(66) (67) (9)

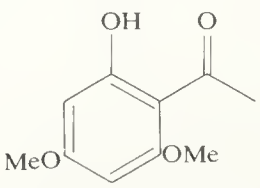
i, $(TMS)_2NLi$; ii, n-$C_5H_{11}CHO$; iii, $H_3\overset{+}{O}$.

Turning to the subject of acetal formation, few methods for the synthesis of glycosides are available. Reaction with tetra-acetylbromoglucose in the presence of either silver oxide or carbonate, or mercuric(II) salts or oxide, followed by deacetylation, is the standard procedure.

Methoxymethyl ethers can be prepared by reaction of a sodium or lithium aryloxide, suspended in an ether or hydrocarbon solvent, with monochloromethyl ether:

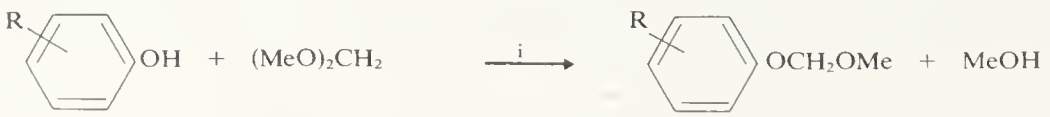
$$ArONa + ClCH_2OMe \rightarrow ArOCH_2OMe + NaCl$$

It is possible to solubilize the alkali-metal aryl oxides by use of a crown ether. Thus the 2,4-dimethyl ether (**68**) of acetylphloroglucinol gives a potassium salt soluble in acetonitrile in the presence of 18-crown-6; excellent yields of the ether are obtained on treatment



(68)

with chloromethyl methyl ether.[88a] The only drawback resides in the carcinogenity of the chloroether. An alternative reagent is the dimethyl acetal of formaldehyde,[88b] which undergoes *trans* acetalization with phenols (Scheme 42) when used in excess with acid catalysis. Methoxymethyl and tetrahydropyranyl (from the addition of phenols to dihydropyran) ethers give back the parent phenol on dilute aqueous acid treatment. The β-methoxyethoxymethyl protecting group[88c] promises to be of value.



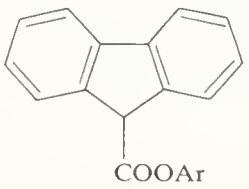
i, TsOH, CH_2Cl_2, molecular sieve.

SCHEME 42

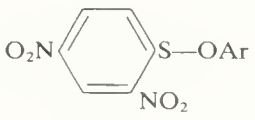
(*b*) *Esterification.* Phenols are not esterified by free carboxylic acids with hydrochloric (Fischer–Speier) or sulphuric acid catalysts. However, the reaction can be pushed forward to completion[89] with trifluoroacetic anhydride, trifluoromethanesulphonic anhydride, or

polyphosphoric acid; dicyclohexylcarbodi-imide has also been utilized. A recent recommendation is a mixed sulphuric–boric acid catalyst with azeotropic distillation of water.

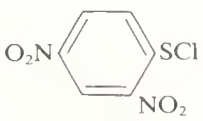
More commonly, carboxylic anhydrides or acid chlorides are used and pyridine is often the preferred solvent;[90] however, care must be taken with acetyl chloride, haloacetyl halides, haloacetic anhydrides, *etc.* which react violently with pyridine and tertiary amines at ambient temperatures. The relative merits of acetates, benzoates, sulphonates, chloroformates, and other esters frequently used in synthesis for protection are discussed by Haslam.[91] Cleavage can be achieved by acid or alkaline hydrolysis, or by reduction. Protecting ester groups which can be removed photochemically have been investigated,[92] and the most useful derivatives for phenols are the esters of fluorene-9-carboxylic acid (**69**), although there are some applications for aryl thioperoxides (**70**), prepared from the arenesulphenyl chloride (**71**). Variable recoveries of phenols are obtained after photolysis.



(**69**)

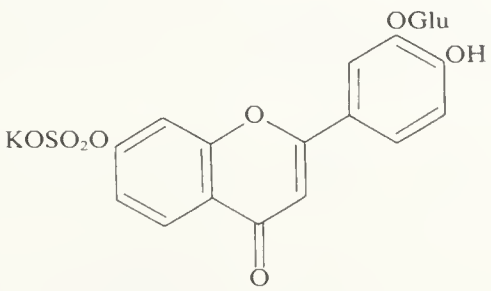


(**70**)

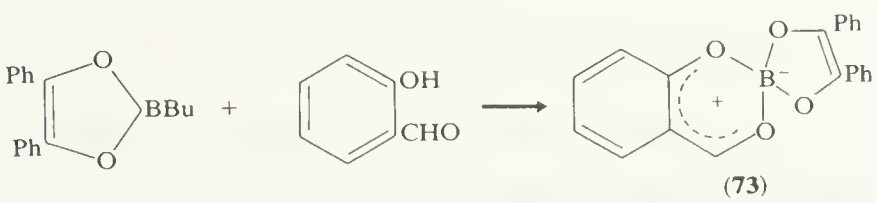


(**71**)

Many inorganic esters of phenols are known, and the formation of phosphates, borates, sulphates, and others have been reviewed.[93] Preparation of phosphates is attended by formation of pyro- and poly-phosphates and purification is difficult; the general methods have been surveyed.[94] Sulphate esters have been discovered in Nature, as flavone pigments (*e.g.* **72**) from the *Palmae*.[95] Borates are of particular interest in catechol chemistry and when formed from chelated phenols often give crystalline complexes, *e.g.* (**73**) (equation 10).[96]



(**72**)



(10)

(**73**)

(*ii*) *Replacement of hydroxy groups*

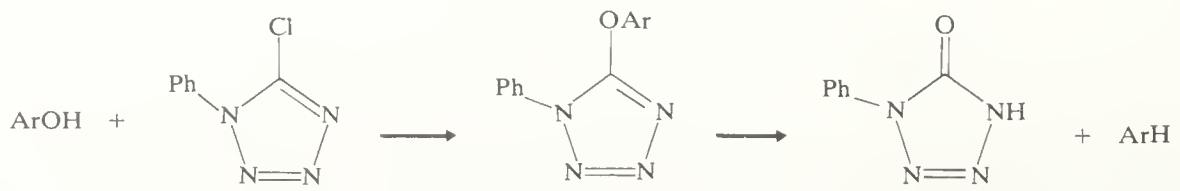
The replacement of hydroxy groups on an aryl ring is attended by the difficulties associated with substitution of other aromatic functional groups. Of the possible heterolytic mechanisms, an S_N1 process is disfavoured by the increased electronegativity of the sp^2-hybridized carbon, inhibiting carbenium ion character. A concerted S_N2 process requires a highly unfavourable rehybridization of the aryl sp^2 carbon, and a stepwise S_N2 process, the best-known mechanism, still demands forcing conditions unless electron-withdrawing substituents are present. Aryl–oxygen bonds are not markedly weaker than

other covalent bonds present in aromatic systems and a low-energy homolytic pathway for their cleavage is not available. None of the methods developed so far are mild and have rarely been shown to be of value in complex or polyfunctional molecules.

(*a*) *By hydrogen.* Direct replacement of phenolic hydroxy groups (and methoxy groups) by lithium aluminium hydride at 350 °C has been reported.[97] Hydrogenolysis of various derivatives is less stringent. Aryloxytetrazoles, formed from phenols and 5-chloro-1-phenyltetrazole, can be reduced to the aromatic hydrocarbon by hydrogen over palladium (Scheme 43).[98] Urethanes behave similarly:[99]

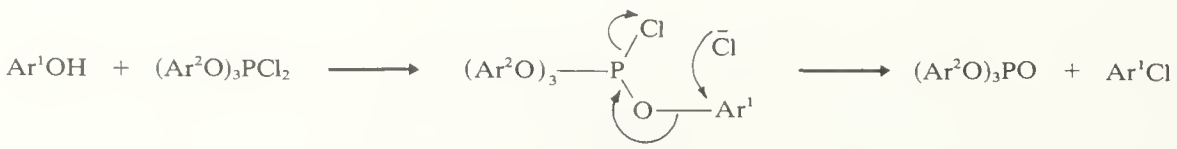
$$ArOH + PhNCO \longrightarrow ArOCONHPh \xrightarrow[Pd/C]{H_2} ArH$$

Both aryl sulphonates and adducts with dicyclohexylcarbodi-imide undergo parallel hydrogenolysis. Phenolic acetals, methoxymethyl and tetrahydropyranyl ethers can be reduced to hydrocarbons by lithium metal in refluxing diglyme (diethylene glycol dimethyl ether).



SCHEME 43

(*b*) *By halides.* The conversion of phenols into aryl chlorides by treatment with phosphorus pentachloride is effective only for nitrophenols. However, the phenol may be heated with tris(*p*-t-butylphenyloxy)phosphorus dihalide; the product, a tetra-aryloxyphosphorus dihalide, is then pyrolysed (Scheme 44). Bromides and iodides may be



Ar^2 = 4-t-butylphenyl

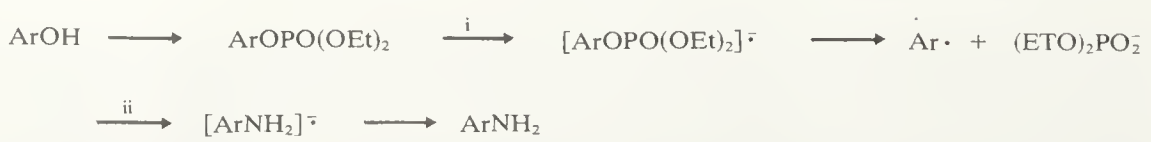
SCHEME 44

prepared by this route. In a related method, an aryloxytriphenylphosphorus dihalide is formed from the phenol, and decomposed thermally to the aryl halide:[100]

$$ArOH + Ph_3PX_2 \xrightarrow{-HX} ArO\overset{+}{P}Ph_3\,X^- \xrightarrow{\Delta} ArX + Ph_3PO$$

Bulky *ortho* substituents alter the course of this reaction.[101]

(*c*) *By nitrogen functions.* Aryl diethyl phosphates are reductively cleaved by potassium with potassamide in liquid ammonia to give primary aromatic amines (Scheme 45).[102]



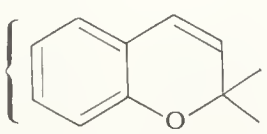
i, K; ii, NH_2^-.

SCHEME 45

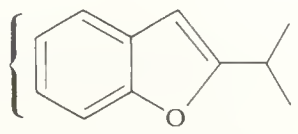
(*d*) *By sulphur functions.* Although phenols may be converted to thiols in moderate yield by heating with phosphorus pentasulphide, the reaction is of little synthetic value. Treatment of phenols with thiols at 180 °C in the presence of hydrochloric acid gives the corresponding sulphides.[103a] Conversions of phenols into thiols through the dialkyl thiocarbamates and into the corresponding sulphonic acids have also been described.[103b,c]

(*iii*) *Participation of phenolic hydroxyl functions in O-heterocyclic synthesis*

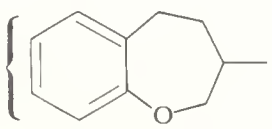
Natural phenols are precursors to an extensive range of O-heterocyclic compounds and some examples to illustrate the structural variety are shown. Six-membered rings are the most common and five-membered rings are frequently found in nearly all conceivable oxidation states. They arise in meroterpenoids (*i.e.* products from natural phenol–terpenoid condensations), for example in chromens (**74**), in dihydrofurans (**75**), and, not so commonly, in oxepins (**76**), in the flavone and isoflavone groups, and in a bewildering variety of more complex polycyclic substances (excellently reviewed by Dean[104]). Rotenone (**77**), morellin (**78**), ellagic acid (**79**), and peltogynol (**80**) may serve here as examples to interest the connoisseur of natural structures.



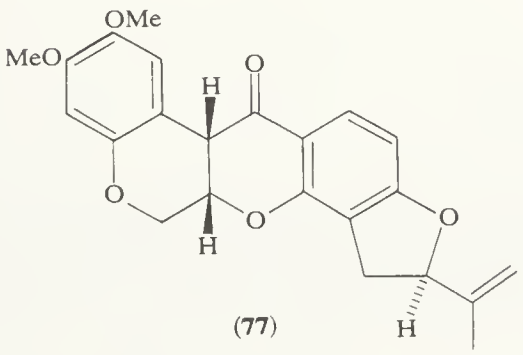
(**74**)



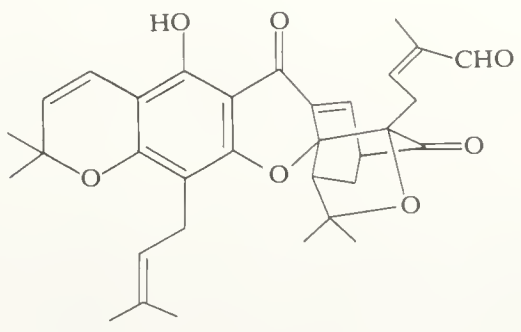
(**75**)



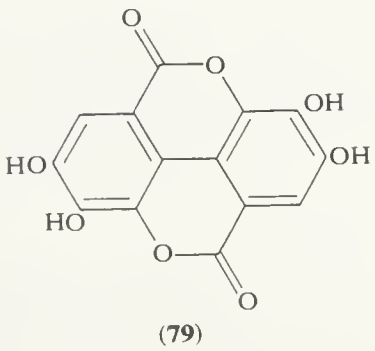
(**76**)



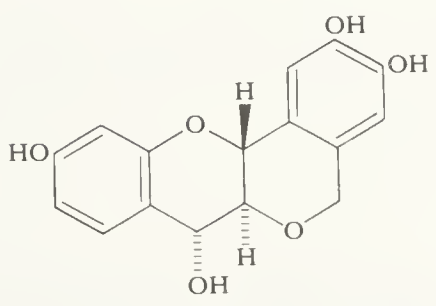
(**77**)



(**78**)



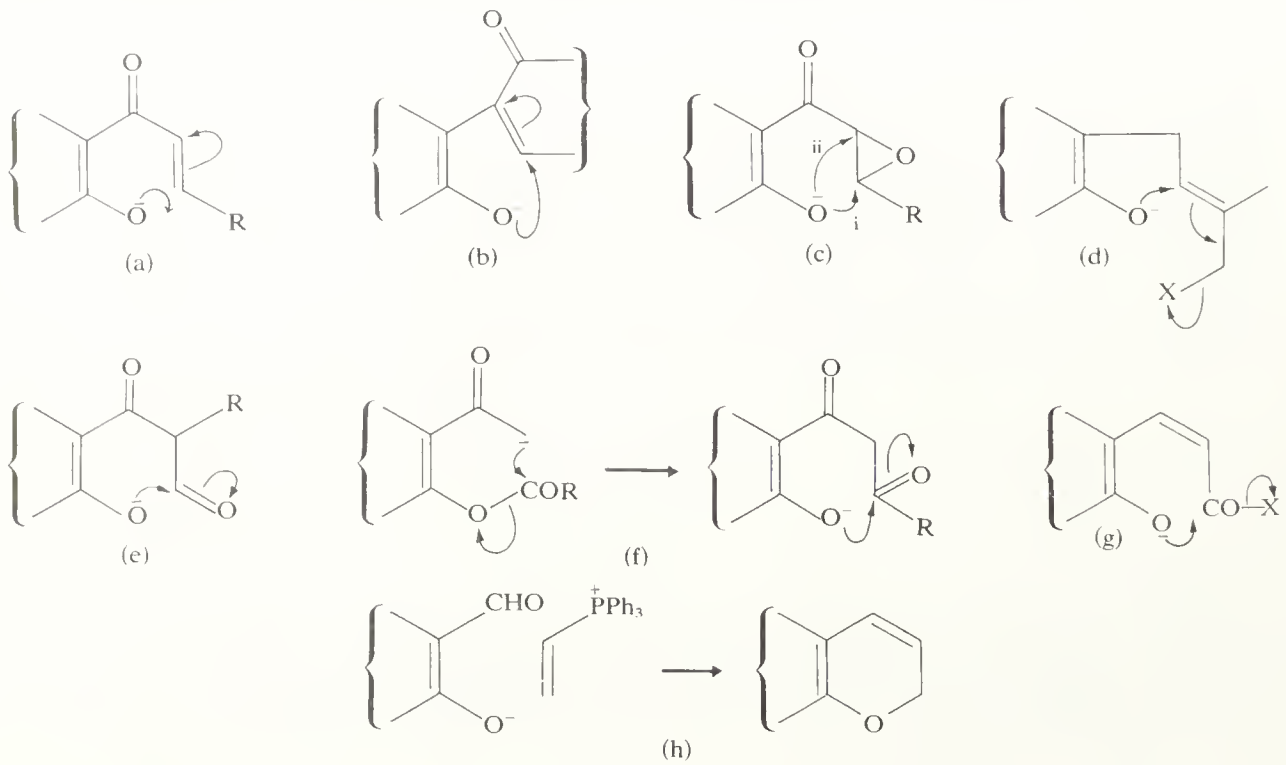
(**79**)



(**80**)

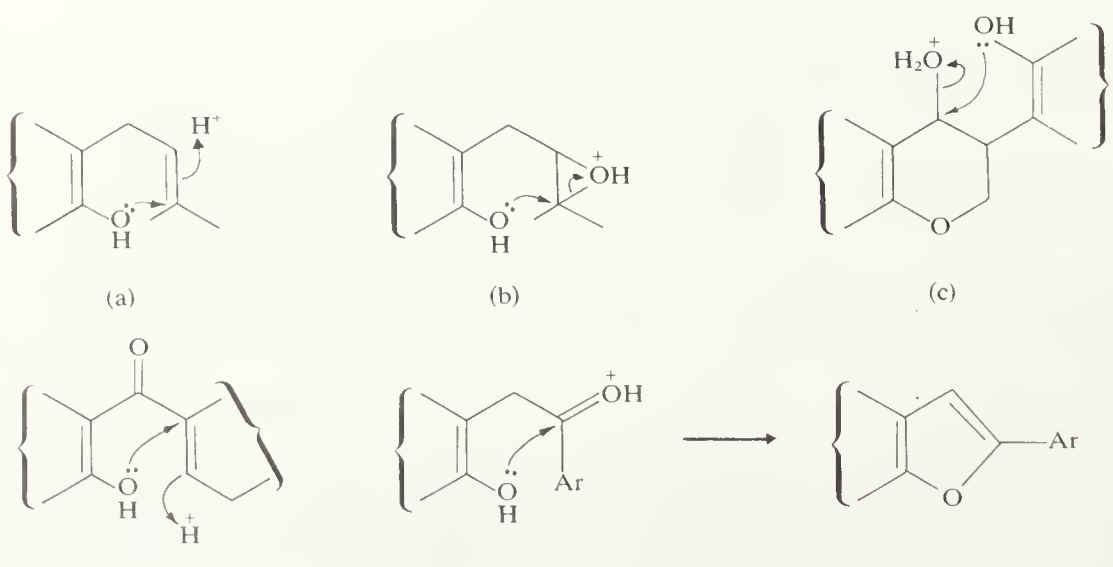
In all cases where the biosynthesis is known, the heterocyclic ring is produced by a cyclization involving the hydroxy group and a high proportion of laboratory syntheses follow this pattern. Without pretence at comprehensive coverage, some examples are given to illustrate the mechanisms by which cyclization has been achieved. These are illustrated in a very brief manner in Schemes 46–50.

Scheme 46 shows a range of base-catalysed processes initiated by the phenolate anion: these include Michael addition to an enone, which may be either (a) thermodynamically favoured, or (b) driven forward by subsequent oxidation; (c) intramolecular epoxide ring-opening (following epoxidation of a chalcone, the Algar–Flynn–Oymada reaction); (d) S_N2' substitution for dihydrobenzofurans; (e) closure on to a carbonyl function, followed by dehydration, as in isoflavone synthesis, or (f) flavone synthesis (Baker–Venkataraman reaction); (g) closure on to a carboxylic function, for coumarin synthesis; and (h) the highly ingenious intramolecular Wittig approach to chromens.

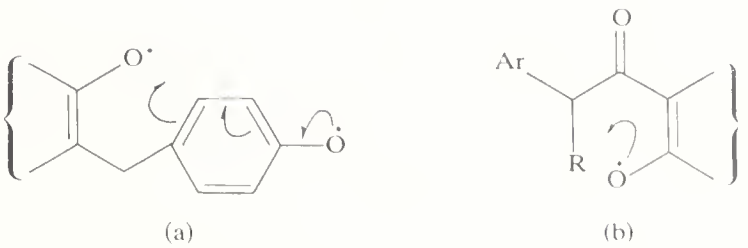


SCHEME 46

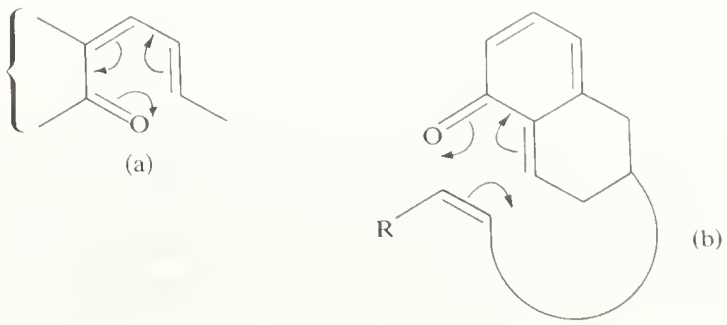
In Scheme 47 some acid-catalysed ring closures are illustrated, affording (a) chromans or (b) chromanols, or (c–e) furan relatives. Two radical processes, (a) and (b), are shown in Scheme 48, and Scheme 49 displays pericyclic closures, either (a) by electrocyclic reaction or (b) by internal Diels–Alder reactions.



SCHEME 47



SCHEME 48



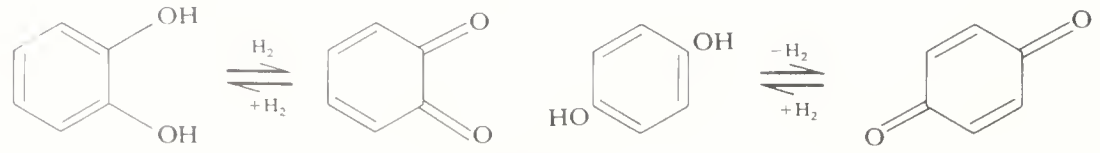
SCHEME 49

4.2.3.2 The oxidation of phenols

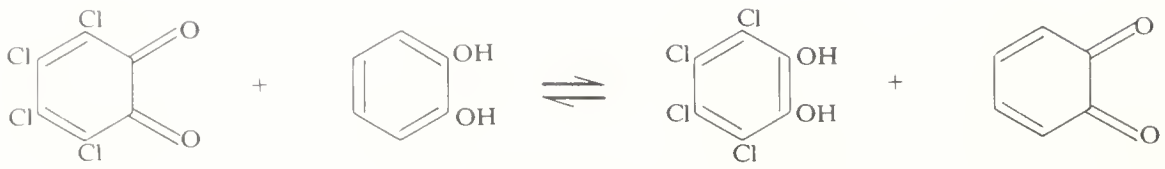
The oxidation of phenols is a complex area. Various mechanistic courses may be followed and several different reactive intermediates can be formed. The initial products are themselves often reactive and the final reaction products often arise after several stages. The combinations and permutations of the structural variants of mono- and poly-hydric phenols with one- and two-electron oxidants from all parts of the Periodic Table lead to an immensely ramified area. The majority of the work is empirical and the variations in methodology make it difficult to compare results. The subject is of importance from several angles: phenols are extensively used as anti-oxidants, *e.g.* for oils and fats;[105] *in vivo* oxidation is also an important step in the biosynthesis of many natural compounds, *e.g.* lignin, lignans, tannins, and many other natural phenolics including large groups of important alkaloids. Various aspects of the subject have been reviewed.[106] In the present text, only the broad scope of the area can be delineated; classification by product formation, rather than by reagent or mechanism, is most feasible in the present state of understanding. No attempt has been made to separate data relating to polyhydric phenols since the topics are so closely related and there is considerable overlap of material between sections.

(*i*) *Oxidation to quinones*

Both 1,2- and 1,4-dihydroxybenzenes are easily oxidized to *ortho*- and *para*-quinones, respectively (Scheme 50). A range of oxidants, including ferricyanide, silver oxide, iodine, Fremy's salt, and *o*-chloranil (Scheme 51) operate. The quinones are readily reduced back to phenols and the equilibrium position in, for example, an *o*-quinone–catechol system (Scheme 51) can be understood in terms of redox potentials. They have been measured for a number of such systems.[107] Quinones with halogen and nitrile substituents, *e.g.* dichlorodicyanoquinone, are high potential oxidants, and are valuable reagents for dehydrogenation.

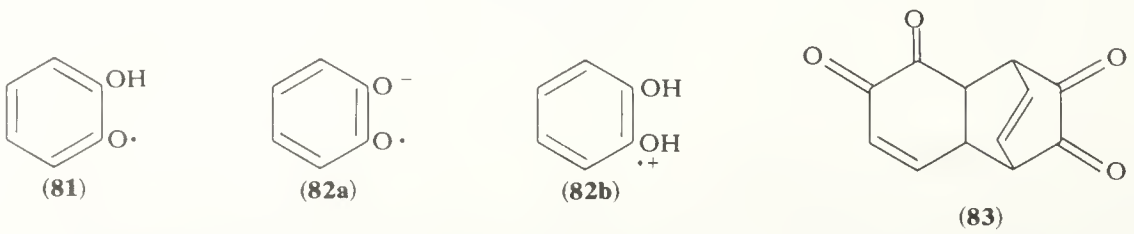


SCHEME 50



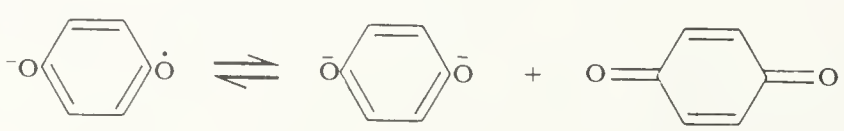
SCHEME 51

The first step in the oxidation of catechol is the semiquinone radical (**81**). In strongly alkaline solution the resonance-stabilized symmetrical radical anion (**82a**) is formed, while in strongly acidic media the protonated radical cation (**82b**) is produced. Electron spin resonance spectra of these radicals in solutions of different pH have been recorded.[108] Further oxidation leads to *o*-benzoquinone, which, although reactive and dimerizing readily[109a] to (**83**) *via* a Diels–Alder reaction, can be isolated as a red solid. A similar

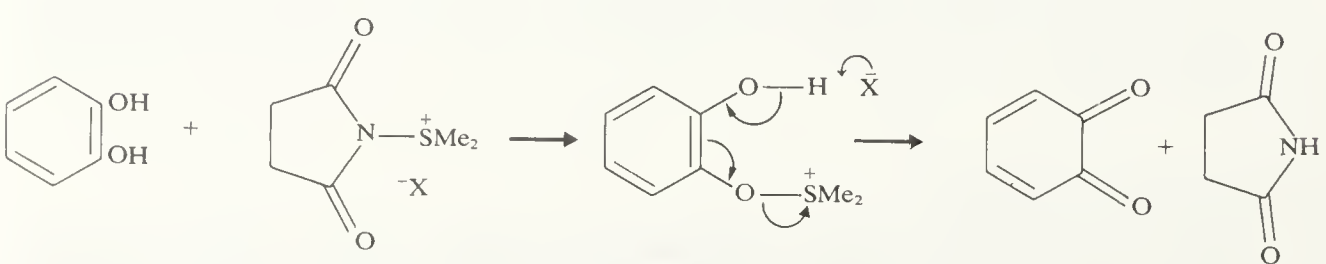


(**81**) (**82a**) (**82b**) (**83**)

pathway is followed for hydroquinone oxidation and the *p*-semiquinone radical anions have been well studied.[108b] The equilibrium in Scheme 52 is set up and the constant has been measured.[109b] A relatively mild method related to the Moffat oxidation (Scheme 53) for catechol oxidation to *o*-benzoquinones has been introduced.[110]



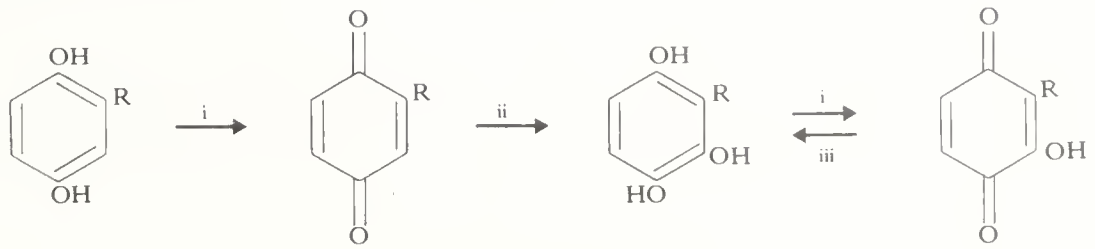
SCHEME 52



SCHEME 53

Anodic oxidation of phenols has attracted much attention in recent years; among its advantages are the attention which can be paid to oxidation potential. Hydroquinones with an electron-withdrawing substituent can be oxidized in this way. The resulting

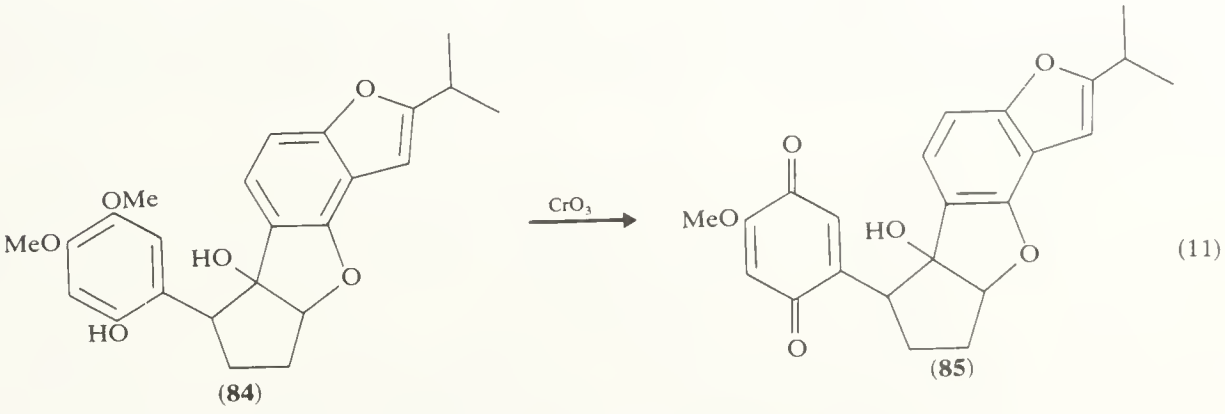
quinones add water to form a 1,2,4-trihydroxybenzene which is then oxidized to the quinone (Scheme 54).



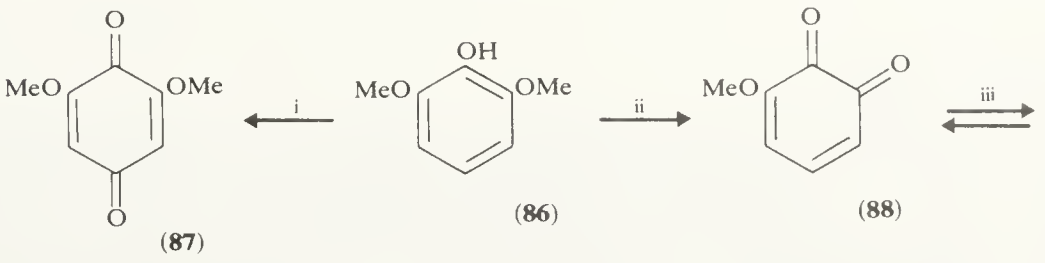
i, anode; ii, H_2O; iii, [H].

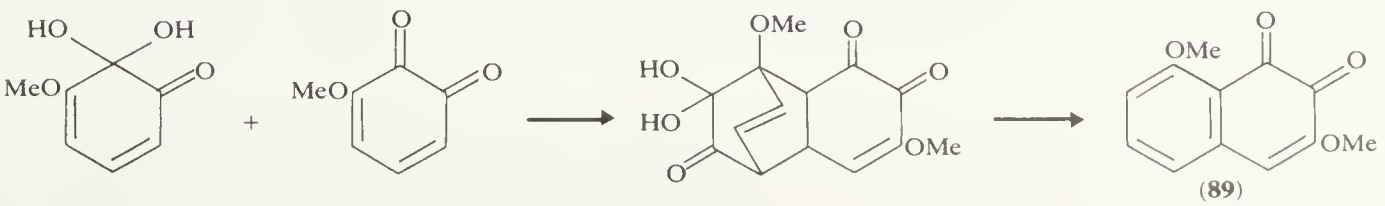
SCHEME 54

Free hydroxy functions are not essential for oxidation to quinones, nor is the presence of two *para* or *ortho* oxygen functions. Thus the phenol (**84**) is oxidized with chromium trioxide to the methoxyquinone (**85**) (equation 11). The pyrogallol methyl ether (**86**) can be oxidized with lead tetra-acetate to 2,6-dimethoxy-*p*-benzoquinone (**87**). If the oxidation is conducted with periodate (or bismuthate) the 3-methoxy-*o*-benzoquinone (**88**) is produced and equilibrates with its hydrate. A Diels–Alder reaction gives a dimer which is oxidized finally to the naphthoquinone (**89**)[111] (see Scheme 55).



(11)

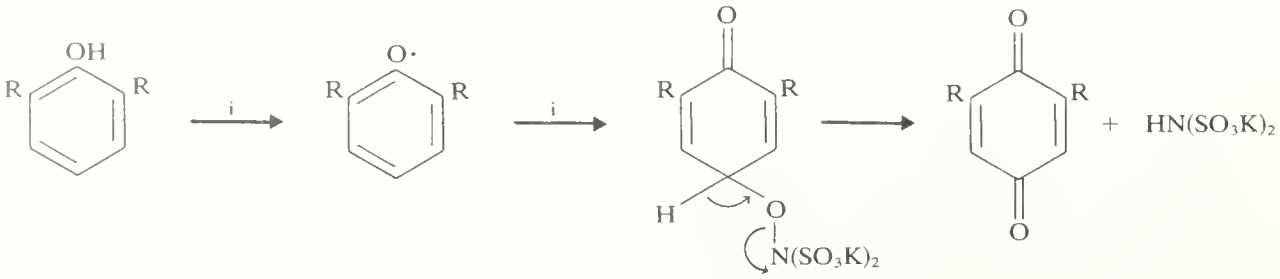




i, $Pb(OAc)_4$, ii, $^-IO_4$ or $^-BiO_3$, iii, H_2O.

SCHEME 55

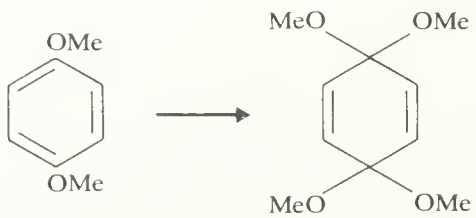
Oxidation at the position *para* to the hydroxy group can be carried out with many reagents. Some are known to act as radical oxidants,[112] *e.g.* Fremy's salt, organic nitroxides, perchloryl fluoride, chromyl choride, and hydroperoxides. The mechanisms of such reactions are illustrated for the case of Fremy's salt in Scheme 56. Other reagents,[113] *e.g.* trifluoroperacetic acid, peracetic acid, nitric acid, lead tetra-acetate, and potassium periodate, probably react in an ionic fashion. Oxidation at the position *ortho* to the hydroxy group can be achieved with phenylselinic anhydride.[114] Aromatic hydrocarbons without hydroxy groups can also be oxidized to quinones, *e.g.* 2-methylnaphthalene to 2-methylnaphthoquinone, with chromium trioxide.



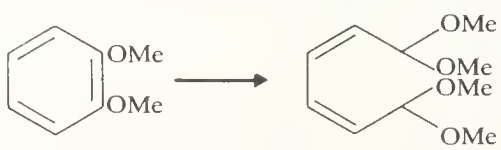
i, $(SO_3K)_2NO^{\cdot}$

SCHEME 56

Electrolysis of 1,4-dimethoxybenzene in methanol gives the otherwise inaccessible *p*-benzoquinone bis(dimethyl acetal) (**90**) (equation 12).[115] The corresponding reaction with 1,2-dimethoxybenzene leads with ring-bond cleavage to *cis,cis*-muconic acetal (**91**) (equation 13).



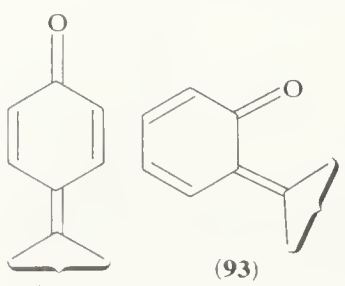
(**90**) (12)



(**91**) (13)

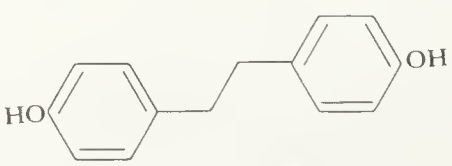
(*ii*) *Quinone methides*

Quinone methides may possess *para* (**92**) or *ortho* (**93**) structures, are as a rule unstable, and are subject to ionic- and cyclo-addition reactions; their chemistry has been reviewed.[116] They can be formed by oxidation of alkylphenols but are also available by other routes. For example, a dihydroxydiphenylethane (**94**) affords the 'stilbene quinone'[117] (**95**). Simple *p*-alkyl phenols yield the corresponding methide with silver oxide reagent[118], while oxidation with dichlorodicyanoquinone in methanol leads to acetals from

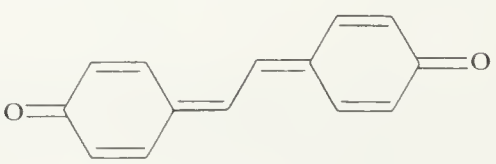


(**92**)

(**93**)

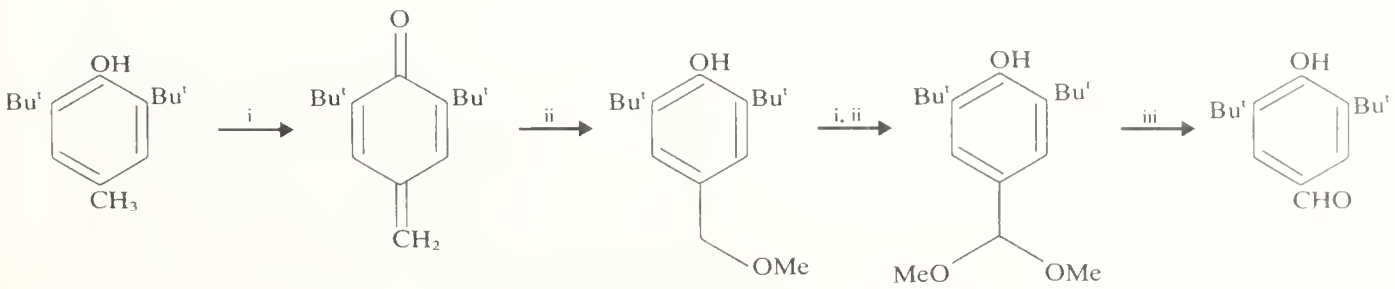


(**94**)



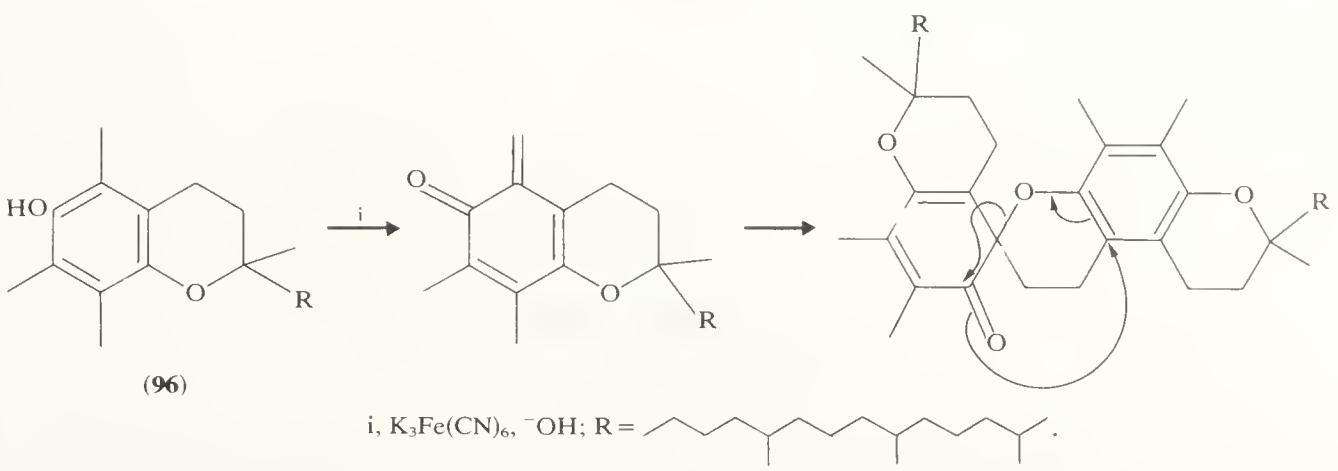
(**95**)

which the carbonyl compounds can be obtained[119] (Scheme 57). Oxidation with ferricyanide of α-tocopherol (**96**) (Scheme 58) gives a dimer in good yield, which is involved in a degenerate sigmatropic rearrangement at 70 °C, as revealed[120] by the temperature-dependent ^{1}H n.m.r. spectra. High-potential quinone dehydrogenation of *o*-3-methylbut-2-enylphenols gives quinone methides set up for the ensuing electrocyclization[121] (Scheme 59). Other methods of generating quinone methides include 1,4-eliminations, *e.g.* pyrolysis of salicyl alcohols,[122] and Wittig reactions with quinone substrates.[123]

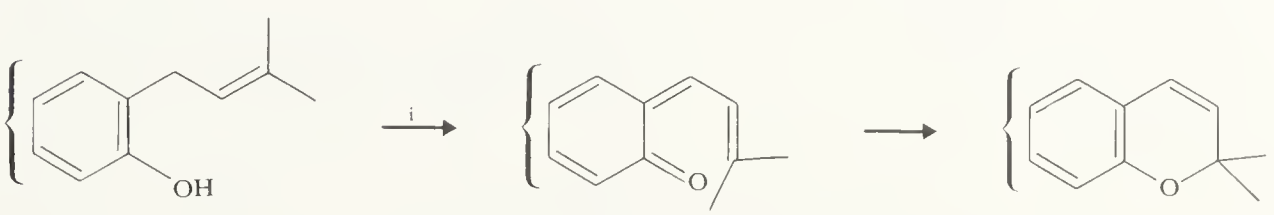


i, Dichlorodicyanoquinone; ii, MeOH; iii, H_3O^+.

SCHEME 57



SCHEME 58

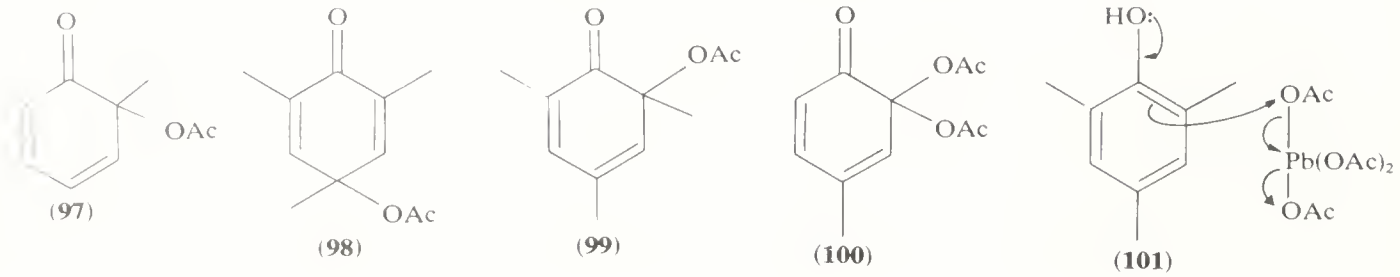


i, Dichlorodicyanoquinone.

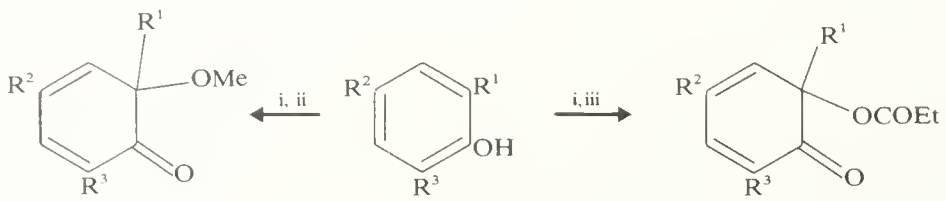
SCHEME 59

(*iii*) *Oxidation to oxycyclohexadienones: the Wessely and related reactions*

(*a*) *Wessely oxidation.* Lead tetra-acetate in acetic acid converts phenols into acetoxycyclohexadienones, a reaction leading to intriguing chemistry and much investigated by Wessely and co-workers.[124] *o*-Cresol gives dienone (**97**); 2,4,6-trimethylphenol gives rise to the constitutional isomers (**98**) and (**99**). *p*-Cresol gives, among other products, the diacetoxydienone (**100**), showing that sequential acetoxylation at an unsubstituted site can take place. The reaction is a valuable synthetic tool for preparing cyclohexadienones

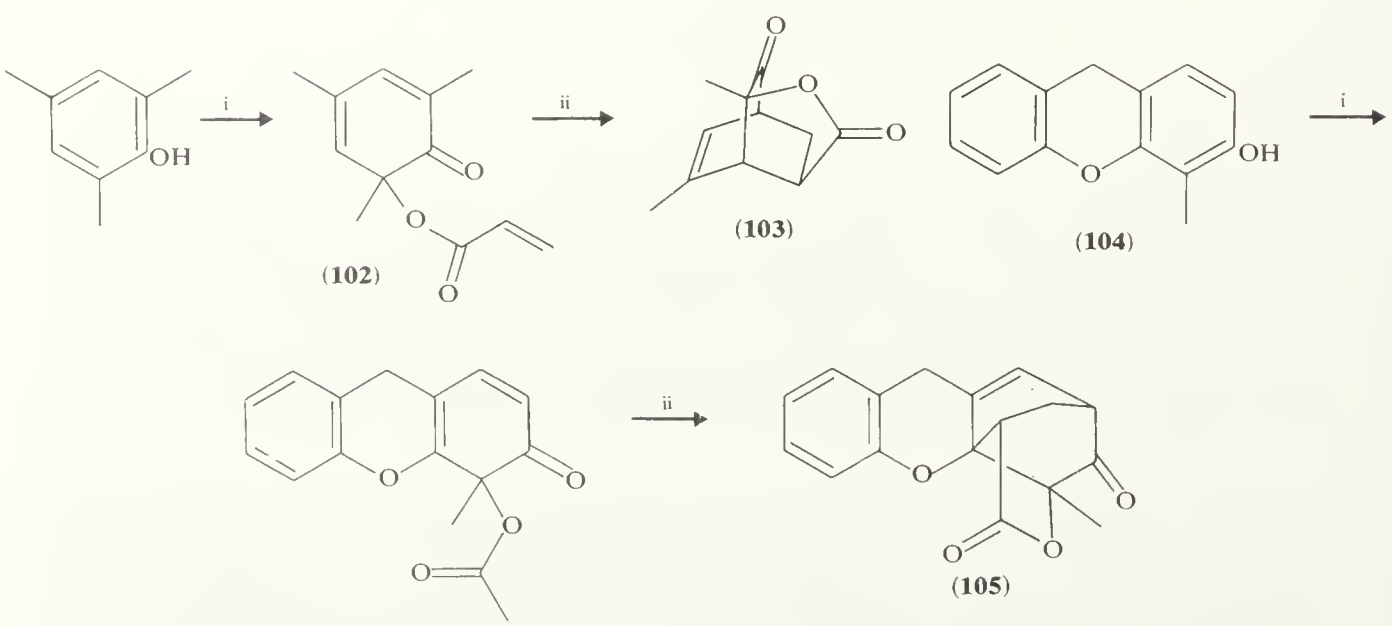


blocked to enolization. The mechanism[125] is considered to be heterolytic and to involve a bimolecular phenol–lead tetra-acetate reaction (**101**); attack is fast at both the *ortho* and *para* positions. A limited number of variations in the carboxylate can be realized. Lead tetrabenzoate can be prepared and can be used to conduct benzoylation. A simple alternative involves using lead tetra-acetate in either an excess (solvent) of an acid other than acetic acid or in alcohol (Scheme 60). This process has been employed (see Scheme 61) to introduce acroyloxy groups:[126] 2,4,6-trimethylphenol gives (**102**), which can be induced into intramolecular Diels–Alder reaction, forming the unusual bridged system (**103**). With the xanthan (**104**), parallel reactions afford (**105**) with a ring system akin to that of the complex natural xanthone morellin (**78**).



i, $Pb(OAc)_4$; ii, MeOH; iii, $EtCO_2H$.

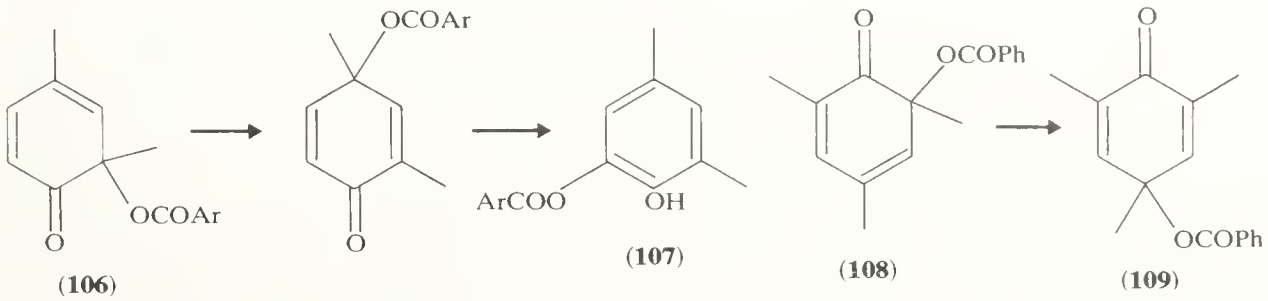
SCHEME 60

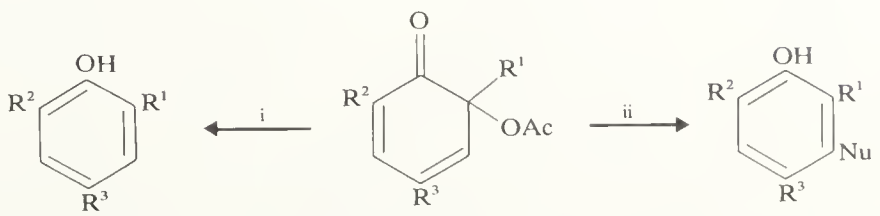


i, $Pb(OAc)_4$, $CH_2{=}CHCO_2H$; ii, Δ.

SCHEME 61

Understandably, Wessely oxidation is slowed down by electron-withdrawing groups but can be catalysed by boron trifluoride etherate using ethyl acetate–methanol solvent. An excess of the reagent is usually employed — in fact, a thick paste of lead tetra-acetate in acetic acid or chloroform, is recommended. The cyclohexadienone products are subject to assorted rearrangements. For example, (**97**) undergoes dienone–phenol transformation in acetic anhydride–sulphuric acid to 2-methylresorcinol acetate. Thermal rearrangements have also been investigated and cyclic concerted pathways involving [3,3]-sigmatropic shifts have been shown to operate during aromatization of (**106**) to (**107**). The reversibility of the isomerization of (**108**) to (**109**) has been demonstrated.[127] Aromatization initiated by nucleophiles is possible, as illustrated in Scheme 62. Reduction of the acetoxycyclohexadienone back to the parent phenol has been achieved with dibenzylideneacetoneiron tricarbonyl.

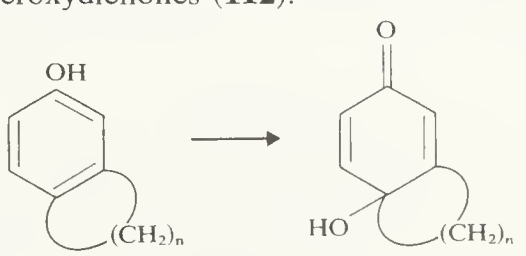




i, $Fe_2(CO)_9$ or (dibenzylideneacetone)$Fe(CO)_3$; ii, Nu^-.

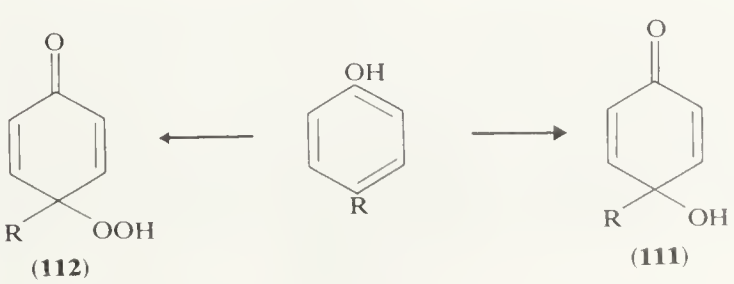
SCHEME 62

(*b*) *Related oxidations.* A few other reagents have been reported to yield oxydienones, *e.g.* thallium(III) perchlorate[128a] in aqueous hydrochloric acid has oxidized certain bicyclic phenols to 4-hydroxydienones (**110**) (equation 14). *para* Hydroxylation can also take place at the anode — the formation of (**111**) in equation (15) — while sodium tungstate–peroxide[128b] gives hydroperoxydienones (**112**).



(14)

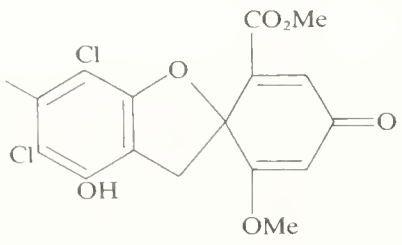
(**110**) $n = 1,2$



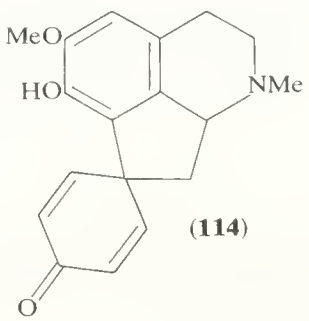
(15)

(iv) Oxidative phenolic coupling

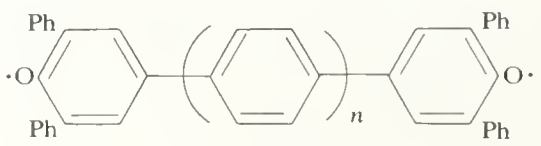
The oxidation of phenols with a great variety of one-electron oxidants leads to coupling reactions involving oxygen and/or carbon centres. The products may arise from intramolecular or intermolecular coupling (usually dimerization in the latter case). A vast amount of information has accumulated in this area, but it is still difficult to make generalizations because of the wide variations in the nature of the oxidizing reagents employed under varying conditions (frequently in heterogeneous systems), and because of the complexity of the product mixtures and low yields of products isolated and characterized. Further product oxidation and the relative shortage of systematic investigations (*e.g.* of the dependence on redox potential or pH) add to the difficulties of understanding the area. In synthetic work it is usual to seek the closest precedent available, by, for example, consulting the reaction lists compiled by Musso.[106d] This author concludes the 'there is no way to predict the *best* reagent for a given coupling'. The reaction is of considerable biological importance and can be mediated by enzyme oxidases; many natural products, *e.g.* geodin (**113**) and orientalinone (**114**), are considered to arise in this fashion. A number of good reviews are available.[106,129]



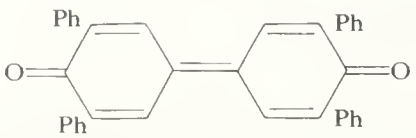
(**113**)



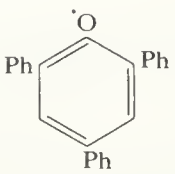
(**114**)



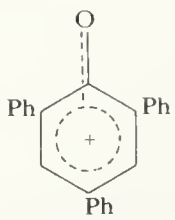
(**115**)



(**116**)

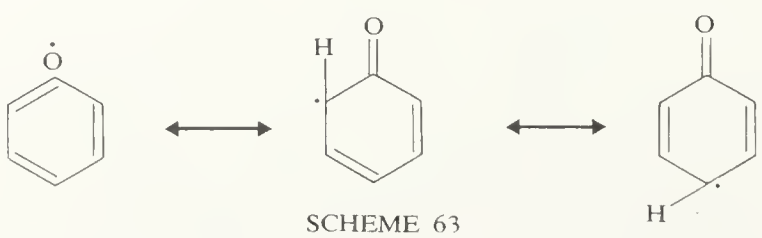


(**117**)



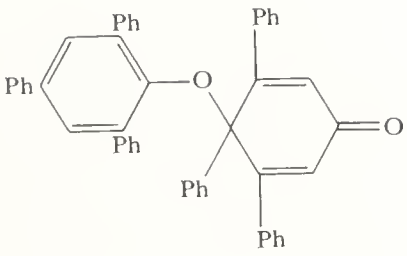
(**118**)

Radical mechanisms are generally considered to operate, with resonance-stabilized aryloxy radicals participating (Scheme 63). Such radicals have been detected by e.s.r. spectroscopy.[130] Where the phenols are heavily substituted, further reactions are inhibited

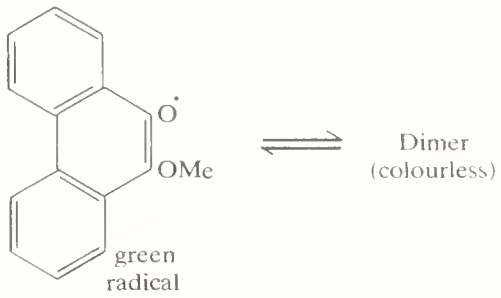


SCHEME 63

and, particularly if additional resonance stabilization is provided, relatively stable radicals may be obtained. Their properties have been studied intensively,[131] *e.g.* in the dihydroxypolyphenyls (**115**) only the member with $n = 0$ exists in the extended quinone form (**116**), those with $n > 1$ preferring the biradical structure. 2,4,6-Triphenylphenoxyl (**117**) may suffer a second one-electron oxidation to a stable phenoxonium cation (**118**). Full accounts of stable aryloxy radicals can be found.[132] Many such radicals dimerize in the solid state, *e.g.* (**117**) → (**119**) (Scheme 64), or combine with other reactive radicals (NO_2, ·OOH, O_2).



(**119**)

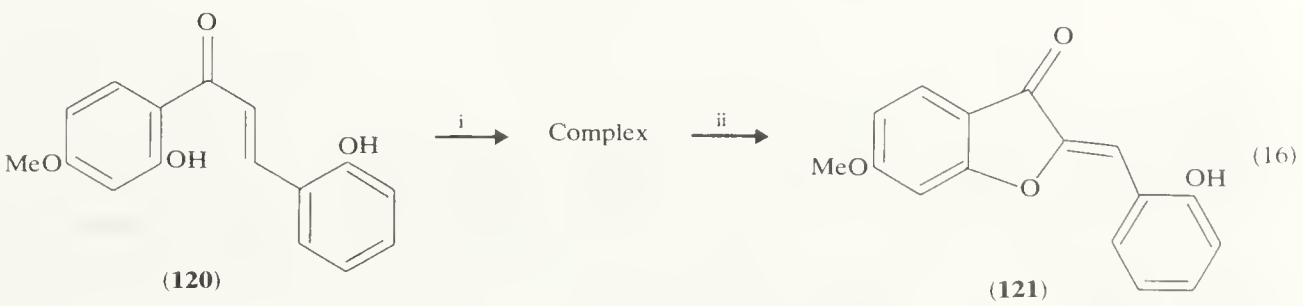


SCHEME 64

Phenoxonium cations can be produced by one-electron oxidation of phenoxyl radicals (as above) or they can be envisaged as a product of disproportionation of phenoxyl radicals:

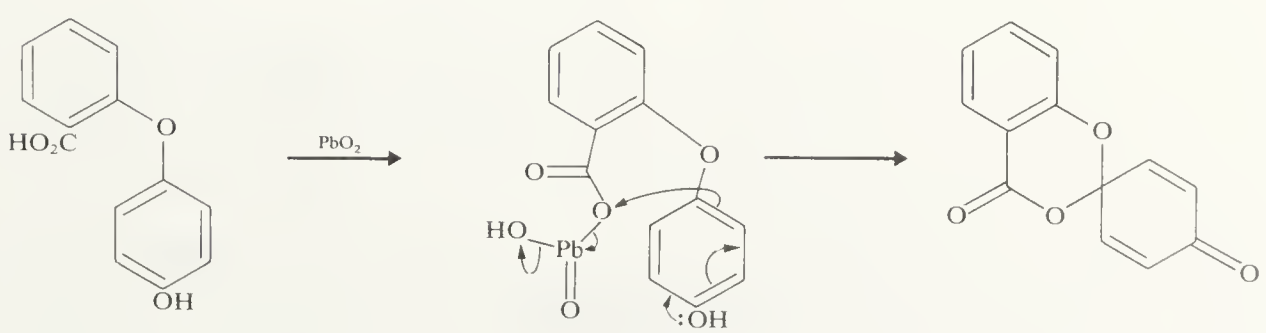
$$2ArO\cdot \xrightarrow{1e^- \text{ transfer}} ArO^- + ArO^+$$

Their intermediacy in coupling has been suggested[133] and related possibilities discussed.[134] In particular, Waters proposed that oxidation with high-potential oxidants in acidic media is likely to form phenoxonium species which are positioned to prefer O—C coupling, whereas alkaline conditions with lower potential oxidants would lead to phenoxyl radicals preferring C—C coupling. Good evidence for cationic intermediates in dichlorodicyanoquinone ($2e^-$ oxidant) oxidations has been forthcoming,[135] but a deliberate search for cations in other systems with $1e^-$ oxidants revealed none[134b] and the extent of their involvement in phenol oxidation remains uncertain. The possibility that the reactive intermediates in reactions brought about by inorganic oxidants may be organometallic species or outer-sphere complexes, rather than discrete radicals or cations, must not be overlooked. Alkaline potassium ferricyanide reacts with 2,2′-dihydroxy-4-methoxychalcone (**120**) to give an insoluble complex, within which the product, 2′-hydroxy-6-methoxyaurone (**121**) is formed, and protected from further oxidation (equation 16). A lead(IV) species is probably involved in the lead dioxide oxidation in Scheme 65. Simple radical coupling would necessitate the oxidation of both carboxyl and phenol functions at similar rates. Geodoxin (**122**) can be prepared in high yield in an analogous fashion.

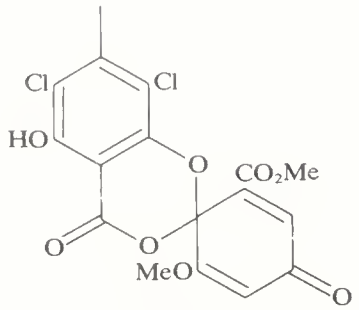


(**120**) (**121**) (16)

i, ^-OH, $K_3Fe(CN)_6$; ii, H_3O^+.



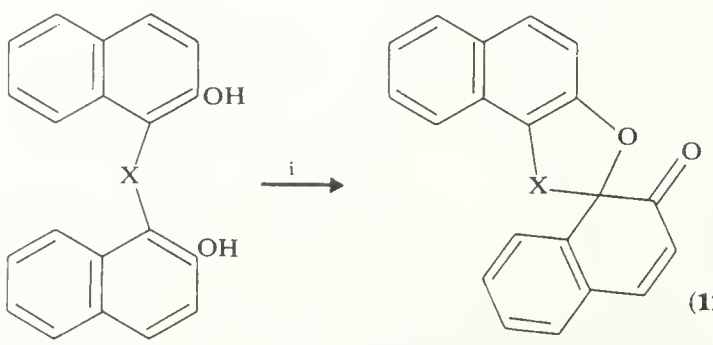
SCHEME 65



(**122**)

There is evidence that phenolic couplings do not proceed by ArO· insertion into neutral phenol or phenyl ether moieties, although it appears that ArO· insertion into phenolate anions is not rigorously excluded. This is of interest in the light of the successful coupling of light-generated radicals with phenolate anions.

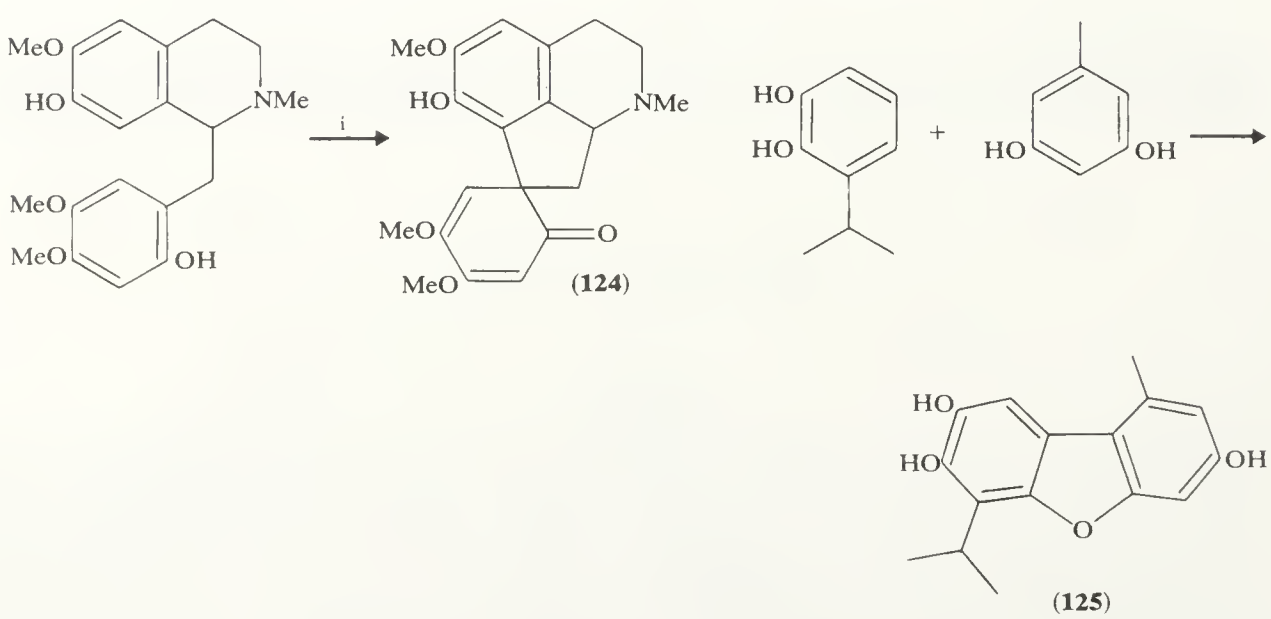
All possible combinations of radical centres may be realised (O–*ortho*-C, O–*para*-C, *ortho*–*ortho*-C, *para*–*para*-C, and *ortho*–*para*-C) and examples[136–140] of each of these are illustrated in the formation of (**123**)–(**130**) in Schemes 66–70.



(**123**)

i, $K_3Fe(CN)_6$, ^-OH. X = S, SO_2, CH_2, *etc.*[136]

SCHEME 66



(**124**)

(**125**)

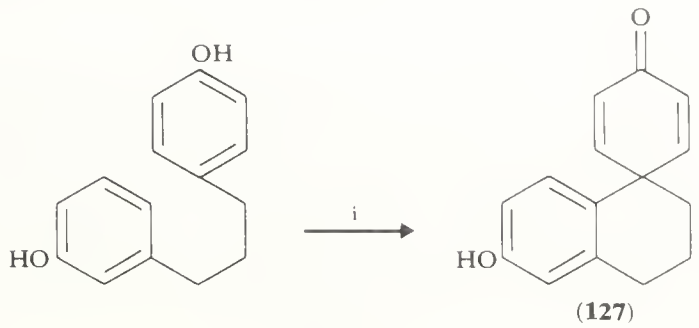
i, $K_3Fe(CN)_6$, ^-OH.[137]

SCHEME 67

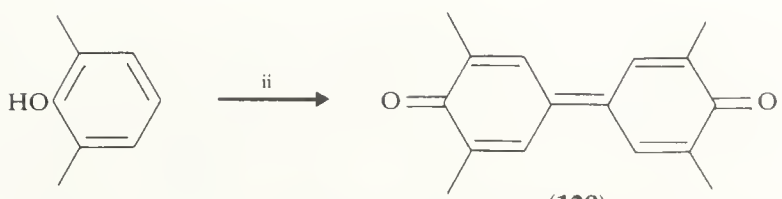
(126)

i, $K_3Fe(CN)_6$, ^-OH.[138]

SCHEME 68



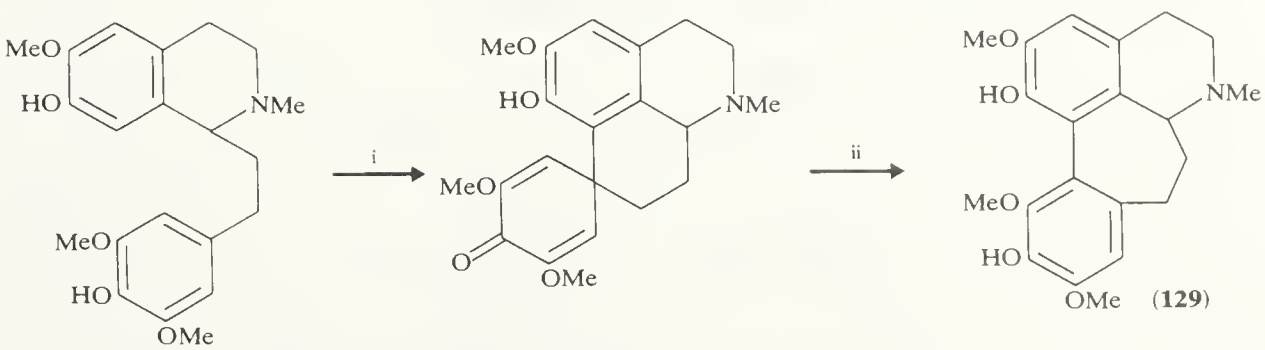
(127)



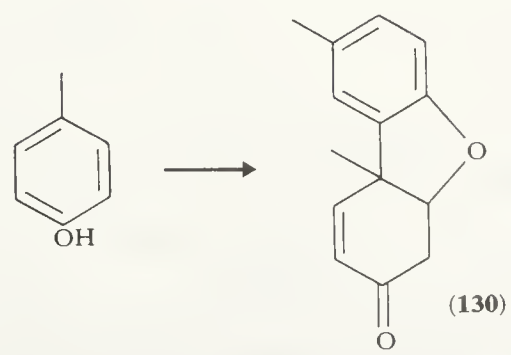
(128)

i, $VOCl_3$; ii, $K_3Fe(CN)_6$, ^-OH.[139]

SCHEME 69



(129)



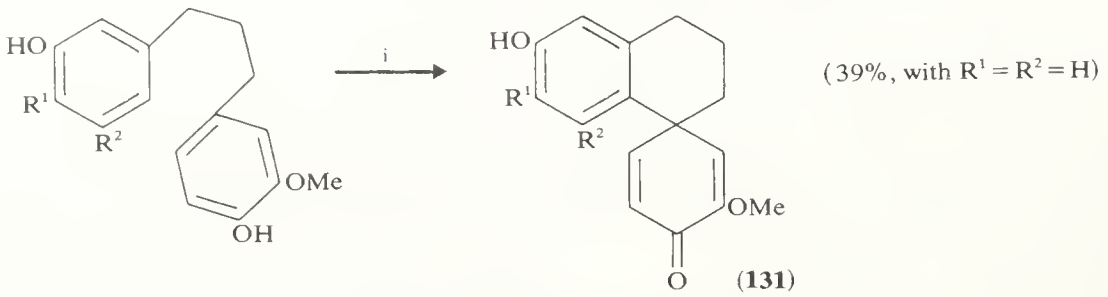
(130)

i, $K_3Fe(CN)_6$; ii, H_2SO_4.[140]

SCHEME 70

Pummerer's ketone (**130**) (*ortho–para* coupling) is formed from *p*-cresol (Scheme 69) with the *ortho–ortho* product and a minor O—C product. This reaction has been examined in detail[141] and the product distribution is insensitive to pH and the redox potential of the oxidant. However, the product ratio is very temperature dependent, reflecting the reversibility of the coupling step and the irreversibility of the following enolization. The *ortho–para* coupling product is kinetically favoured but dissociates readily; with silver carbonate on Celite in benzene, no Pummerer's ketone (**130**) is formed (dissociation > enolization), but in acetonitrile, 63% of the dimeric product was Pummerer's ketone (**130**) (increased enolization rate).

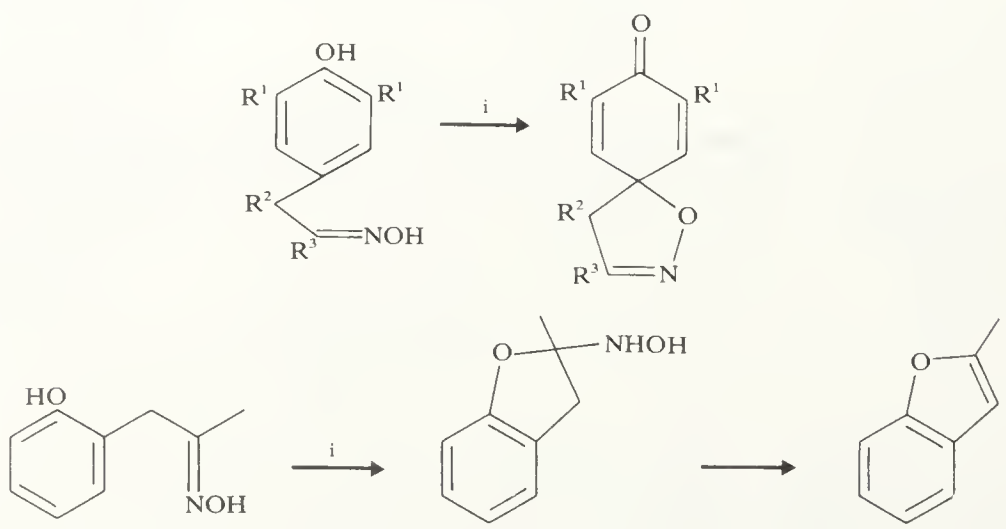
A number of new reagents have been tried to supplement the ferric compounds widely used in the older literature. Potassium ferricyanide itself is employed in heterogeneous conditions, *e.g.* with aqueous alkali–methylene chloride. The action of phase-transfer reagents has not been explored. The oxidation potential is much reduced in dilute acid,[142] when the reagent fails to oxidize phenol itself. Aqueous ferric chloride can be replaced by the complex ion $Fe(DMF)_3Cl_2 \cdot FeCl_4$, which when used in homogeneous DMF solution[143] mediates the coupling efficiently to give (**131**) as shown in Scheme 71.



i, $Fe(HCONMe_2)_3Cl_2 \cdot FeCl_4$.

SCHEME 71

Manganese(III) acetylacetonate[144] can be used in organic solvents, *e.g.* acetonitrile and carbon disulphide, with no quinone by-products. It works well for the oxime *O*-coupling of Scheme 72; *ortho*-hydroxy compounds give benzofurans.

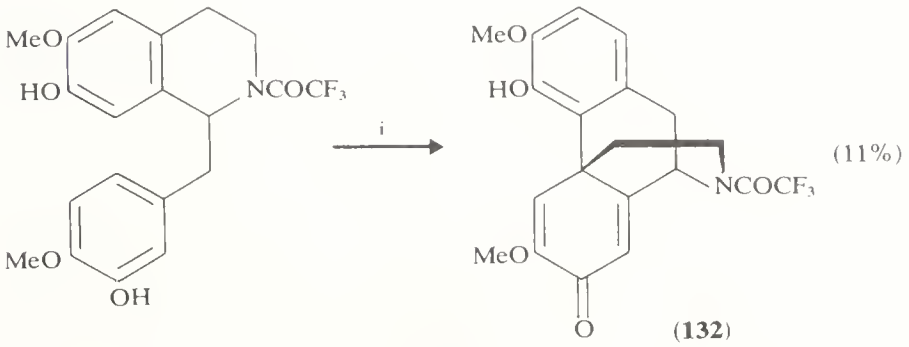


i, Mn(III) acetylacetonate.

SCHEME 72

The multifarious uses of thallium in organic chemistry include several applications to biaryl formation. For example, Scheme 73 shows the oxidation of *N*-trifluoroacetylnorreticuline to *N*-trifluoroacetylnorsalutaridine (**132**) with thallium(III) trifluoroacetate;[145] although the yield (11%) is poor in absolute terms, yields with other reagents were

negligible. The *N*-acylnorsalutaridine has been converted on into the thebaine–morphine series.

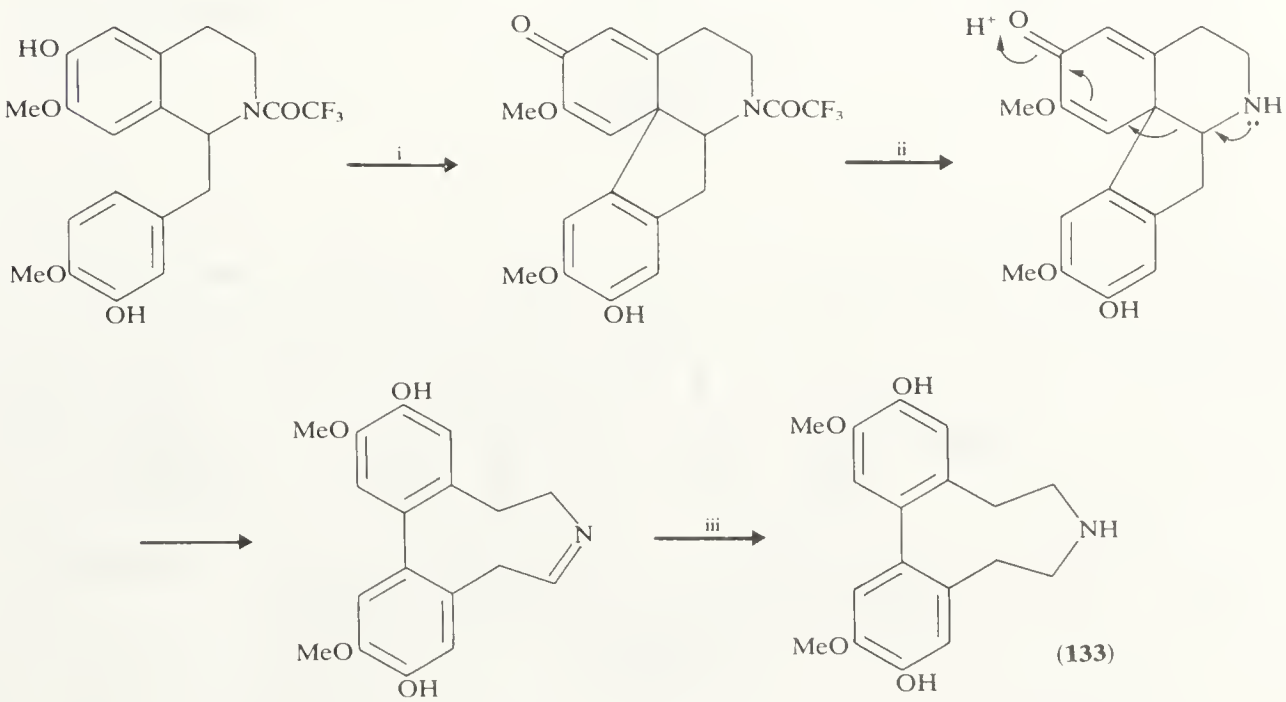


i, $Tl(OCOCF_3)_3$.

SCHEME 73

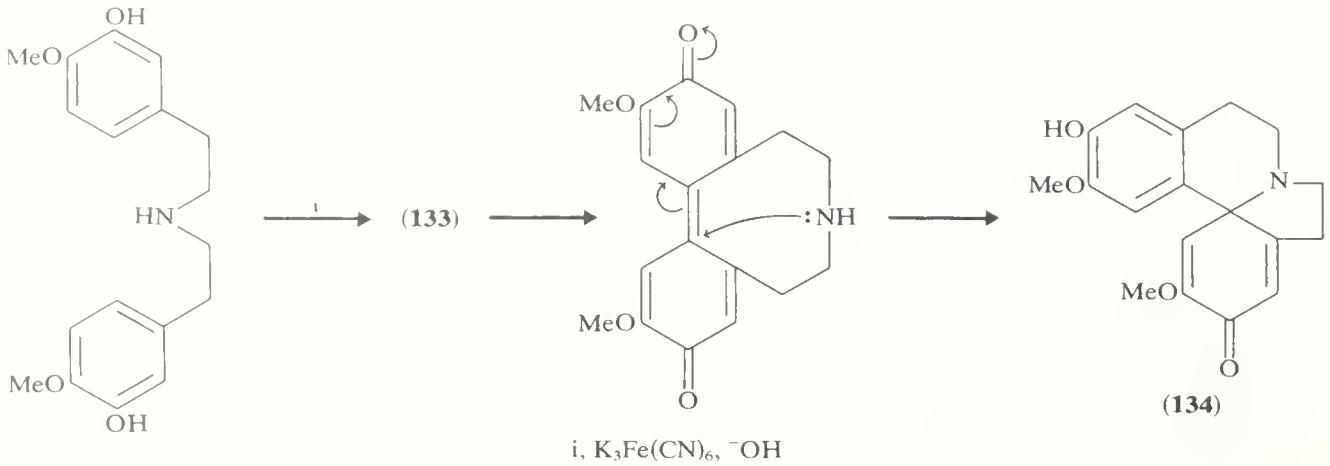
Fetizon's reagent (silver carbonate on Celite) has been applied to oxidative coupling,[146] providing entirely heterogeneous coupling and displaying a prediliction for C—C coupling: the case of Pummerer's ketone discussed above shows the importance of solvent.

Vanadium oxytrichloride or oxytrifluoride oxidation[147] is referred to above (Scheme 69) and high (76%) yields of (**127**) were obtained for the case shown. Another use is displayed in Scheme 74 in producing a subtle synthesis of the *ortho–ortho* bridged biphenyl alkaloid (**133**). The same compound (**133**) is an intermediate in the oxidation cited in Scheme 75 leading to erysodienone (**134**),[147b] an *Erythrina* alkaloid; however, this is not the biosynthetic pathway.[147c]



i, VOF_3; ii, ^-OH; iii, $^-BH_4$.

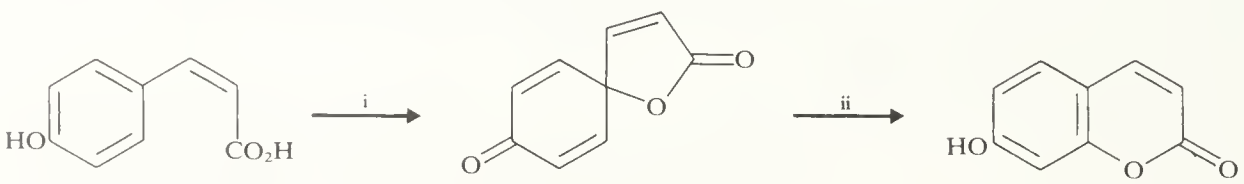
SCHEME 74



i, $K_3Fe(CN)_6$, ^-OH

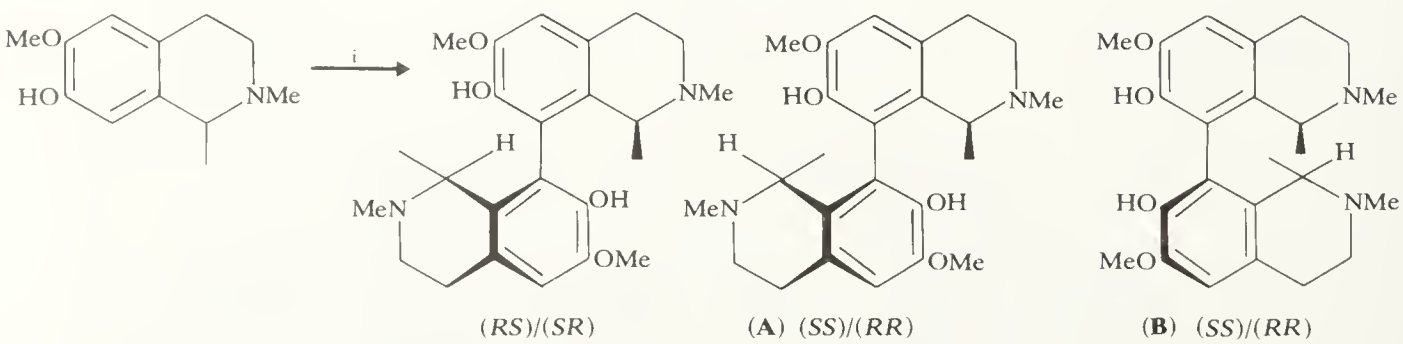
SCHEME 75

Although anodic oxidation has been known and used in organic chemistry since the nineteenth century, there has been a surge of interest in its application to oxidative coupling in the hope (only partly realised, as with other reagents) of exerting more control over the reaction. Many useful references have been collected.[148] Inter- and intramolecular C—C and C—O couplings have been described. From the many examples available,[149,150] those in Schemes 76 and 77 will serve as illustrations. The former scheme shows a model for coumarin biosynthesis,[151] the latter an interesting case of stereochemical control, presumably by participation of the anodic surface.[152]



i, Anode, ii, H^+.

SCHEME 76



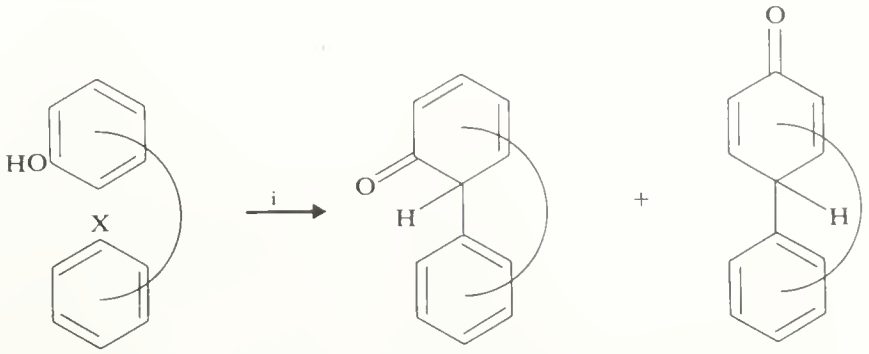
i, O_2, Pt, all isomeric products; or i, anode, only (**A**) (*SS*)/(*RR*)

SCHEME 77

Anodic oxidations are not confined to the free phenols but apply also to their ethers. Thus (±)-laudanosine is oxidatively cyclized to *O*-methylflavinantine (52%) and reactions similar to those shown in Scheme 68 can be conducted with phenyl methyl ethers.[153,154]

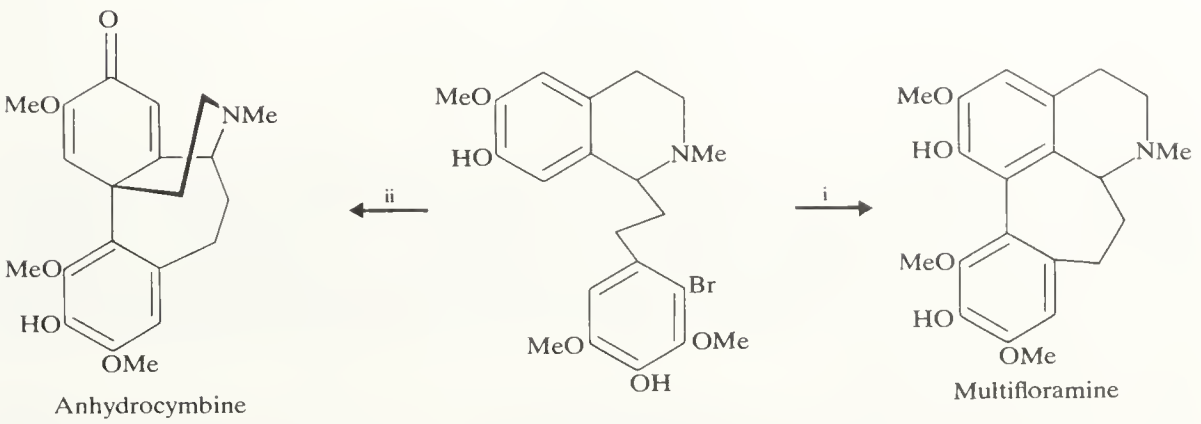
(*v*) *Photochemical methods*

Kametani and his co-workers[155] have been prominent in employing photochemical reactions to achieve oxidative coupling in alkaloid synthesis, following the general reaction of Scheme 78 where X = halogen (or N_2^+, the photo-Pschorr reaction). Basic conditions are employed. The products are dependent on the nature of the medium[156] (Schemes 79 and 80). In the second example, the low yield of the initial dienone (unless



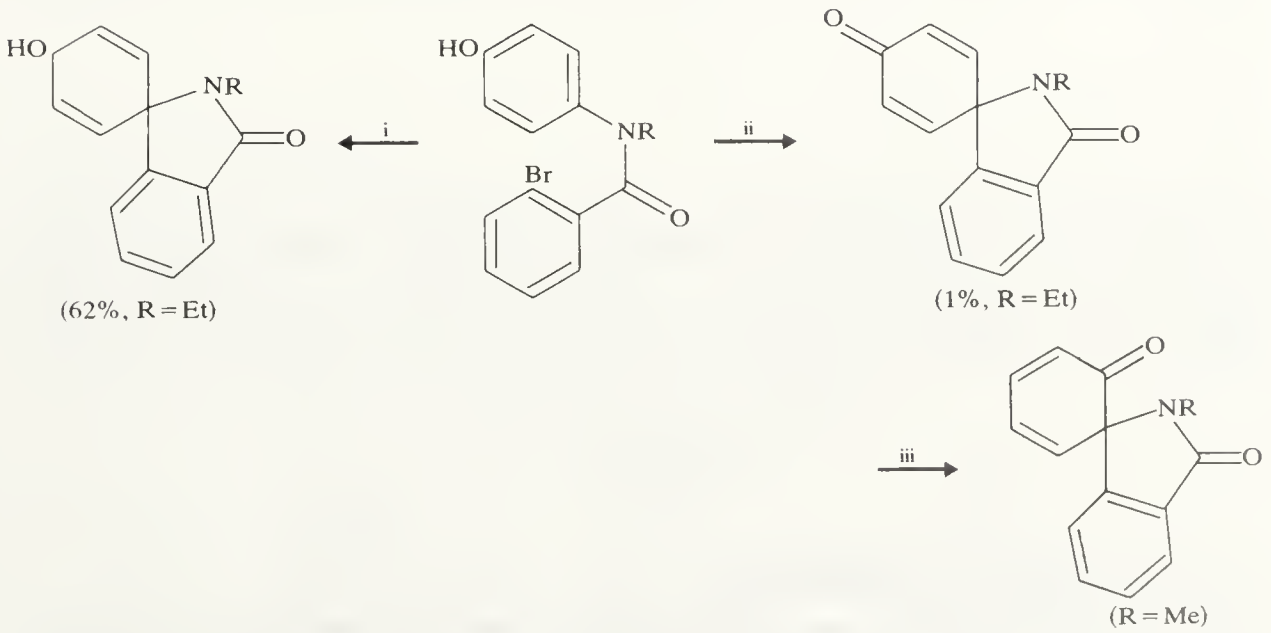
i, *hν*, base.

SCHEME 78



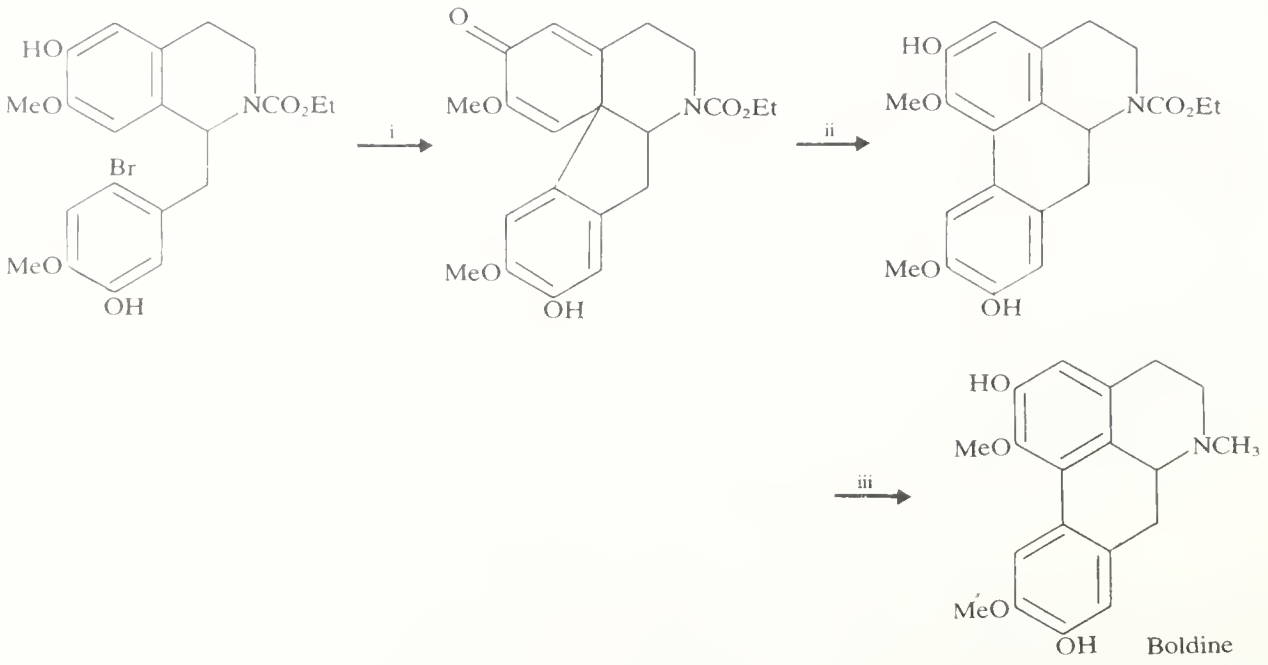
i, *hν*; ii, *hν*, NaI.

SCHEME 79



i, *hν*, ^-OH, $^-BH_4$; ii, *hν*, ^-OH; iii, *hν*, C_6H_6.

SCHEME 80

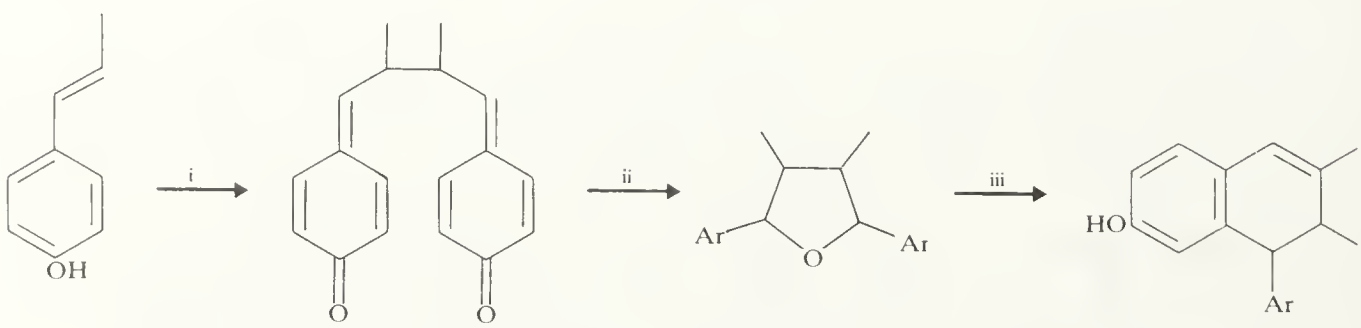


i, $h\nu$, ^-OH; ii, $h\nu$, iii, $LiAlH_4$.

SCHEME 81

intercepted by reduction) is in part due to further photochemical rearrangement, *p*-dienone → *o*-dienone.[157a,b] Light-catalysed dienone → phenol rearrangement features in the synthesis[157c] of (±)-boldine (Scheme 81). Related reactions have been reviewed;[158] the best yields arise with coupling between an aryl halide and the *para* position of a phenol. The mechanism is generally considered, without much experimental investigation, to involve aryl carbon–halide bond homolysis, followed by trapping of an aryl radical by phenol or phenolate anion.

Finally, oxidative coupling of propenyl phenols, *e.g.* cinnamyl alcohol and coniferyl alcohol, is the accepted mechanism for lignin and lignan biosynthesis.[159] Model couplings have been investigated several times.[160] Two recent examples are shown in Schemes 82 and 83.

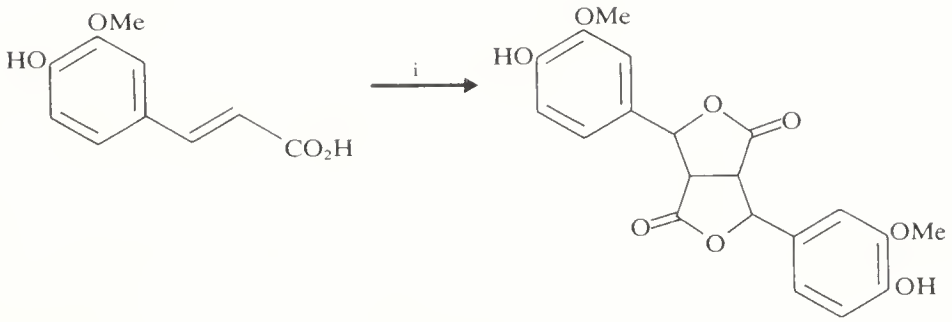


i, H_2O_2 + peroxidase; ii, H_2O; iii, H^+.

SCHEME 82

4.2.3.3 Reactions of the aromatic ring

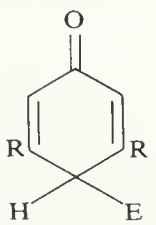
Electrophilic substitution occurs more readily in phenols than in benzene. Phenol *ipse* is nitrated by dilute nitric acid, nitrosated by nitrous acid, tribrominated by bromine, and coupled with diazonium salts (in all cases rapidly at temperatures not higher than



i, $FeCl_3$, $HCONMe_2$.

SCHEME 83

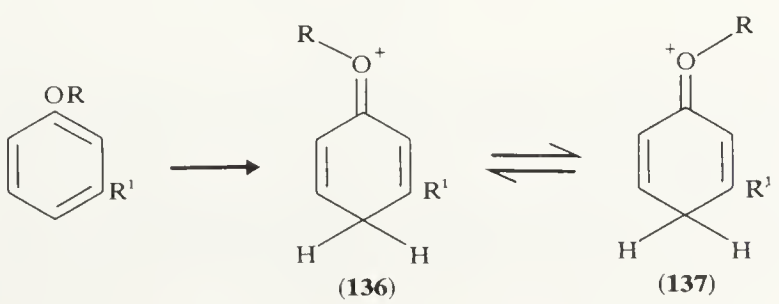
ambient). Substitution rates in phenols are unexpectedly high[161] in comparison with those for phenyl ethers (*e.g.* for bromination, $k_{anisole}/k_{phenol} = 92$). This has been explained by an inductomeric effect (of O—H bond electrons) on conjugation in the transition state and hydrogen bonding to the solvent has also been emphasized as an important factor. Most reviews deal with aromatic substitution from a reagent-mechanism viewpoint (not separating out phenol chemistry), but much useful information is to be found in general reviews.[162] Electrophilic substitution in phenol itself has been surveyed.[163] Nitration of phenol in organic solvents is irreversible, reactions in different solvents displaying a constant *ortho*/*para* ratio. Halogenation is also irreversible but with a lower *ortho*/*para* ratio than with nitration, while sulphonation and Friedel–Crafts alkylation are reversible. In the sulphonation reaction, chiefly *ortho* products are produced at low temperatures and *para* products at higher temperatures. *meta* Sulphonic acids accumulate substantially in prolonged reactions, desulphonation of the *meta* acid being the slowest of the reverse processes. The kinetic and thermodynamic *ortho*/*para* ratios are also different for the Friedel–Crafts alkylation. A dienone intermediate (**135**) in bromination of 3,5-dialkylphenols has been isolated.



(**135**)

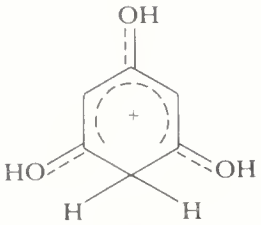
(*i*) *Proton and Lewis acids*

Hydrogen isotope exchange has been widely studied[164] and follows the S_E pathway in proton acids with ready exchange of *ortho* and *para* hydrogens. The protonations of phenols and their ethers in superacid systems (in which sufficiently high proportions of protonated species are formed to permit spectroscopic investigation) have also been examined.[165] *para* Protonation of simple phenols and their ethers (**136, 138**) was mainly observed; interconversion between stereoisomers (**136, 137**) becomes apparent (equation



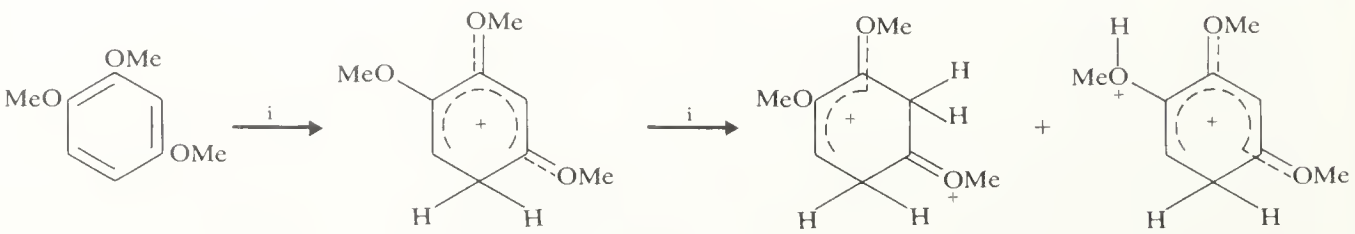
(**136**) (**137**)

(17)



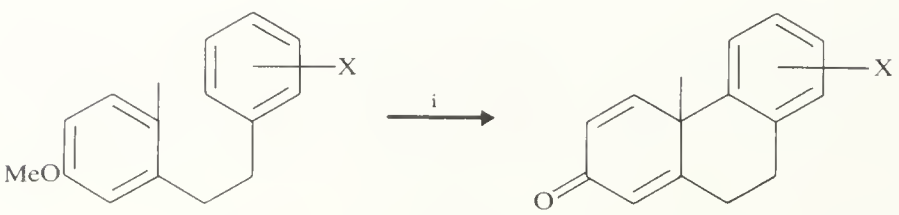
(138)

17). *O*-Protonation and diprotonation have also been observed (Scheme 84). *C*-Protonation provides a carbon electrophile and this has been put to use in synthesis[166] (Scheme 85). Ring protonation may also lead to retro-Friedel–Craft reactions.[167] Lewis acids may behave similarly (Scheme 86) and the relative ease of removal of a t-butyl group has suggested the use of this group for blocking ring positions. The *m*- and *p*-cresols may be separated *via* their di-t-butyl derivatives. Alkyl migrations can also be induced by Lewis acids, *e.g.* myricanone to isomyricanone[168] (Scheme 87).



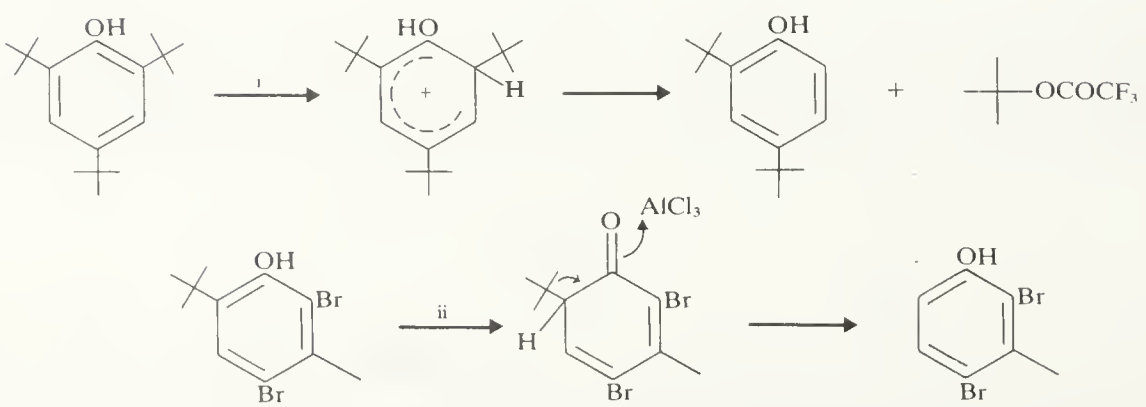
i, 'super-acid'.

SCHEME 84



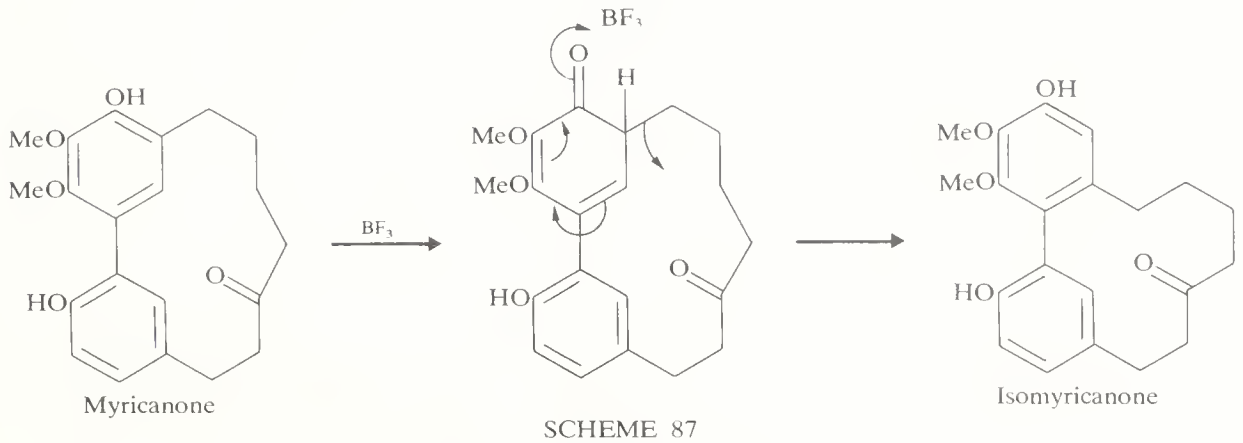
i, SbF_5, HF.

SCHEME 85



i, CF_3CO_2H; ii, $AlCl_3$, CH_3NO_2, C_6H_6.

SCHEME 86

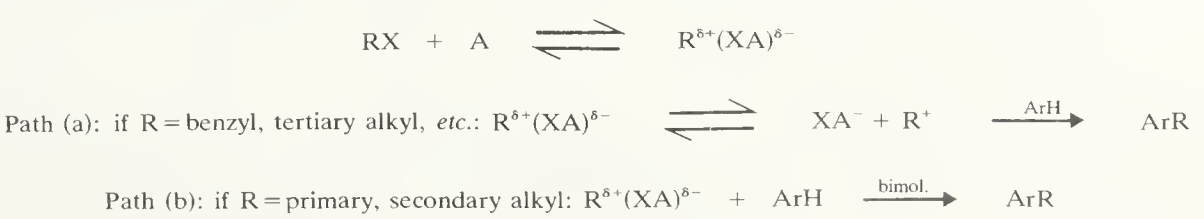


SCHEME 87

(*ii*) *Group IV electrophiles*

(*a*) *Acid-catalysed alkylation.* The extent of this reaction may be judged by the extent (5188 pages!) of Olah's text on the Friedel–Crafts and related reactions.[169] It encompasses all those reactions in which an electrophilic carbon centre substitutes into an aryl ring, and there are very many (related) ways in which such reactive centres can be created. These include (i) the addition of positive species (Lewis or Brønsted acid) to an alkene, to a carbonyl compound, or to another unsaturated system, (ii) the removal of a negative leaving group catalysed by an acid, *e.g.* from an alcohol or halide, (iii) acid-catalysed ring-opening, *e.g.* of an epoxide or cyclopropane, or (iv) by removal of hydride ion, *e.g.* by trityl cation. The reaction will give a product with a new C—C bond. The attached group may be simply alkyl (acyclic or a ring-residue) or it may contain a new function, *e.g.* halide (from a dihalide) or hydroxyl (from a carbonyl compound) which may lead to a second Friedel–Crafts reaction and possibly to polymerization. Because of the high reactivity of phenols, some reactions proceed under very weak acid catalysis and these are often of biogenetic interest. Various aspects of the Friedel–Crafts reaction have been reviewed.[170]

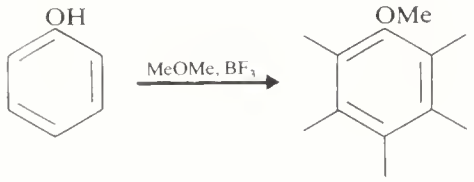
Alkylation with alkenes mostly employs concentrated sulphuric acid, $ZnCl_2$, BF_3, $AlCl_3$, $SnCl_4$, and cation-exchange resins. These reactions are of major interest in industrial processes because of the favourable cost and availability of alkenes in relation to alternative alkyl sources. The alkyl group, which may isomerize (primary → secondary → tertiary) during substitution, enters at the *para* (predominantly) and *ortho* positions, although ethers may be formed at low temperatures. *o*-Alkylphenols can be produced preferentially with aluminium phenoxide as catalyst under controlled conditions.[171]



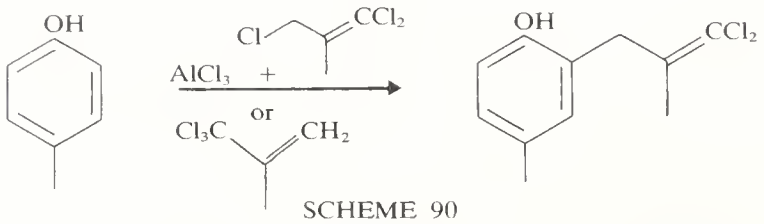
SCHEME 88

With alcohols and alkyl halides the general course of the reaction is as shown in Scheme 88. If path (a) is followed then the reaction is insensitive to X and the nature of the catalyst and displays a low selectivity of *ortho*/*para* substitution; the converse factors apply to path (b). Aliphatic ethers can be used in the reaction, *e.g.* as in Scheme 89. With alkyl halides, certain vinyl polyhalides will participate, and rearrangement before substitution is not unusual (Scheme 90). Among less well-known catalysts for alkylation with alkyl halides are acidic oxides such as alumina, aqueous metal halides, and free metals,

including Cu, Zn, Cr, Se, Sn, Pb, Mo, W, and Al (*in situ* formation of the metal halide is likely in some cases).



SCHEME 89

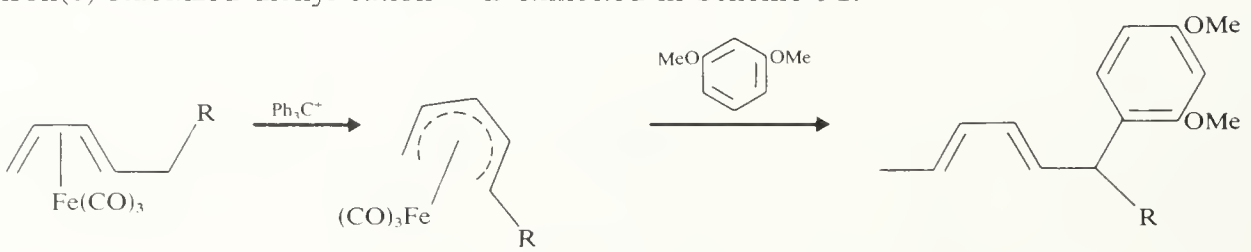


SCHEME 90

Other recent methods for alkylation include the use of oxonium salts,[172] variously generated, and made more available by the use of superacid systems, for example:

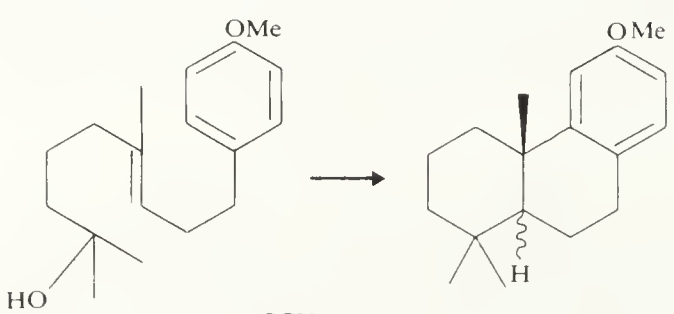
$$PhOMe + MeO_2CCl + AgSbF_6 \rightarrow Ph\overset{+}{O}Me_2\ \bar{S}bF_6$$

This Meerwein salt rapidly methylates anisole. Esters of benzene di- and poly-sulphonic acids are also good alkylating agents[173] and anisole can be phenylated[174] by benzenediazonium fluoroborate in trifluoroethanol. An interesting substitution, involving an iron(0) stabilized dienyl cation[175] is exhibited in Scheme 91.

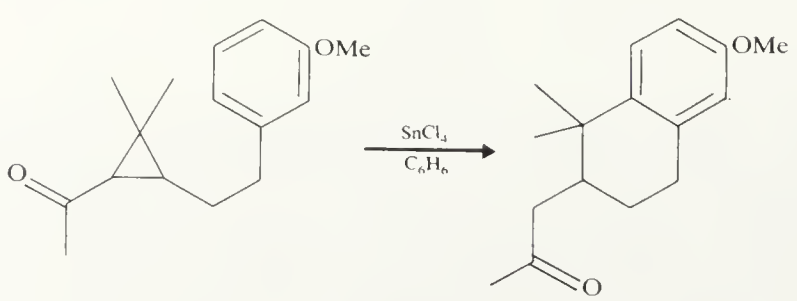


SCHEME 91

(*b*) *Cycloalkylation.* The general Friedel–Crafts reaction is easily exploited for cyclization. Two nice examples are shown in Schemes 92[176] and 93.[177]

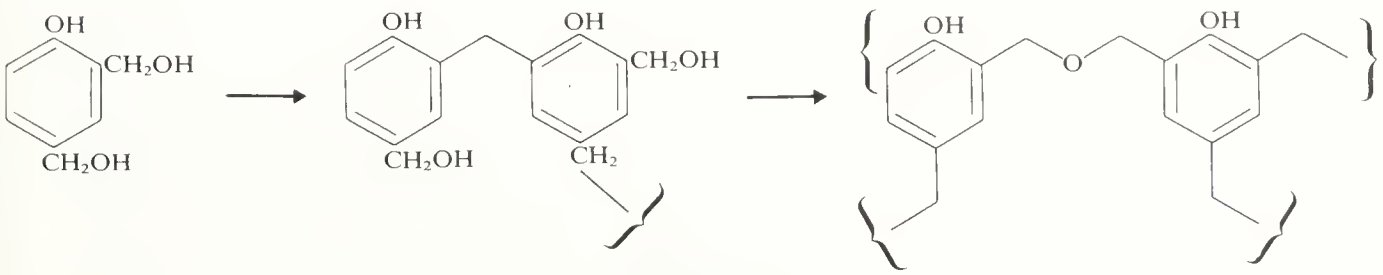


SCHEME 92



SCHEME 93

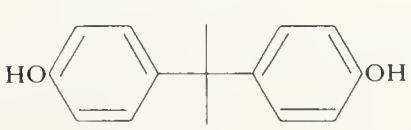
(*c*) *Hydroxymethylation.* Phenols reacts with formaldehyde in aqueous alkaline solution at low temperature to give a mixture of *o*- and *p*-(hydroxymethyl)phenols. Unless conditions are strictly controlled, di- and tri-substitution products, diarylmethanes, and resinous materials are also formed (see Scheme 94). The polymers, the 'Bakelite' resins



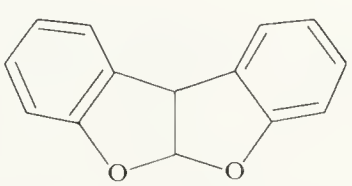
SCHEME 94

(after L. H. Baekeland,[178a] their discoverer) are of the great technical importance. Initially used for insulating material, their use has been extended to many moulded and laminated products and surface treatments. Polymerization is usually carried out in two stages: the first stage (acid or base catalysed) gives a polymer of low molecular weight, which is soluble and fusible, while in the second stage an insoluble but fusible polymer with light cross-linking is formed. Further treatment can give a highly cross-linked insoluble and infusible polymer. If base is used in the first stage the product is chiefly a mixture of di-, tri-, and poly-nuclear diphenylmethanes called *resoles.*[178b] The resoles are neutralized or made slightly acidic and heated to *ca.* 150 °C to promote cross-linking. If acid is used in the first stage, diphenylmethanes joined mainly through the *para* position are formed.[178c] Oligomers (M, 600) are produced termed *novolacs*; uncontrolled cross-linking is prevented by manipulation of the phenol–formaldehyde ratio. A catalyst, usually hexamethylenediamine, and heat are required to effect cross-linking in the second stage. Depending on the catalyst proportions, cross-links may be methylene or secondary amino groups. Variation of all the parameters can be called upon to produce many resins of differing physical properties. Full accounts of this branch of polymer technology are given in other specialized publications.[179]

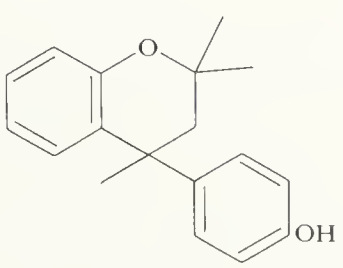
Phenol also condenses with acetone in the presence of hydrochloric acid to yield 'bisphenol A' (**140**);[180] many such products have been prepared and used as antioxidants and monomers in condensation polymerizations. Glyoxal also condenses with phenol in acid to give dihydrobenzofuran derivatives (**141**).[181] With mestyl oxide, phenol gives Dianin's compound (**142**)[182] which forms inclusion compounds on crystallization from many organic solvents.



(**140**)

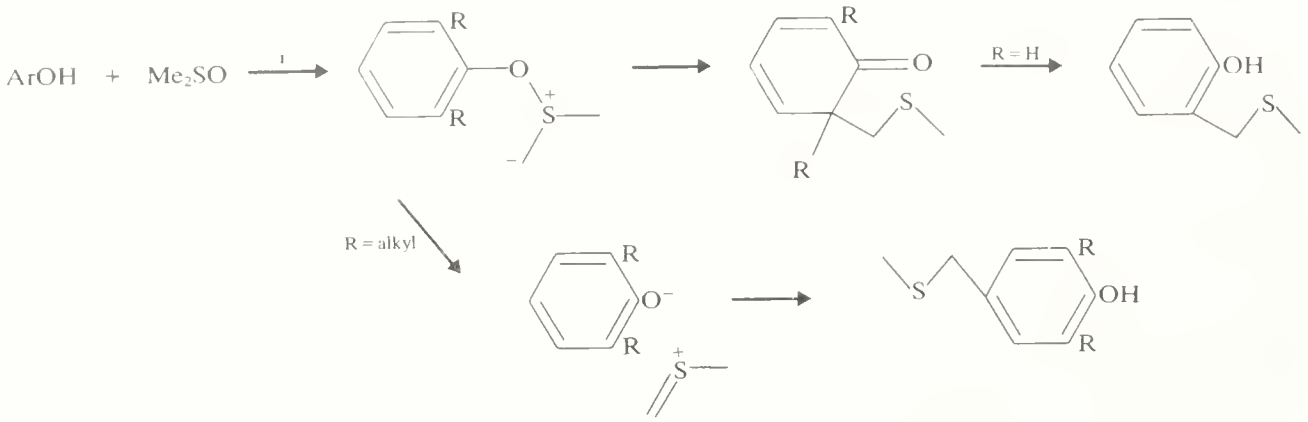


(**141**)



(**142**)

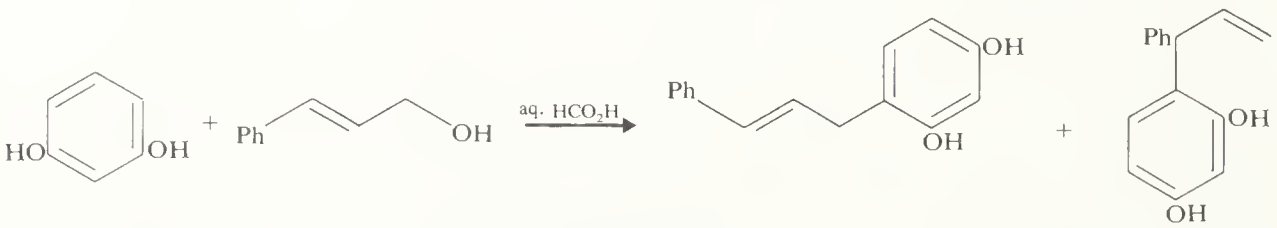
Thiomethylation of phenols in the *ortho* positions may be achieved using dicyclohexylcarbodi-imide, dimethyl sulphoxide, and acid;[183] mechanisms and other catalysts have been investigated.[184] If an *ortho* position is 'free', the reaction involves a [2,3]-sigmatropic rearrangement (Scheme 95).



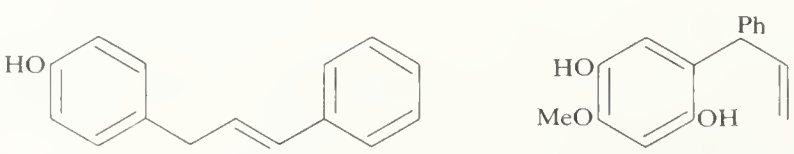
i, Dicyclohexylcarbodi-imide, H^+.

SCHEME 95

(*d*) *Biogenetic models.* Cinnamyl alcohols react with resorcinol and other reactive phenols in the presence of mild carboxylic acid catalysis to yield compounds akin to natural cinnamyl phenols and neoflavonoids[185] (Scheme 96). In this way, obtusastyrene (**143**) can be obtained from phenol and cinnamyl alcohol, and obtusaquinol (**144**) from 1-phenyl-

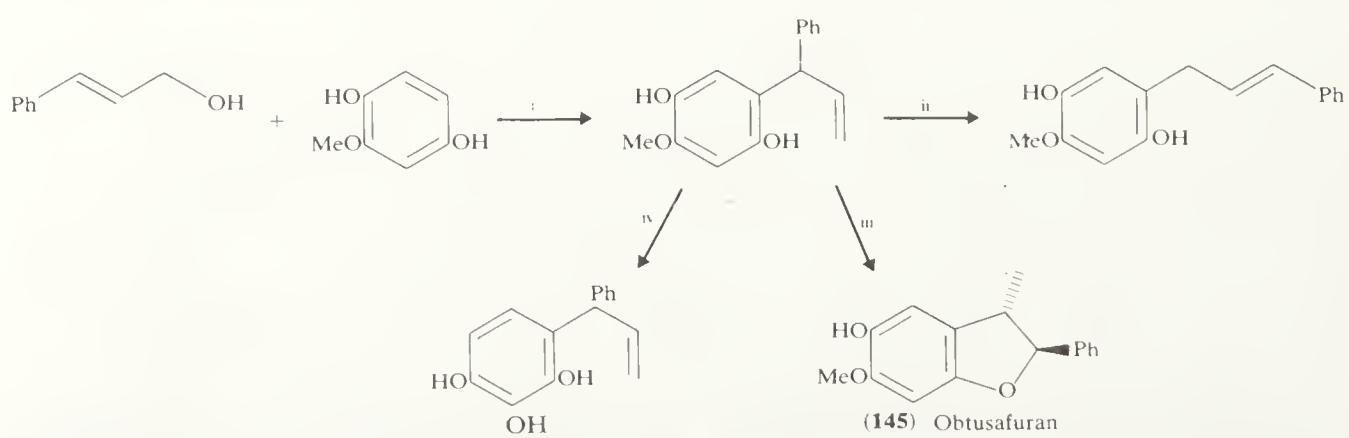


SCHEME 96



(**143**) (**144**)

allyl alcohol and methoxyhydroquinone. Such substitutions are reversible;[186] thus the phenol (**144**), which is exclusively formed with citric acid as catalyst, rearranges in aqueous formic acid as shown in Scheme 97. If pyrogallol is added, a new biaryl propene is formed. Also, thermal ring closure of (**144**) to (**145**) (obtusafuran) has been noted. The



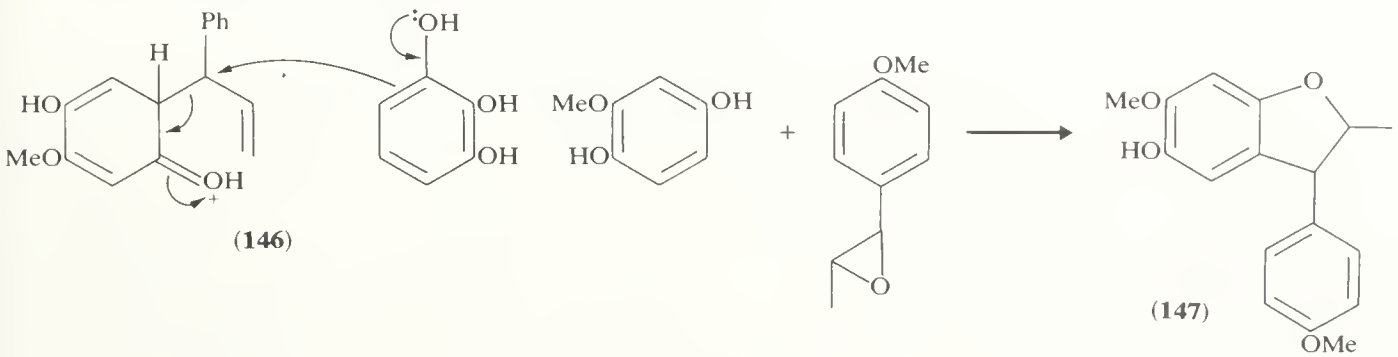
(**145**) Obtusafuran

i, Aq. citric acid; ii, aq. formic acid; iii, Δ, iv, acetic acid + pyrogallol.

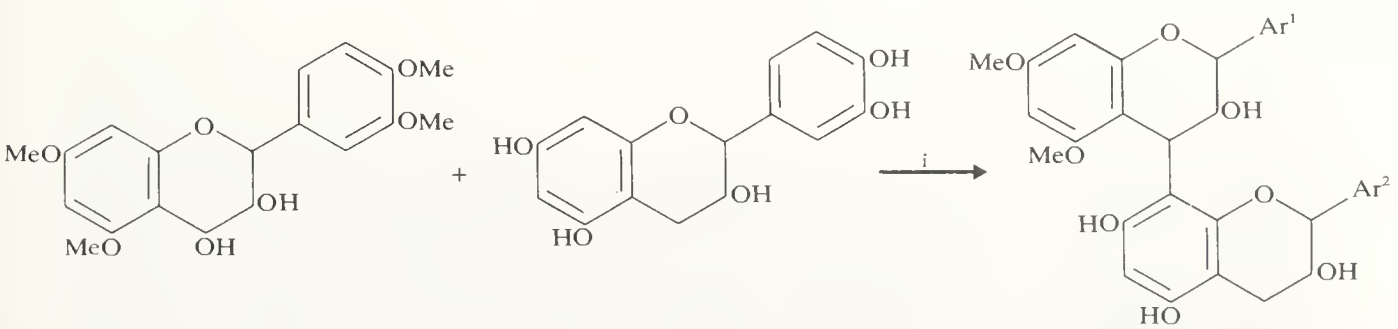
SCHEME 97

reaction is simply written in terms of carbenium ions as a reversible Friedel–Crafts alkylation, but in view of the weak acid conditions, concerted reactions seem more likely (see **146**). Epoxides can participate in a similar reaction[186b] (*e.g.* formation of **147**). Benzylic alcohols also take part in weak acid condensations of biogenetic interest. Scheme 98 shows a model reaction for proanthocyanidin (a flavonoid tannin) formation.[187] Other similar reactions have been employed in terpene–phenol condensations, both with boron trifluoride and weak proton acid catalysis. Examples of phenol prenylation drawn from the chemistry of cannabinoids[188] are shown in Schemes 99–101.

(*e*) *Acylation and related reactions.* Friedel–Crafts acylation[189] can be effected by 'oxo-carbocations'. Various modes of generation from carboxylic acid derivatives can be envisaged, and most, *e.g.* carboxylic esters or acids, have been realised with strong proton acid catalysts (H_2SO_4, H_3PO_4, HF). Acid halides and anhydrides are converted by Lewis acid catalysts, *etc.* The mechanisms encountered for the best-known case, acid halide with

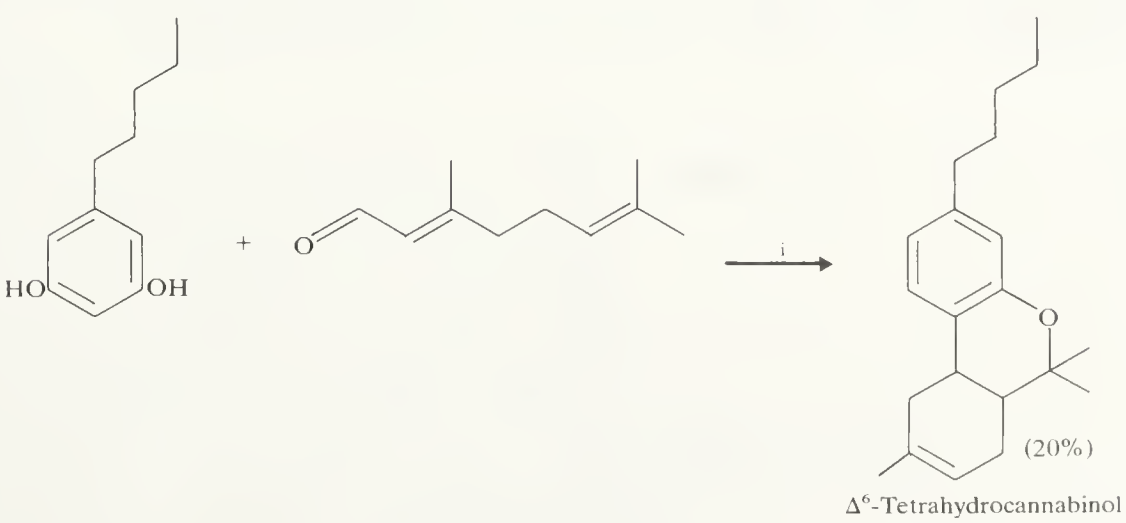


(**146**) (**147**)



i, 0.1N HCl, aq. dioxan

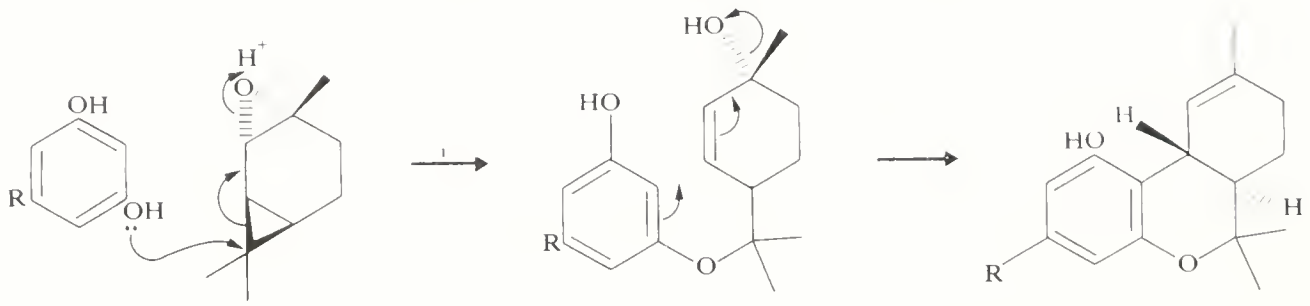
SCHEME 98



Δ^6-Tetrahydrocannabinol

i, $BF_3.Et_2O$, 5–10 °C.

SCHEME 99

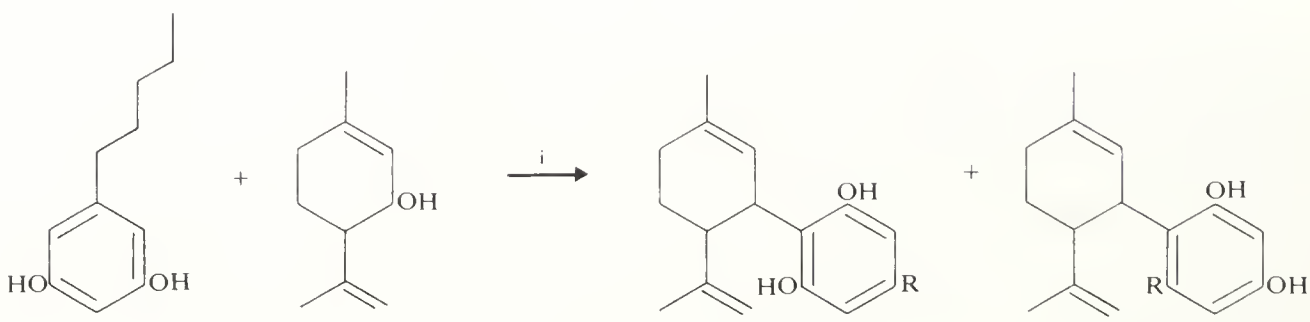


R = n-pentyl

trans-Δ'-Tetrahydrocannabinol

i, BF_3 or TsOH

SCHEME 100

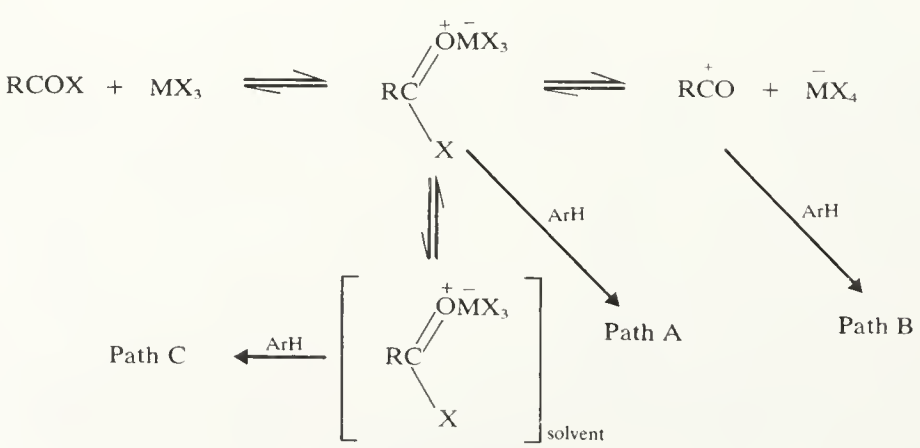


R = n-pentyl

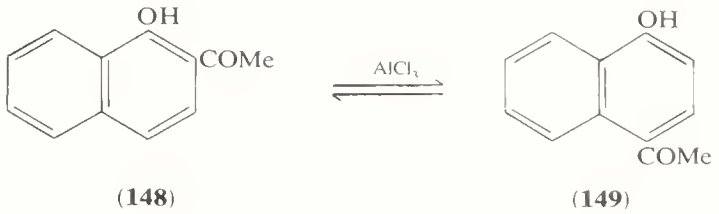
i, 5% Citric acid, r.t., 3 days.

SCHEME 101

Lewis acid, are summarized in Scheme 102. High catalyst ratios of at least 1 mol equivalent are used. Path A is the most commonly met and has large steric requirements, which are increased by solvation, as in Path C. The reaction is homogeneous in nitrobenzene but largely heterogeneous in carbon disulphide or tetrachloride. Solvents like methylene chloride do not dissolve aluminium chloride, but dissolve the acylating complex. Acylation may be reversible, especially in polycyclics, as in (**148**) ⇌ (**149**) in equation (18). Variants of acylation are used for heterocyclic synthesis, *e.g.* malonic esters give 4-hydroxycoumarins,[190] and β-ketoesters give coumarins or chrom-3-ones.[191] Reaction with phthalic anhydride leads to phthaleins or hydroxyanthraquinones.



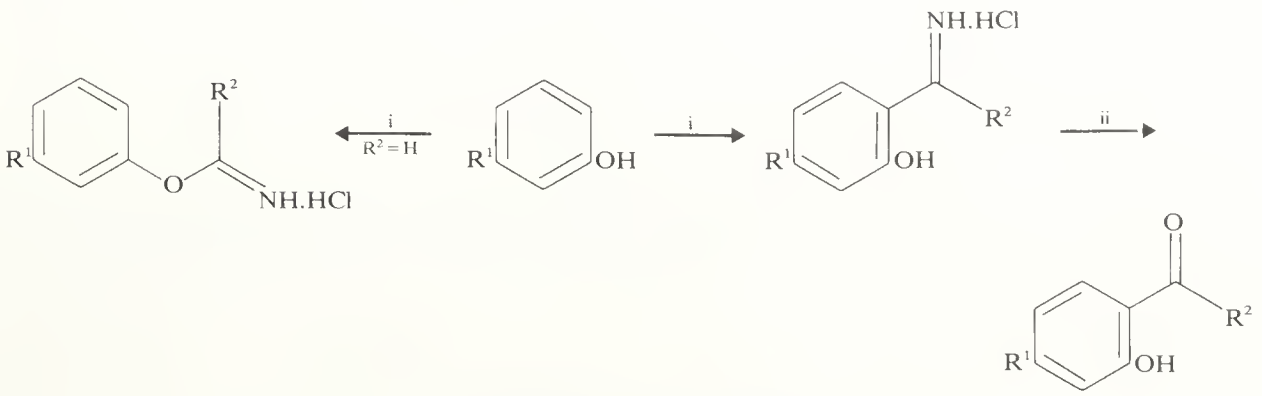
SCHEME 102



(18)

(148) **(149)**

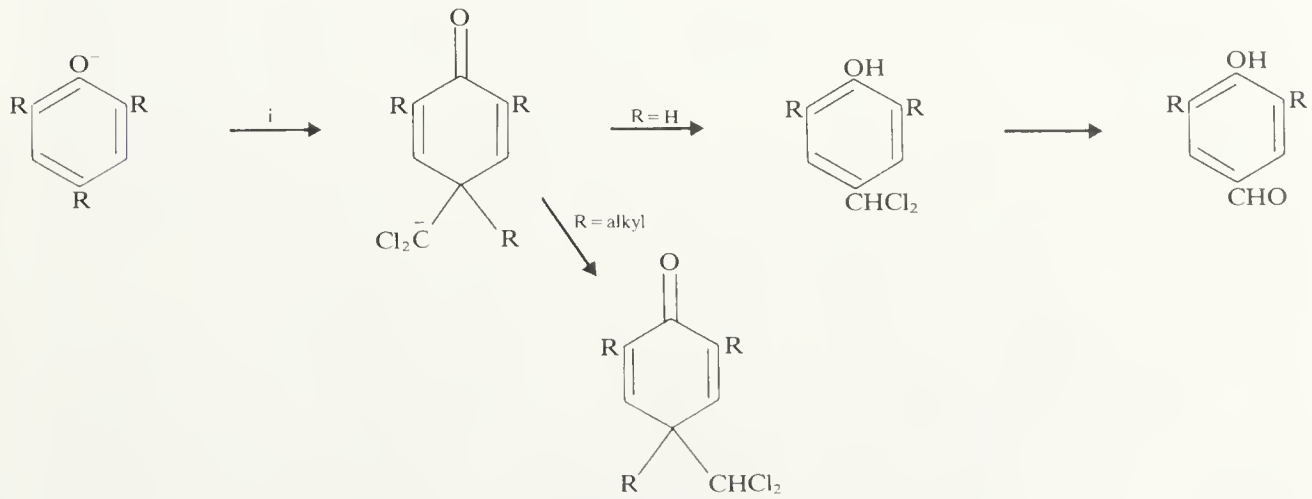
(*f*) *Houben–Hoesch reaction.* Reactive (usually *m*-dihydric) phenols can be acylated by alkyl cyanides under acid catalysis (Scheme 103); phenol itself affords only iminoesters. α-Halonitriles are more reactive, *e.g.* trichloroacetonitrile will trichloroacetylate monohydric phenol ethers. Interesting anomalies arise with trifluoroacetonitrile.



i, R^2CN, HCl, $ZnCl_2$; ii, H_2O.

SCHEME 103

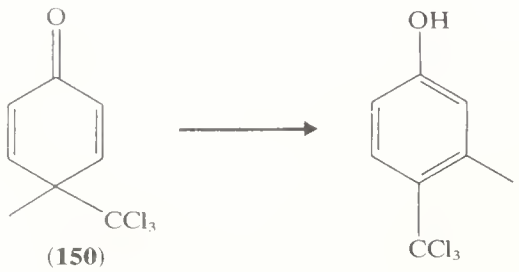
(*g*) *Formylation.* This may be achieved using hydrogen cyanide and hydrogen chloride with aluminium or zinc chloride (Gattermann aldehyde synthesis);[192] hydrogen chloride with dry zinc cyanide is a more convenient alternative for more reactive phenols (Schmidt modification). Various alternative single-carbon electrophiles can be used, *e.g.* dichloromethyl methyl ether (with titanium tetrachloride) or *N,N*-dimethylformamide (with phosphorus oxychloride, sulphur trioxide, *etc.* — the Vilsmeier reaction). The Reimer–Tiemann synthesis (heating a phenol in alkaline solution with chloroform[193]) depends on the generation *via* α-elimination of electrophilic dichlorocarbene, which is then trapped by phenolate anion (Scheme 104). These, and other methods, are reviewed.[194]



i, $CHCl_3$, ^-OH.

SCHEME 104

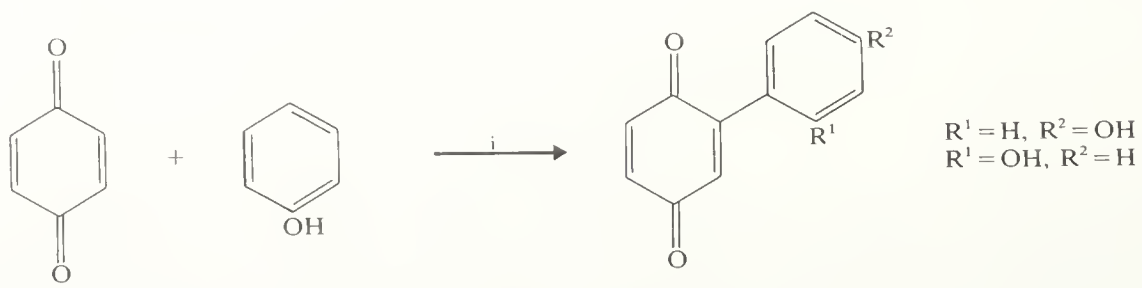
(*h*) *Carboxylation.* Direct carboxylation can be achieved by heating an alkali metal phenolate in an atmosphere of carbon dioxide (or $CO+CO_3^{2-}$) (Kolbe–Schmitt reaction).[195] *o*-Hydroxy acids (salicylates) predominate below 200 °C, but at higher temperatures, and with potassium salts, the *para* isomer is favoured. An alternative method involves heating the phenol with carbon tetrachloride in alkali with copper salts. Carbon tetrachloride–aluminium chloride will effect trichloromethylation (Zincke–Suhl reaction).[196] *p*-Cresol gives the dienone (**150**), which undergoes dienone–phenol rearrangement in acid, as shown in equation (19).



(**150**)

(19)

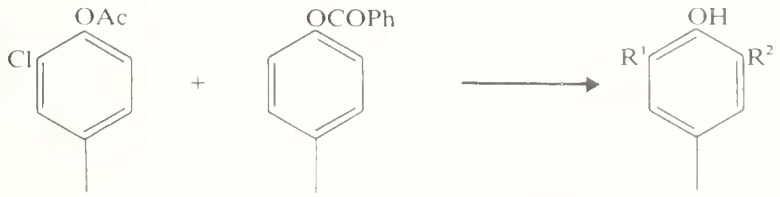
(*i*) *Miscellaneous.* Phenols react with *p*-benzoquinone under conditions of either acid or base catalysis to give modest yields of the coupled product,[197] as shown in Scheme 105.



i, acid or alkali.

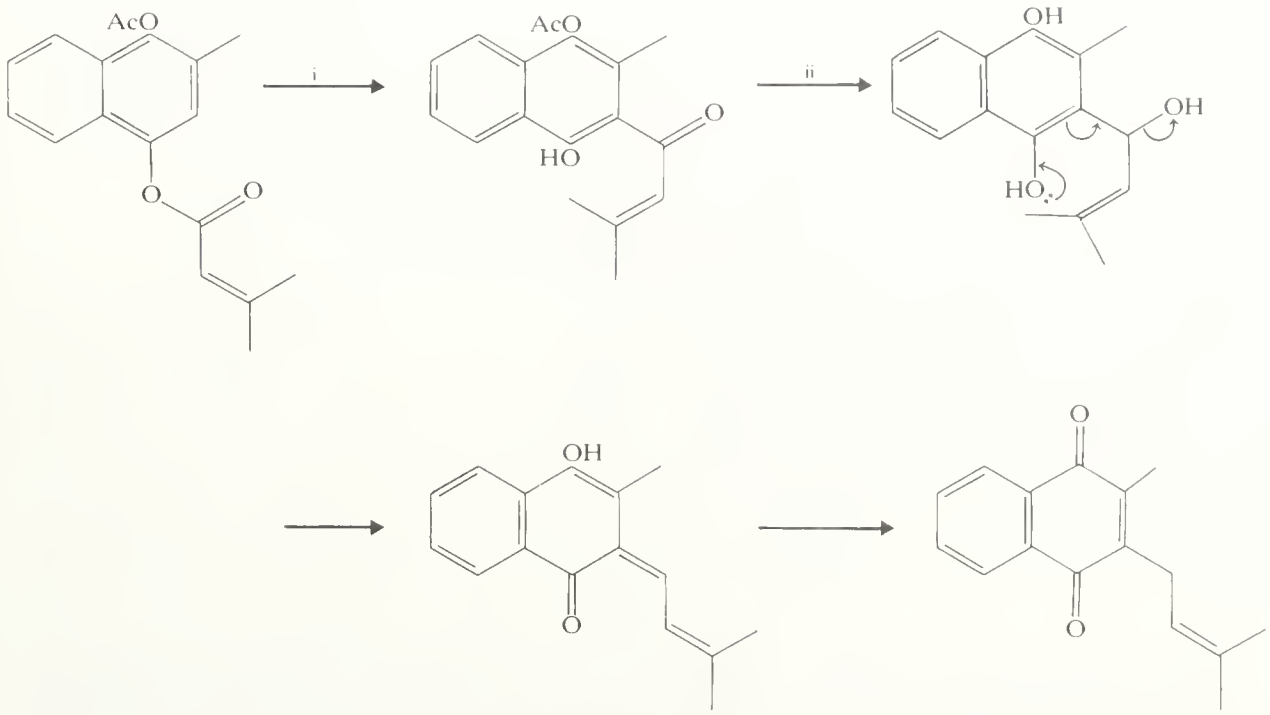
SCHEME 105

(*j*) *Acyl migration.* Indirect phenol acylation is achieved by rearrangement of phenyl esters, *e.g.* phenyl acetate to *o*- and *p*-hydroacetophenone, the well-known Fries rearrangement.[198] In its classic form this reaction is acid catalysed. The mechanism can be envisaged as either intra- or inter-molecular. However, it would seem that it is commonly intermolecular, at least in part; thus aluminium chloride treatment of the mixed esters in Scheme 106 leads to all four possible *o*-hydroxyketones.[198b] It has been suggested that although the *para* products arise by deacylation–reacylation, the *ortho* products may arise by an intramolecular route. *ortho* Products may be thermodynamically preferred and/or they may be formed irreversibly, since a chelated complex is produced in their case. Hydrogen fluoride has been recommended as a catalyst.[199] A typical use in synthesis, drawn from model reactions in the vitamin K series,[200] is displayed in Scheme 107. The Fries reaction may also be photochemical, a variation which has attracted a good deal of mechanistic attention; the topic has been reviewed.[201] The primary product is a pair of solvent-caged singlet radicals which recombine to rearranged product;[202] CIDNP signals have been observed in the ^1H n.m.r. spectrum. Aryloxyacetones undergo a similar process.[203] As a synthetic tool, the reaction is detracted from by alternative paths involving decarbonylation and decarboxylation. However, it has been used to obtain an epoxide from a 2′-hydroxychalcone under non-oxidizing conditions[204] — an alternative approach to the intermediates of the Algar–Flynn–Oyamada reaction. The epoxide was not isolated but reacted further to yield flavonoids (Scheme 108).



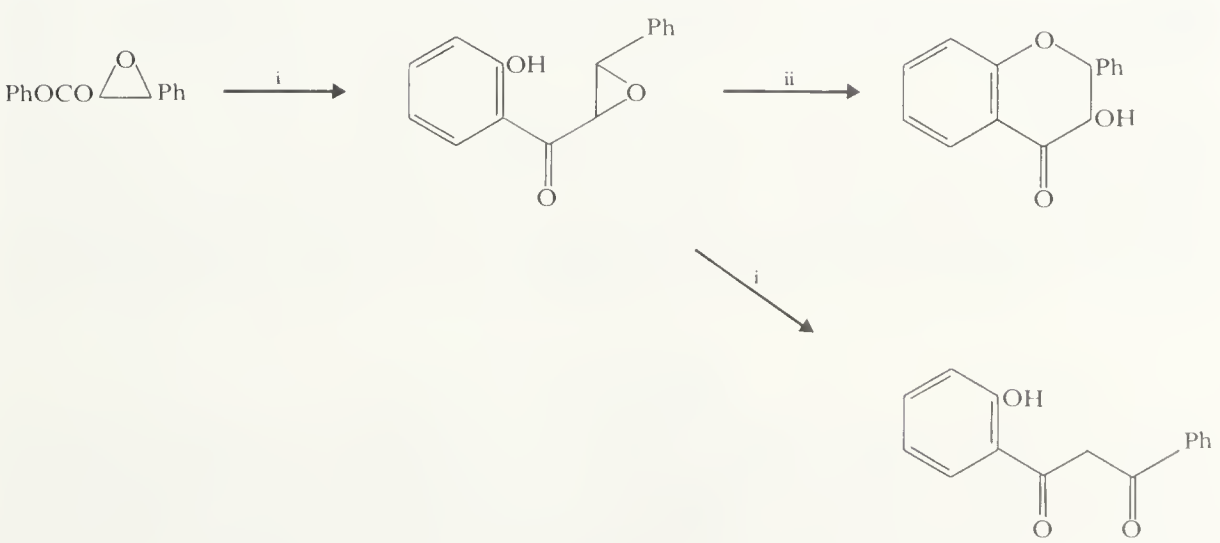
$R^1 = Cl$, $R^2 = Ac$
$R^1 = Cl$, $R^2 = COPh$
$R^1 = H$, $R^2 = Ac$
$R^1 = H$, $R^2 = COPh$

SCHEME 106



i, $AlCl_3$; ii, $LiAlH_4$.

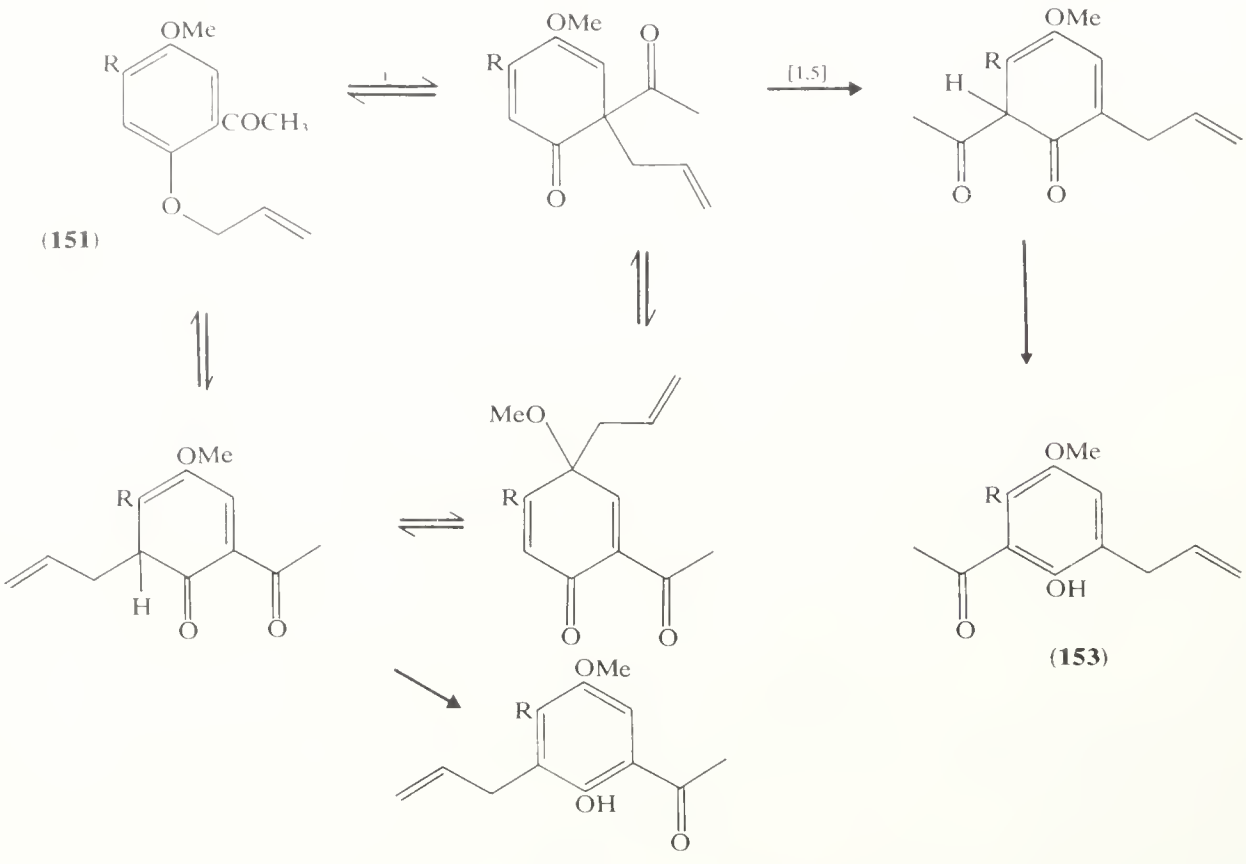
SCHEME 107



i, $h\nu$; ii, ^-OH.

SCHEME 108

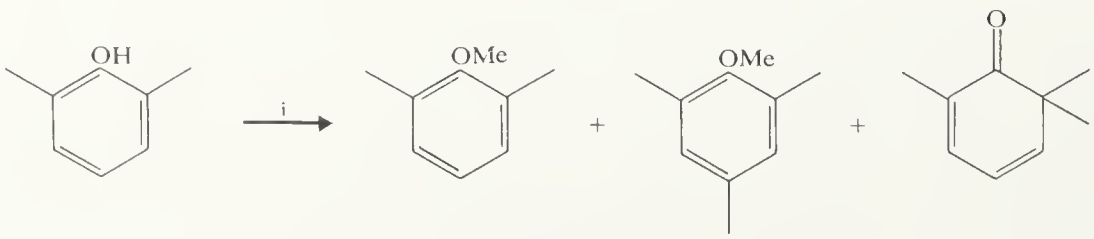
Acyl migration need not be associated with either ionic or radical reactions but can arise through sigmatropic shifts in dienone intermediates in phenol chemistry. Thus in the Claisen rearrangement of the allyl ether (**151**), both phenols (**152**) and (**153**) are formed. The mechanism proposed[205] (Scheme 109) requires a [1,5]-acetyl shift as illustrated.



i, 170 °C, $PhNMe_2$.

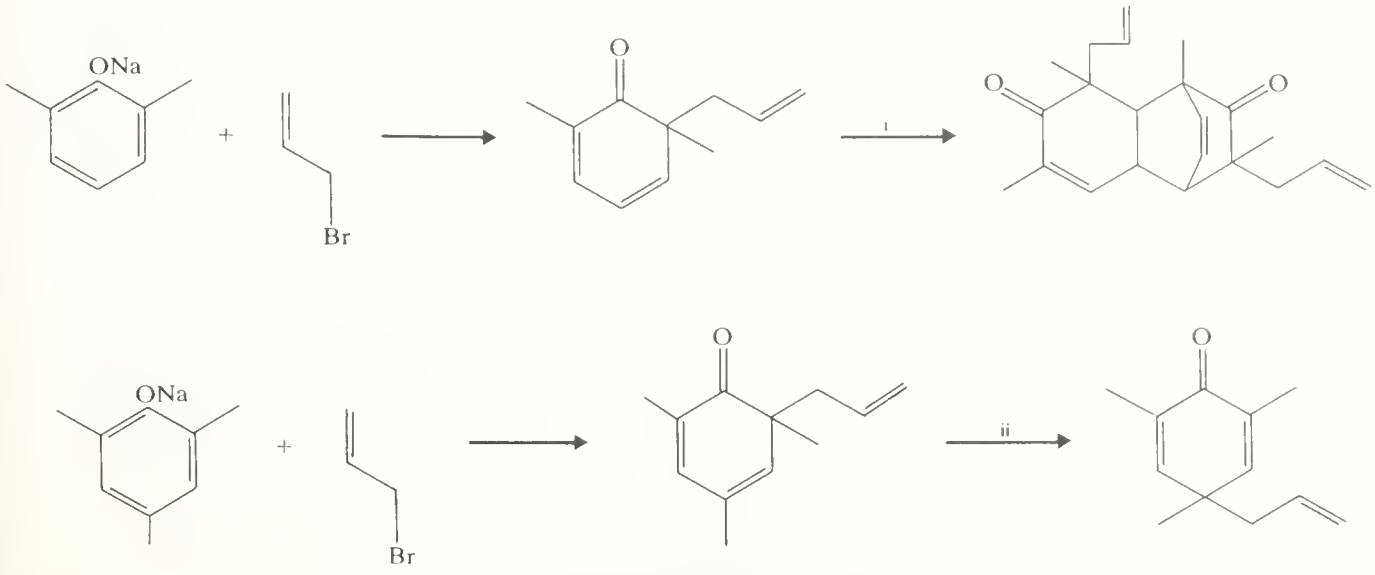
SCHEME 109

(*k*) *Base-catalysed* S_E *reactions.* Metal phenolate salts or phenols in organic bases may undergo S_E reactions with electrophiles, including some of low reactivity. Since some of these reactions are of synthetic importance a few examples are drawn together at this point. *C*-Alkylations of phenolates (*cf.* Section 4.2.1.3) with alkyl halides, *etc.* are of this type. Such reactions can involve cyclohexadienone formation, even if there are other positions free for substitution with retention of aromatic character, as in the reactions[206] of 2,6-dimethylphenol illustrated in Scheme 110. The dienone products are reactive[207] and, apart from rearrangements to phenols, thermal dimerization can take place, and, with other substituents, other migrations. Examples are displayed in Scheme 111. An unusual and highly reactive spirodienone (**155**)[207c] results from intramolecular alkylation



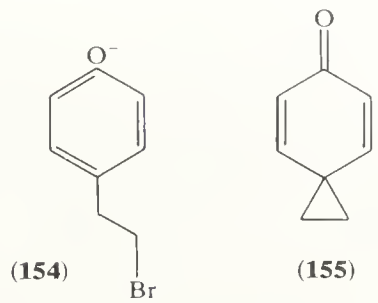
i, MeX, base.

SCHEME 110



i, Ambient temperature; ii, 100 °C.

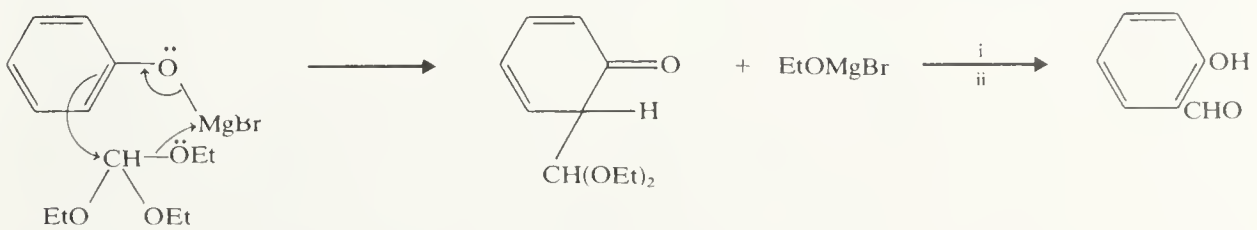
SCHEME 111



(154) **(155)**

in (**154**). *C*-Benzoylation of phenols in the presence of tertiary amines has been noted.

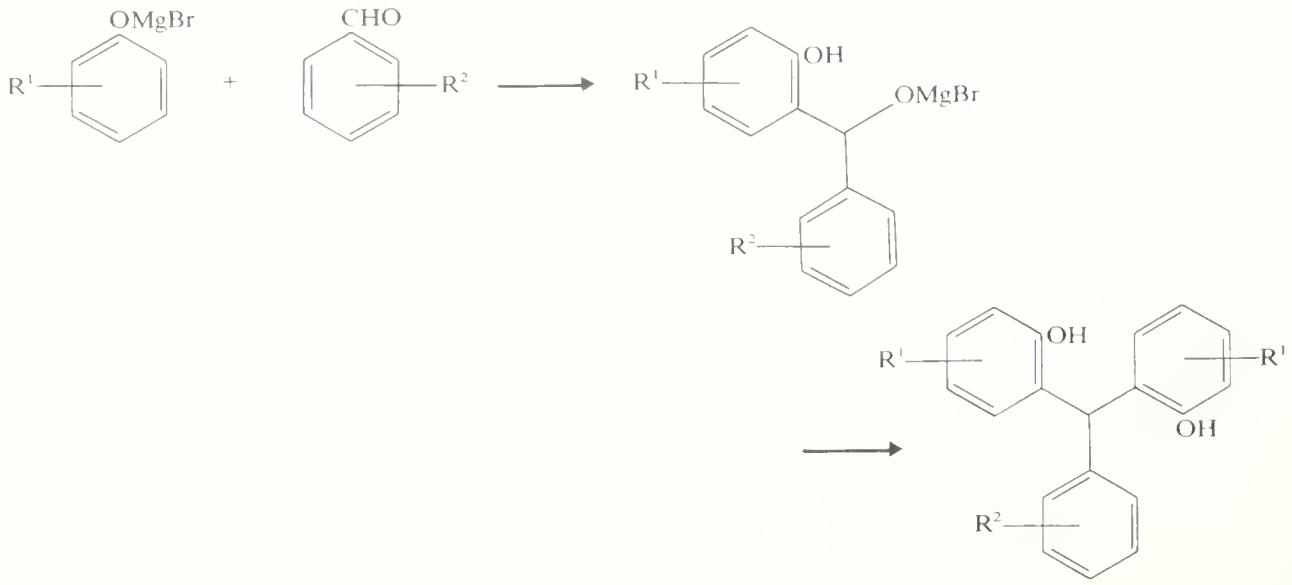
Aryloxymagnesium halides react with ethyl orthoformate, with *ortho* substitution (Scheme 112), and hydrolysis of the product affords *o*-hydroxyaldehydes.[208] A mechanistically related process[209] has been described in which aryloxymagnesium halides react in refluxing benzene in the presence of aryl aldehydes along the reaction course of Scheme 113. Using cinnamaldehyde the reaction follows a modified pathway, in which the first stage is followed by cyclization rather than a second substitution (Scheme 114). Flav-2-ene and flav-3-ene products are obtained which can equilibrate under certain conditions. Similar reaction conditions have been employed to induce reaction between hydroquinones (and



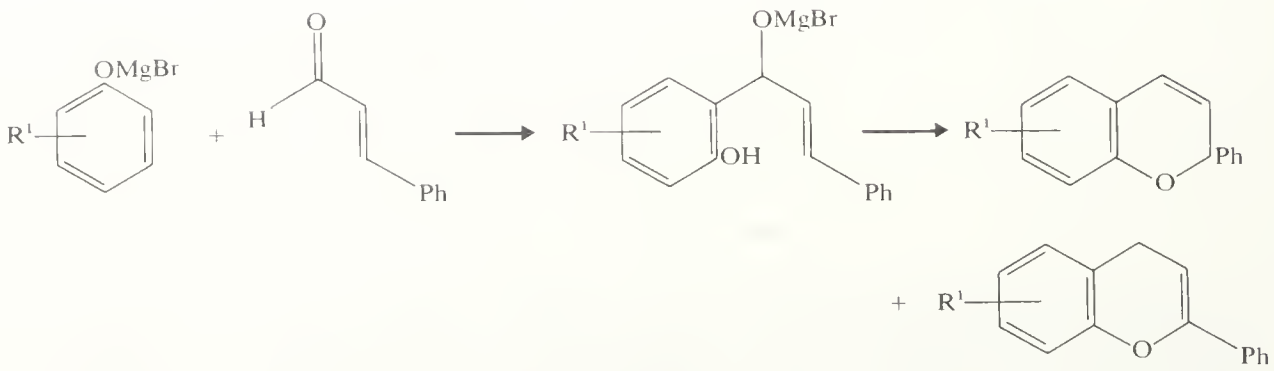
i, Enolization; ii, H_3O^+.

SCHEME 112

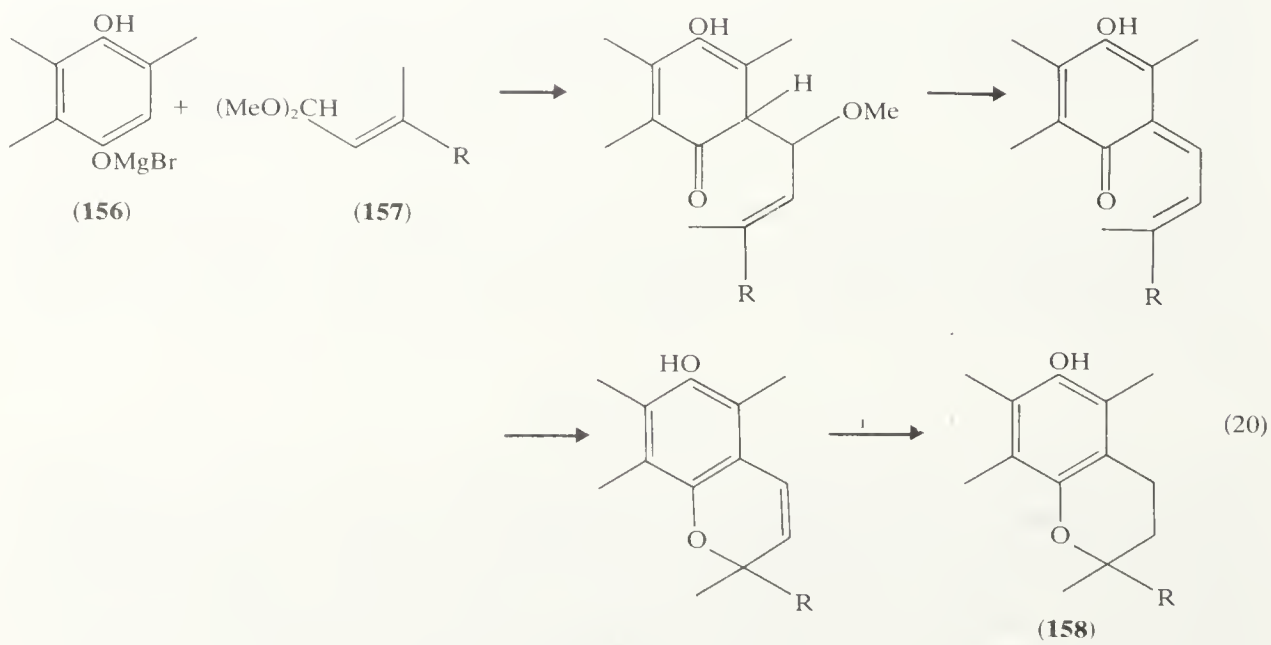
their monoethers) and the acetals of α-unsaturated acetals.[210] When using trimethylhydroquinone (**156**) and phytal dimethyl acetal (**157**), a chromen is obtained which on hydrogenation affords 2-(*RS*)-α-tocopherol (**158**) (vitamin E) in useful overall yield (equation 20). Further chromenylation reactions of this type are discussed in Section 4.2.4.2. An interesting base-catalysed cyclization of an aryloxyacetone unit to a 3-methylfuran was used in the synthesis[211] of psoralene (**159**), as shown in Scheme 115.



SCHEME 113

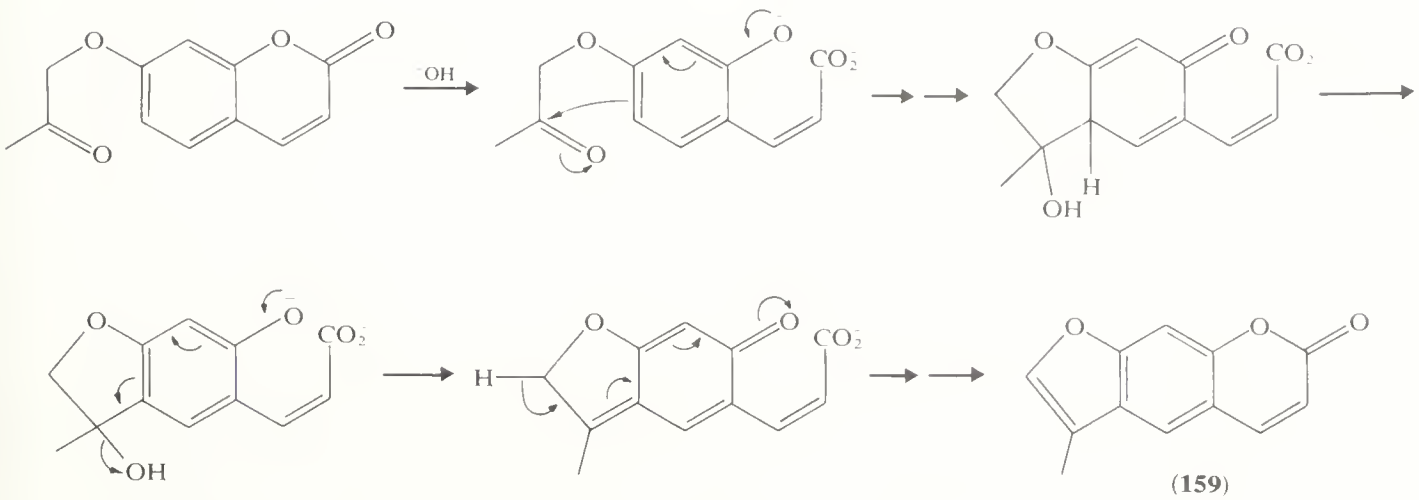


SCHEME 114



(20)

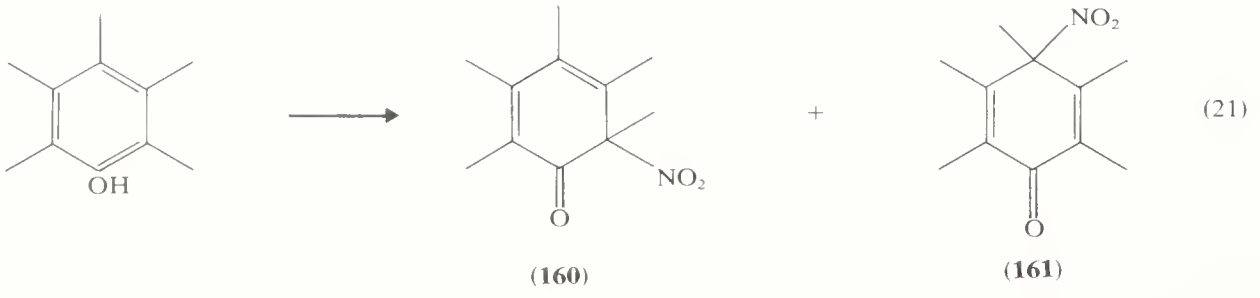
R = ; i, H_2, Pt.



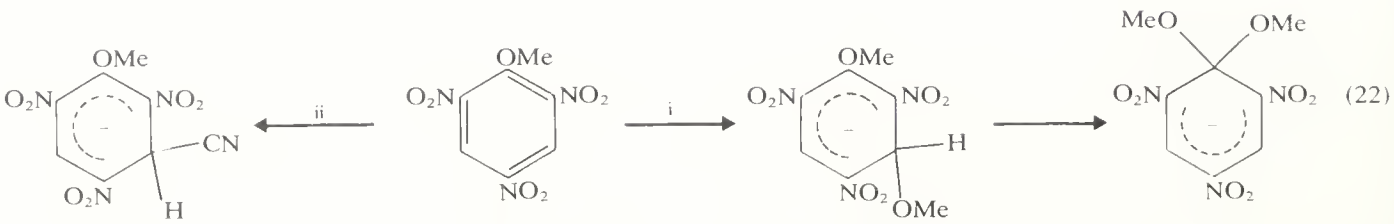
SCHEME 115

(*iii*) *Group V electrophiles*

(*a*) *Nitrophenols.* Phenols are easily mononitrated by dilute nitric acid, giving the *ortho* and *para* isomers. The *ortho* forms have strong intramolecular hydrogen bonds and may in simple cases be separated from the *para* compounds by virtue of their volatility in steam. A review of nitration is available[212a] and the mechanisms of nitration of phenol and anisole have been discussed in detail.[212b] With dilute nitric acid, nitration is strongly catalysed by nitrite and some product arises by nitrosation followed by nitric acid oxidation. The *ortho*/*para* ratio is sensitive both to solvent and to nitrous acid concentration.[212c] An organic solvent, often acetic acid, can be used, when higher yields of *o*-nitrophenols result. Other nitrating agents are dinitrogen tetraoxide, its boron trifluoride complex, and acetyl nitrate. Nitration of aniline with N_2O_4 gives 2,4-dinitrophenol (25%). High yields of *o*-nitrophenols can be obtained by treatment of aryl chloroformates with silver nitrate in acetonitrile.[213] Frequently encountered side reactions are oxidation to quinones and replacement of a ring substituent. Nitrations of polyalkyl- or polyhalo-phenols often give nitrocyclohexadienones: 2,4,6-tri-t-butylphenol with nitric acid at 0 °C gives a nitrodienone[214] which loses nitrogen dioxide on heating, and pentamethylphenol gives the enones (**160**) and (**161**) (equation 21). Di- and trinitrophenols are obtained with concentrated nitric acid or a nitrating mixture. Mercuric nitrate has been used to promote such reactions and presumably mercuration precedes nitration in these cases. Nitrophenols can be obtained indirectly, *e.g.* by direct hydroxylation with ferricyanide of 1,3-dinitro- and 1,3,5-trinitro-benzenes, through diazotization of nitroanilines, and by hydrolysis of nitrophenyl ethers, halogenonitrobenzenes, nitroanilines, nitrophenylhydrazines, *etc.*, where the nitro function is *ortho* or *para* to the leaving group. Nucleophilic aromatic substitution in general has been reviewed.[215] The addition of an anion to an aromatic ring, usually containing nitro groups, proceeds readily to yield coloured adducts known as 'Meisenheimer' complexes; these complexes have attracted much study and their chemistry has been reviewed.[216] Taking a few examples from the host available,[217] methyl picrate (**162**) reacts with methoxide ion in DMSO; kinetic control gives the C-3 adduct (**163**), which is converted slowly into the more stable C-1 adduct (**164**), while with cyanide ion the C-3 adduct (**165**) is preferred both kinetically and thermodynamically (equation 22). Trinitro-*m*-hydroxybenzoic acid (**166**) reacts with acetone in the presence of potassium hydroxide to give the dark-red trianion adduct (**167**), which adds a further hydroxide ion to give the red tetra-anion (**168**) (equation 23). Picric acid also reacts with acetone in alkali to give isomeric monocyclic (**169**) and bicyclic (**170**) dianions (equation 24).[218]

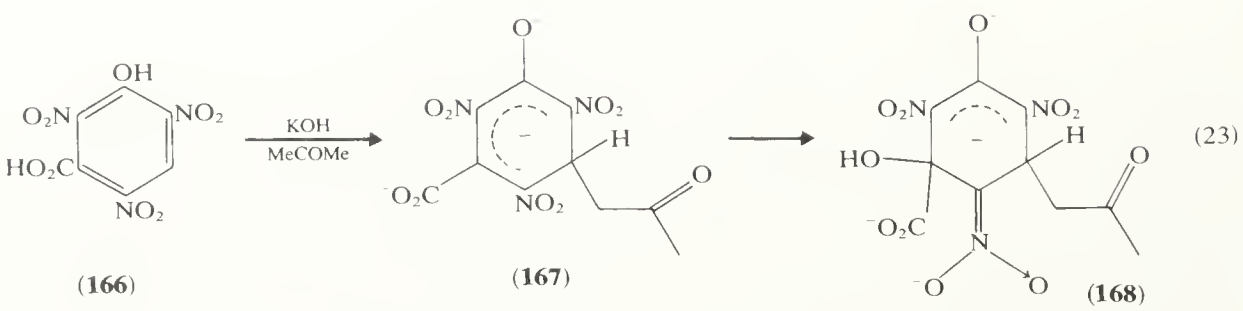


(160) (161) (21)

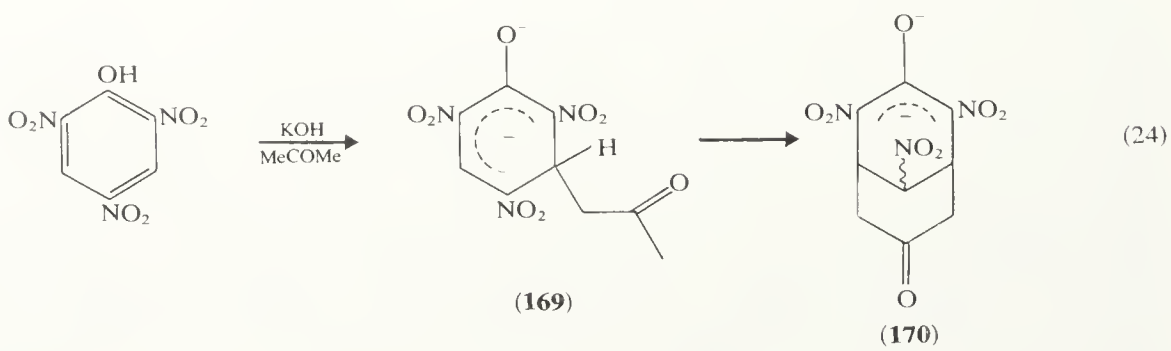


(165) (162) (163) (164) (22)

i, $\bar{O}Me$, Me_2SO; ii. $\bar{C}N$.



(166) (167) (168) (23)



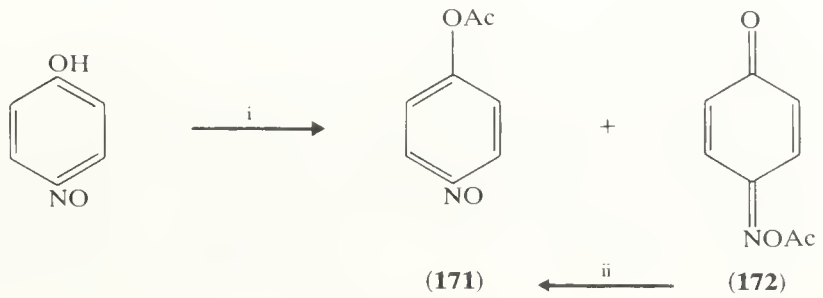
(169) (170) (24)

The best-known nitrophenol is picric acid, 2,4,6-trinitrophenol, which was first obtained by Woulfe (1771) from indigo, and later by Welter from treatment of silk with nitric acid. It was long known as Welter's bitter yellow. Dumas renamed it picric acid from the Greek word *pikros*, meaning bitter. As well as nitration of phenol, preparative methods include oxidative nitration of benzene by nitric acid and mercuric nitrate, and ferricyanide oxidation of 1,3,5-trinitrobenzene. Picric acid explodes violently on heating or shock and has been used as a military explosive (lyddite); aqueous solutions have been used to dye silk and wool a green-tinted yellow. Picric acid forms molecular complexes with aromatics, particularly electron-rich aromatics, and they have been used for separation and identification of, for example, polycyclic arenes. The complexes are charge-transfer in type, as opposed to amine picrates, which are salts.[219]

Many alkyldinitrophenols have been prepared since the discovery that they are useful herbicides. 2-Alkyl-4,6-dinitro- and 4-alkyl-2,6-dinitro-phenols are the most active.

(*b*) *Nitrosophenols.* Nitrosophenols exist in solution as tautomeric mixtures of phenol and quinone monoximes in which the latter predominate. Preparation may proceed either from oximation of the appropriate quinone or from nitrosation of the phenol.[220] Nitrous acid in alkaline solution usually gives good yields, although in some cases the nitrophenol is the main product. *para* Substitution is the general rule, unless the position is blocked; even then the *para* substituent may be displaced.[221] Nitrosylsulphuric acid or nitrosyl chlorides have been utilized. *o*-Nitrosophenols can be prepared directly from an aromatic hydrocarbon by oxidation with hydrogen peroxide in the presence of hydroxylamine and a copper salt (Baudisch reaction).[222] The mechanism is not fully understood but best yields are obtained at pH 2.5–3.5. The nitroso group is an interesting and unexploited function, giving rise to changes in reactivity: thus *p*-nitrosoanilines or *p*-nitrosoalkylarylamines can be hydrolysed with aqueous alkali to the *p*-nitrosophenols with displacement of ammonia or amine. Imino-oxime tautomers are presumed to mediate and the reaction has been used to make amines.[223]

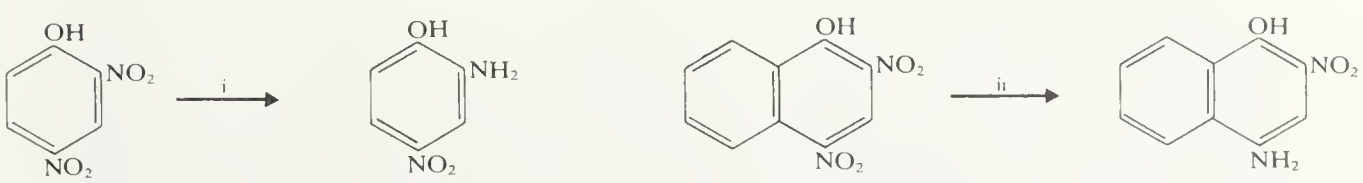
Reactions of nitrosophenols follow the pattern expected for a mixture of tautomers. Thus acetylation of *p*-nitrosophenol gives the phenol and oxime acetates, (**171**) and (**172**) (equation 25), and the latter rearranges thermally to the former.



(25)

i, Ac_2O; ii, Δ.

(*c*) *Aminophenols.* Aminophenols are obtained by reduction of nitro- and nitrosophenols, and hydroazo compounds. Many reducing agents, *e.g.* zinc and sodium dithionite, have been used.[224] Partial reduction of polynitrophenols is possible (Scheme 116), using sodium or ammonium sulphide, or other reagents.[225] *p*-Aminophenols are formed by rearrangement of arylhydroxylamines under acid influence (Bamberger rearrangement).[226a] The reaction is intermolecular, and *p*-phenetidine is formed from phenylhydroxylamine when the reaction is carried out in ethanol (Scheme 117). *ortho* Hydroxylation of aromatic amines can be effected by treatment with potassium persulphate, followed by acid hydrolysis of the resulting *o*-aminophenyl sulphate. Udenfriend's reagent hydroxylates aniline in the *para* position. *m*-Aminophenols can be prepared indirectly by Wessely oxidation, and reaction of the acetoxycyclohexadienone with an amine (Scheme 118). Alternatively, resorcinols yield *m*-aminophenols on heating with aqueous ammonia and ammonium chloride.

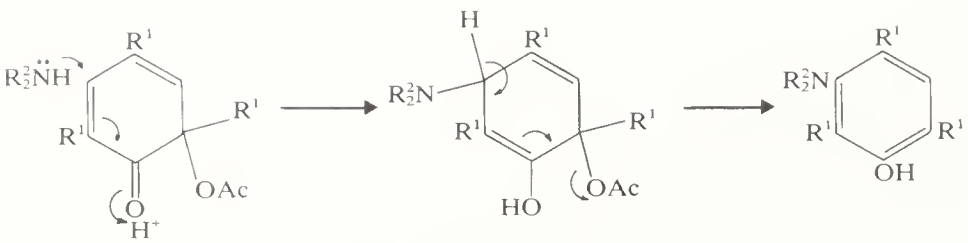


i, Na_2S, ii, $SnCl_2$.

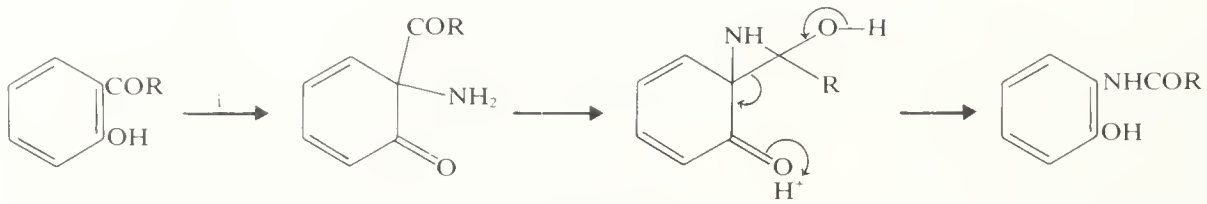
SCHEME 116

i, H_3O^+, ii, EtOH, H^+.

SCHEME 117



SCHEME 118



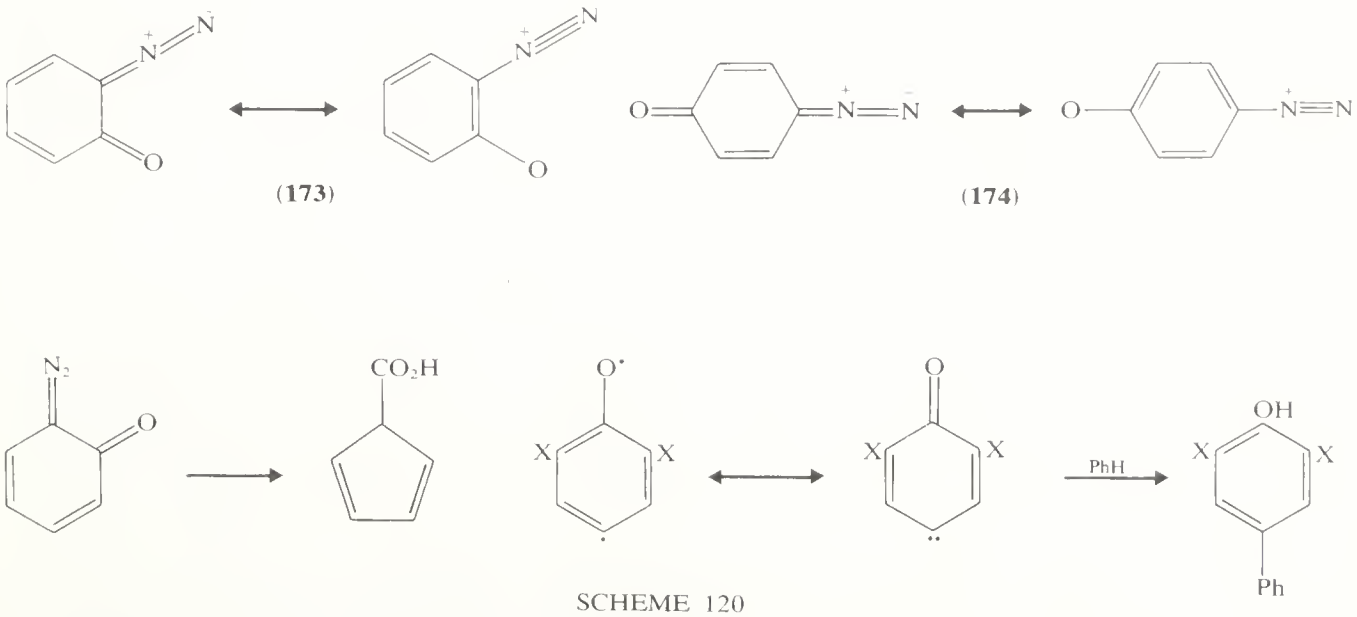
i, NaOH, NH_2Cl.

SCHEME 119

An interesting reaction, reminiscent of the Dakin oxidation, has been described (Scheme 119) which provides a pathway to *o*-aminophenols from *o*-hydroxycarbonyl compounds.[226b]

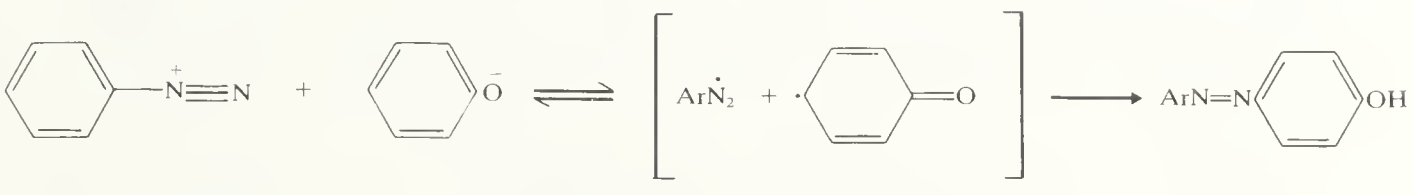
(*d*) *Hydroxybenzenediazonium salts and diazophenols.* Diazotization of aminophenols gives hydroxybenzenediazonium salts in the usual way, but difficulties can be encountered when the aminophenol is of low acid solubility or easily oxidized. Alternative procedures include the use of nitrogen oxides in organic solvents, nitrosylsulphuric acid in concentrated sulphuric acid, and nitrous acid derivatives. *o*- and *p*-hydroxybenzenediazonium salts have also been obtained by nucleophilic substitution of suitably-substituted halogeno-, methoxy-, and nitro-benzenediazonium salts, reactions of industrial importance in the manufacture of hydroxyazo dyes.[227] Crystalline diazonium salts have been isolated by diazotizing aminophenol salts under anhydrous conditions.

o- and *p*-diazophenols may be obtained from phenolic diazonium salts by neutralization, or by dilution with water, or in non-aqueous media, by shaking solutions with silver oxide and precipitating from cold ethereal solutions. These compounds exist as resonance hybrids (**173**) and (**174**). The considerable amount of work on these compounds, which are used in the manufacture of light-sensitive papers, has been reviewed,[228] and includes some interesting photochemistry[229] (Scheme 120). Thus *o*-diazophenols undergo a useful ring-contraction to give cyclopentadienecarboxylic acids, while *p*-diazophenols yield diradicals which are trapped by solvent, *e.g.* benzene to give *p*-arylphenols: the reaction has characteristics of an electrophilic substitution.



SCHEME 120

(*e*) *Azophenols.* Azophenols or hydroxyazobenzenes are well-known to be produced by diazonium salt coupling with phenols (see Ref. 227 for discussions of azo dye manufacture). The union between the positive diazonium ion and a phenolate anion, apparently one of the most simple of heterolytic reactions, has recently been shown to involve, at least in part, a radical pair intermediate (Scheme 121), by observation of ^{15}N CIDNP signals[230] in the ^{15}N n.m.r. spectrum.



SCHEME 121

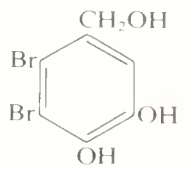
(*iv*) *Group VI electrophiles*

Substitution by oxy electrophiles has been dealt with in connection with phenol synthesis. Of the sulphur electrophiles, S(VI) reagents are best known; methods for introducing sulphur at a lower oxidation state are more rare.

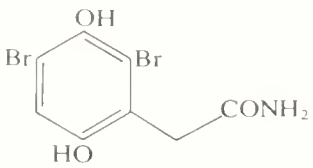
(*v*) *Group VII electrophiles*

Halophenols are of practical interest as bactericidal and fungicidal agents. They have also been found in Nature; bromophenols, *e.g.* (**175**), have been detected in sea water, and other halophenols in marine organisms, *e.g.* (**176**) in the sponge *Verongia aurea.* Fewer examples in land organisms are as yet known, but 2,6-dichlorophenol (**177**) is the sex pheromone of the female tick *Amblyomma americanum.*[231] Direct chlorination, bromination, and iodination occur easily in phenols;[232] acetic acid, the chloromethanes, and nitromethane are common solvents. Halogen enters the *ortho* and *para* positions and mono-, di-, and tri-halo compounds may be prepared as required. Iodination is reversible, and an oxidant is employed to re-oxidize the hydrogen iodide produced to iodine. Direct

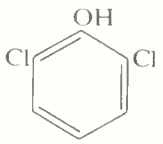
fluorination cannot be satisfactorily controlled. Detailed accounts of aromatic halogenation are given in various review articles. Exhaustive chlorination or bromination may yield halogenated cyclohexanones,[233] and more complex reactions may follow, *e.g.* chlorination in cold alkali of phenol gives the trichlorocyclopentenecarboxylic acid (**178**) (a starting material for caldariomycin synthesis[234]).



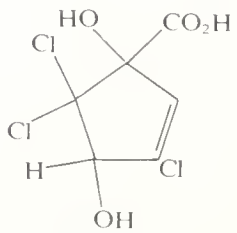
(**175**)



(**176**)



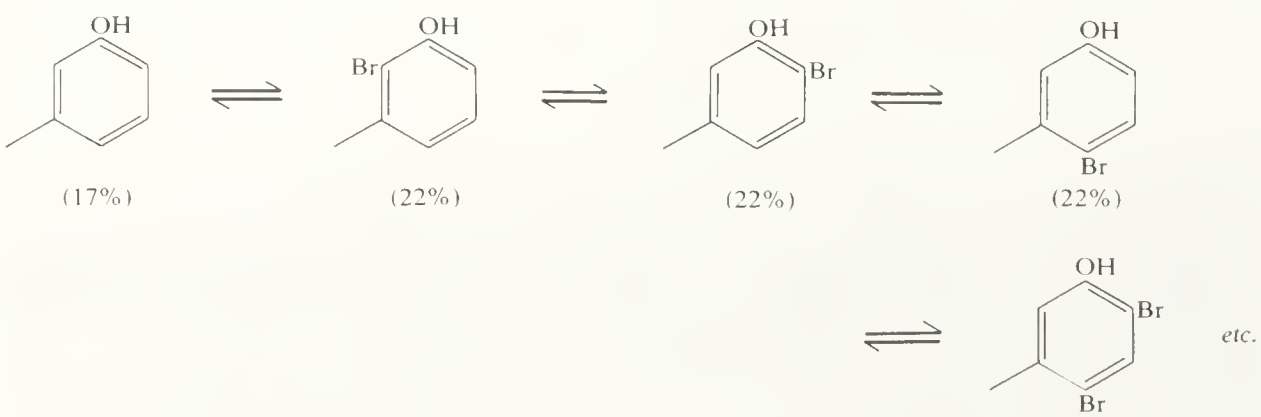
(**177**)



(**178**)

Many reagents apart from the free elements effect halogenation and can be employed with advantage to achieve selectivity, both in the number of halogen atoms introduced and in the position of substitution. Thus cupric chloride in DMF selects *para* chlorination;[235a] more *ortho* product (~75%) can be obtained by direct chlorination in carbon tetrachloride. The *ortho*/*para* ratio is solvent dependent. t-Butyl hydrochlorite[235b] and *N*-chloroamides are also useful.

Dioxan dibromide is a useful mild brominating agent; iodine monobromide and bromine chloride act similarly. *N*-Bromosuccinimide preferentially brominates phenol in the *para* position:[236a] a procedure for *ortho* bromination has been described. Thionyl bromide (but not thionyl chloride) readily halogenates phenols at room temperature.[236b] Certain *p*-bromophenols suffer hydrogen bromide catalysed isomerization through debromination–rebromination.[236c] This can occur under surprisingly mild conditions (Scheme 122). *ortho* Bromination of phenols is preferred under Ti(IV) catalysis.[236d]



Equilibria at 25 °C; HBr, $CHCl_3$.

SCHEME 122

For iodination, mercuric oxide, iodic acid, potassium persulphate, and hydrogen peroxide with acid are commonly used oxidants. Iodination with iodine and silver perchlorate is thought to involve the iodinium ion. Iodine monochloride has been used to iodinate phenols and phenolic acids;[237a] other mild reagents[237] are a morpholine–iodine complex and di-iodomethylhydantoin. Iodine–silver trifluoroacetate is a good non-oxidative method for small-scale work. Iodination can be carried out by indirect methods, *e.g.* *o*-iodophenol is prepared by treatment of *o*-chloromercuriphenol with iodine. Another procedure

involves bis(trifluoroacetoxy)thallation, the intermediate then being decomposed with potassium iodide:

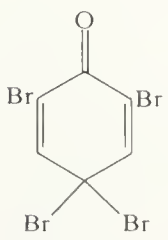
$$ArH + Tl(OCOCF_3)_3 \longrightarrow ArTl(OCOCF_3)_2 \xrightarrow{KI} ArTlI_2 \xrightarrow{\Delta} ArI + TlI$$

ortho Substitution takes place if a basic directing group (OR) is present (initial complexation).

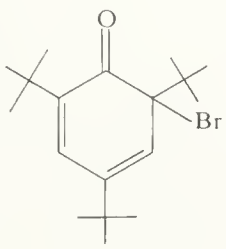
It is frequently necessary to utilize ring position blocking groups (*e.g.* CO_2H and SO_3H) to synthesize[238] a required halogenophenol, *e.g.* *o*-bromophenol and 2,6-dichlorophenol.

Fluorophenols are usually obtained from hydroxyarene diazonium salts by treatment with fluoroboric acid, followed by thermal decomposition of the resulting solid diazonium fluoroborate (Schieman reaction);[239a] it is usually advantageous to block the hydroxy group during the sequence. Replacement of one halogen in a polyhalobenzene by hydroxide has been used to make *p*-fluorophenol and pentafluorophenol.[239b]

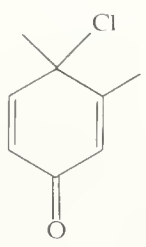
Cyclohexadienones can also be formed during halogenation, *e.g.* 2,4,6-tribromophenol gives the relatively stable tetrabromide (**179**), readily debrominated by proton acids. A more stable bromodienone (**180**) is obtained from 2,4,6-tri-t-butylphenol. Rearrangement of these compounds is catalysed by light or heat, *e.g.* (**179**) gives 2,3,4,6-tetrabromophenol on standing. Eliminations of t-butyl, CH_2OH, CHO, and CO_2H groups during bromination have also been noted.[240] It is not necessary for all *ortho* and *para* positions to be blocked for cyclohexadienones to be produced. Thus 3,4-dimethylphenol gives[241a] (**181**) on chlorination, and 2,6-di-t-butylphenol affords (**182**) on bromination. Enolization of (**182**) to the bromophenol proceeds relatively slowly.[241b]



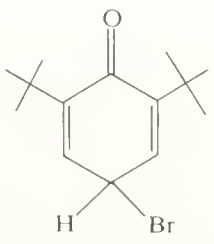
(**179**)



(**180**)



(**181**)



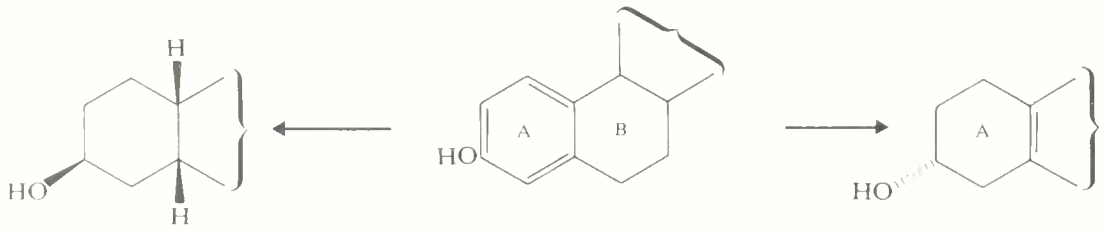
(**182**)

(*vi*) *Reduction*

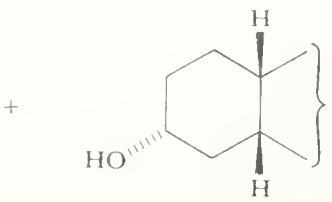
Reduction of phenols to arenes has been treated in Section 4.2.3.1. Hydrogenation of phenols to cyclohexanols, accompanied by cyclohexanones and cyclohexanes, can be achieved over platinum or nickel in the vapour and liquid phases, and is an important industrial process.[242a,b] Reduction of phenol itself with sodium in liquid ammonia gives cyclohexanone; with a large excess of lithium, cyclohexen-4-ol can be obtained.[242c] The photoreduction of phenols is also interesting.[242d] Thus oestrone (**183**), on irradiation in ethanol containing sodium borohydride, gives (**184**) and (**185**), while with sodium sulphite the diastereoisomer (**186**) is produced (equation 26).

(*vii*) *Miscellaneous*

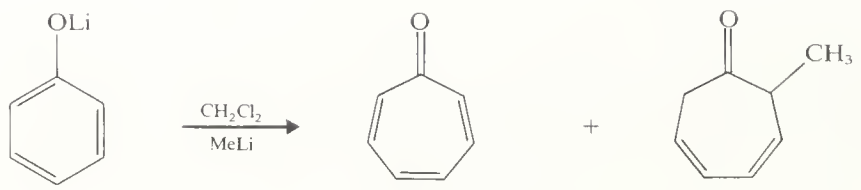
(*a*) *Ring-expansion.* Lithium phenolate reacts with chlorocarbene (from methylene chloride and methyl-lithium) to give tropone and 2-methylcyclohepta-3,5-dienone (Scheme 123).[243] Phenoxide ions also react with chloramine to yield aminodienones which ring-expand to dihydroazepinones (Scheme 124).[244]



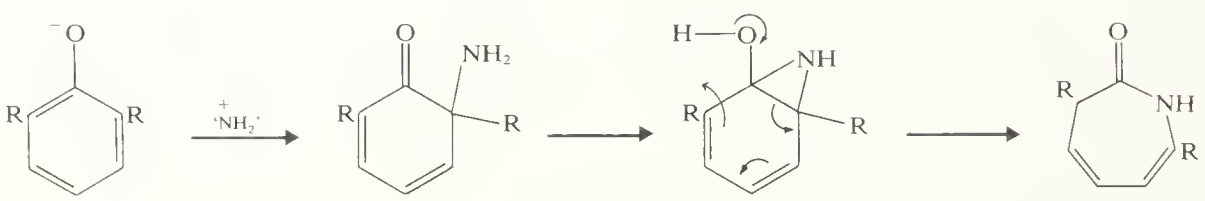
(**186**) (**183**) Oestrone (**184**)



(**185**) (26)



SCHEME 123



SCHEME 124

(*b*) *Photosubstitution.*[245] Photo-dehalogenation of halophenols and their ethers has been described. Irradiation of *p*-halogenophenols in the presence of cyanide ion gives *p*-cyanophenols, which may further be transformed to *p*-hydroxybenzaldehydes. Nitriles are also formed by irradiation of nitrophenyl ethers in the presence of cyanide ion with introduction of the cyano group *meta* to the nitro function (Scheme 125).

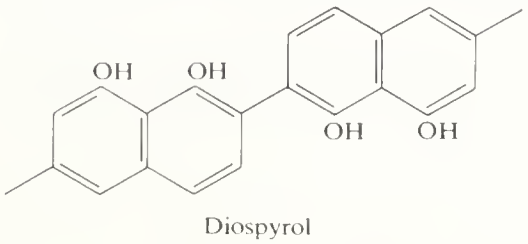
i, $h\nu$, O_2, ^-CN.

SCHEME 125

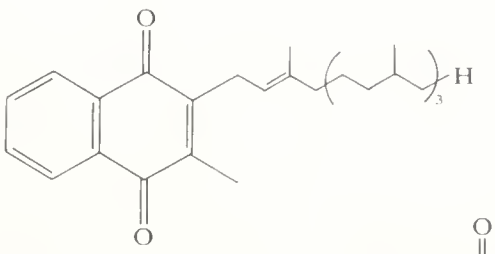
4.2.3.4 Hydroxypolynuclear hydrocarbons

The chemistry of naphthols, hydroxyphenanthrenes, *etc.* is in general terms covered by the foregoing sections on synthesis and chemistry of phenols. The chemistry of these

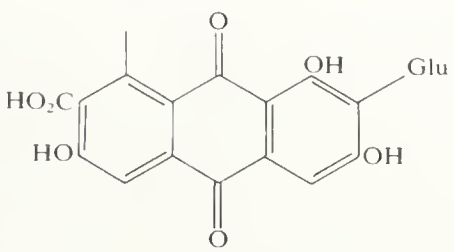
compounds, and their derived quinones, is important in the dyestuffs industry and in natural products chemistry. The extent of the variety and complexity of structures to be found is barely illustrated by the few examples of natural pigments[246] displayed in Scheme 126. The chemistry of these important specialized areas is outside the scope of this chapter, but a few comments on naphthol chemistry are appropriate. All the general methods for direct hydroxylation are applicable to naphthols. Direct construction of naphthols by the Diels–Alder route has been investigated[247] (Scheme 127). Bicyclizations of trienoic dicarboxylic acids also give naphthols[248] (Scheme 128) and it is possible that electrocyclic reactions, as in (**187**), mediate, as they may also do in the thermal cyclization of arylbutadienoic acids (Scheme 129).



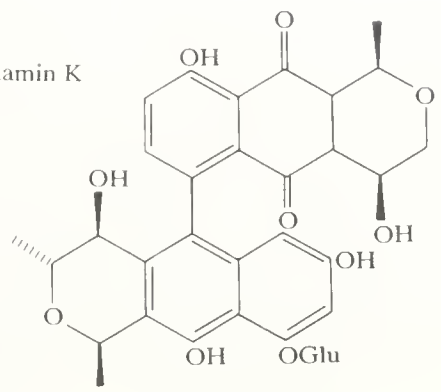
Diospyrol



Vitamin K

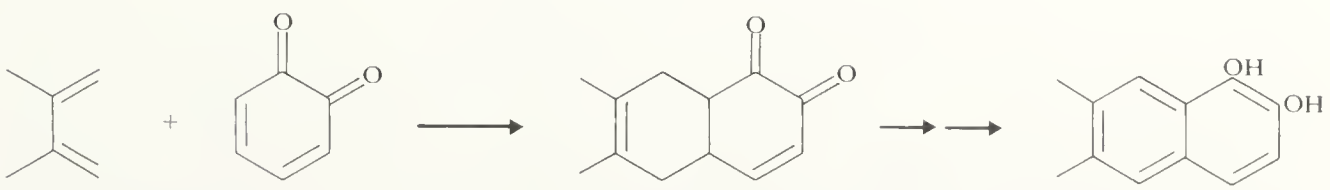


Carminic acid

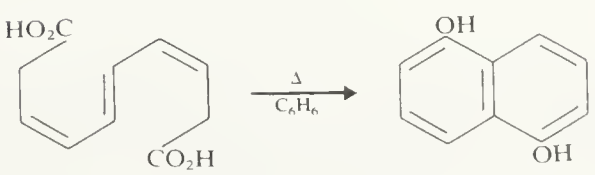


Protoaphin-fb

SCHEME 126

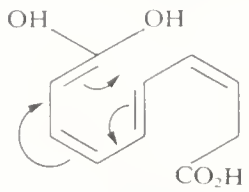


SCHEME 127



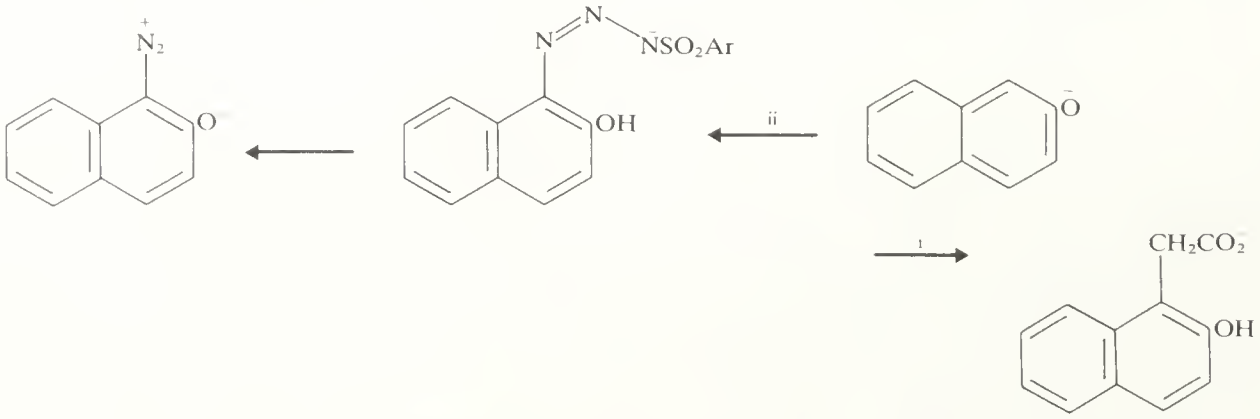
SCHEME 128

SCHEME 129



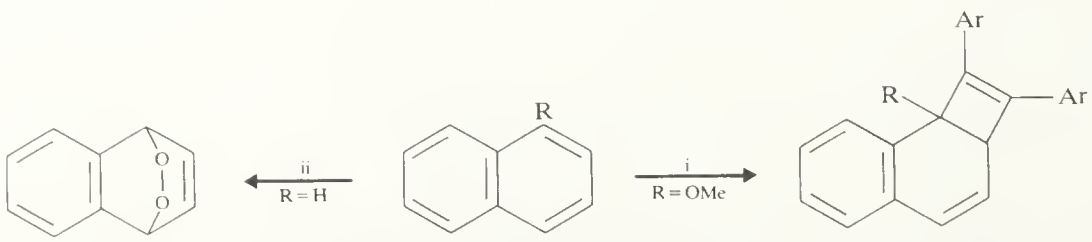
(**187**)

The naphthols, as with all the polynuclear hydrocarbons, show a greater degree of bond fixation and less aromaticity than do benzene derivatives. Thus naphtholate anions are relatively good carbon nucleophiles, *i.e.* a much closer balance between *O*- and *C*-alkylation is found. β-Naphthol reacts in alkali both with mercaptoacetic acid and with arenesulphonyl azides (soft electrophiles), both reactions involving predominantly carbon substitution. The second reaction can be used to prepare diazonaphthols (Scheme 130).



i, $HSCH_2CO_2H$, ^-OH; ii, $ArSO_2N_3$, ^-OH.

SCHEME 130



i, ArC≡CAr, *hν*; ii, O_2, *hν*, Methylene Blue.

SCHEME 131

Addition reactions with naphthalenes also occur more readily than in benzenes. Naphthalene itself reacts with singlet oxygen in the Diels–Alder mode, giving a direct method for 1,4-oxygenation.[249] A [2+2] cycloaddition between α-naphthol methyl ether and diarylacetylenes has also been demonstrated.[250] Both these reactions are shown in Scheme 131.

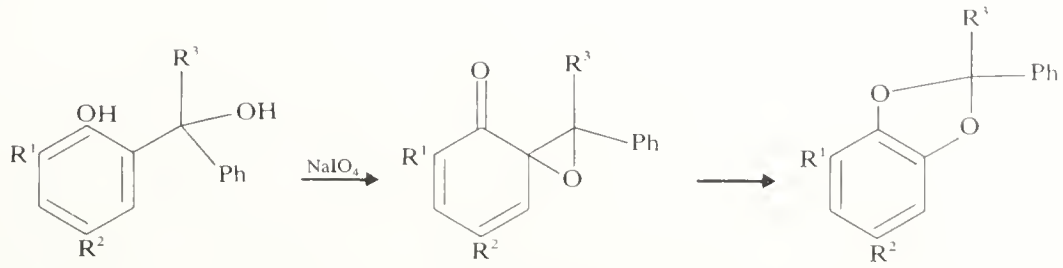
4.2.4 DI-, TRI-, AND POLY-HYDRIC PHENOLS

4.2.4.1 Catechol and relatives

1,2-Dihydroxybenzene (catechol) and some of its simple derivatives are found in plants and can be obtained by breakdown of natural materials, *e.g.* wood and lac. Catechol is used in manufacture of alizarin (phthalic anhydride condensation), as a fine grain

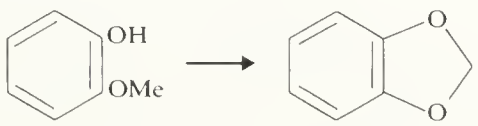
developer in photography, and as an antioxidant. The compound of bismuth and tetrabromocatechol is dispensed in pharmacy.

Catechol can be obtained by standard methods, *e.g.* Dakin oxidation of salicylaldehyde. Alkali fusion of halophenols, disulphonic acids, *etc.* can be used, but rearrangement to the thermodynamically most stable *meta*-dihydric phenols takes place at higher temperatures. An unusual rearrangement leading to catechols has been discovered. Phenols with an *o*-hydroxyalkyl group are oxidized by sodium periodate. An *exo*-epoxydienone results which undergoes [1,3]-sigmatropic rearrangement to the cyclic catechol acetal (Scheme 132).[251]



SCHEME 132

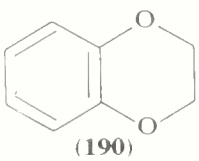
Catechol forms chelate complexes with many metallic elements,[252] especially those with a high affinity for oxygen; the elements include Ti, Zr, Hf, V, Nb, Cr, Mo, As, Sn, Pb, and Sb. A resolvable arsenic complex $H[As(C_6H_4O_2)_3]\cdot 5H_2O$ is known. Such complexes can affect catechol chemistry. Thus the Friedel–Crafts reaction with proton acids gives 4-monoalkyl- and 4,5-dialkyl-catechols, but with aluminium alkoxide–alkene reagents, 3-mono- and 3,6-di-alkylcatechols dominate. A catechylaluminium alkoxide is probably formed, with intramolecular reaction to the *ortho* products.[253] The acid-catalysed Fries rearrangement gives 4-acylcatechols whereas the photo-Fries variant provides comparable yields of the 3- and 4-acylcatechols.

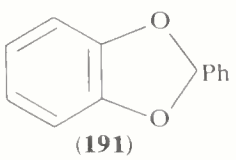


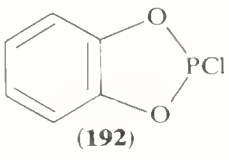
(188) (189) (27)

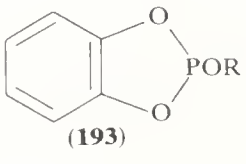
Catechol forms many cyclic derivatives, including a variety of ethers. The methylene ether (**189**) is formed by reaction with methylene dihalides in base. This 'methylene-dioxy' group is often found in natural phenols, derived by oxidative coupling in an *o*-methoxyphenol unit, *i.e.* (**188**)→(**189**) (equation 27). The group releases formaldehyde on treatment with concentrated sulphuric acid (basis of the Labat colour test). Catechol ethylene ether (**190**) (1,4-benzodioxan) is formed by heating catechol with ethylene dibromide, alkali, and copper powder. Cyclic acetals, *e.g.* with benzaldehyde (see **191**), are easily formed and are useful protecting groups for either component. Many cyclic esters of organic acids and of di- and poly-basic inorganic acids, *e.g.* those of phosphorus, boron, and sulphur, are known. For phosphorus acids the following types have been reported: (i) (**192**)–(**195**) from phosphorus trichloride, (ii) (**196**) from phosphoryl chloride, (iii) (**197**) from methylphosphorus dichloride, and (iv) (**198**) and (**199**) from phosphorus pentachloride. Several boron analogues are known.[254] Phenylborinic esters have been used to form crystalline derivatives characterizing the 1,2-dihydroxybenzene unit; compounds are heated in benzene with phenylborinic anhydride, PhBO. Catechols give characteristic changes in u.v. maxima when treated with boric acid–sodium acetate, which are useful in structure diagnosis.[255] Catechol forms the starting point for the synthesis of many dibenzo heterocyclic systems.[256] Heating with *o*-phenylenediamine gives dihydrophenazine (**200**), with *o*-aminophenol, phenoxazine (**201**), and with aminothiophenol,

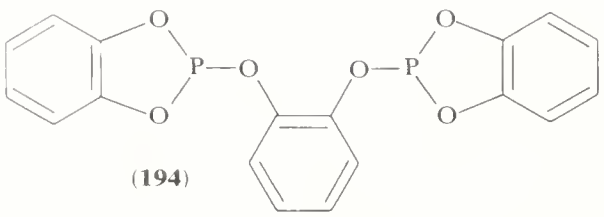
phenothiazine (**202**). The oxidation of catechols to *o*-quinones has been dealt with in Section 4.2.3.2. More drastic oxidation causes ring cleavage. Both chemical oxidants and enzymes give *cis,cis*-muconic acid (**203**);[257] the reaction is of biogenetic interest.

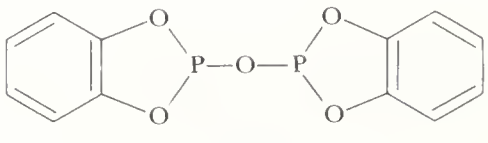

(**190**)

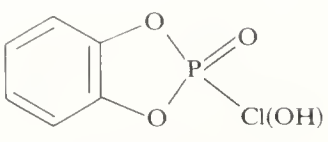

(**191**)

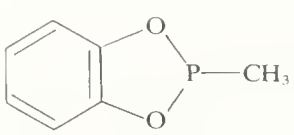

(**192**)

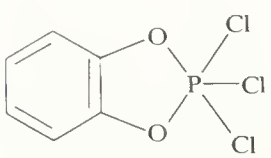

(**193**)

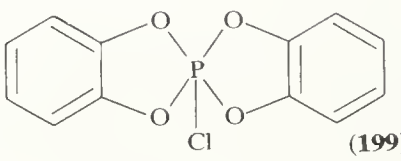

(**194**)

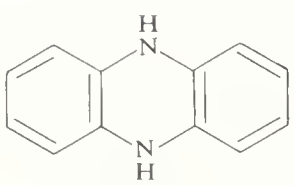

(**195**)

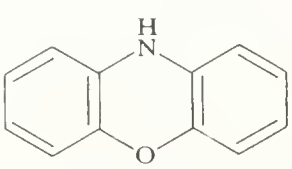

(**196**)

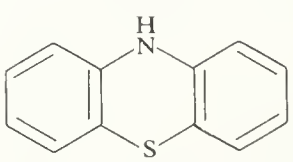

(**197**)

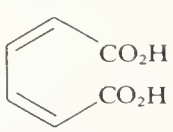

(**198**)


(**199**)


(**200**)

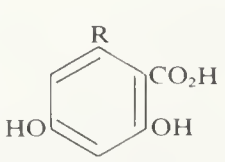

(**201**)

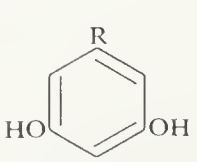

(**202**)


(**203**)

4.2.4.2 Resorcinol and relatives

Resorcinol, *m*-dihydroxybenzene, is the most thermodynamically stable of the dihydroxybenzenes, and was first obtained in 1864 by alkaline fusion of *Galbanum* and *Asafetida* resins; dry distillation of Brazil wood also gives resorcinol. Simple 1,3-dihydroxybenzenes are rare in Nature although the 2,4-dihydroxybenzoic acids are well known, *e.g.* orsellinic acid (**204**) from the lichens *Rocella* and *Lecanora*. Orsellinic acid, which is acetate-derived, decarboxylates readily to orcinol (**205**). Analogues are known, *e.g.* the acid (**206**), corresponding to 5-n-pentylresorcinol (olivetol, **207**) is prenylated *in vivo* in *Cannabis sativa* and with modifications yields the cannabinoid group of natural compounds.


(**204**) R = Me
(**206**) R = n-pentyl

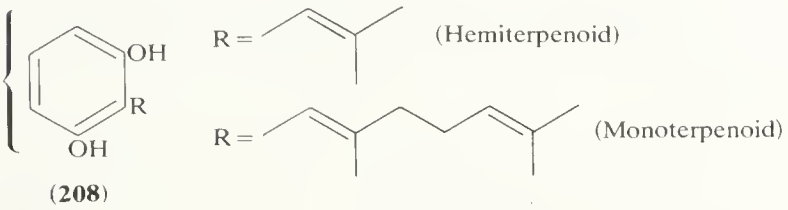

(**205**) R = Me
(**207**) R = n-pentyl

Resorcinol cannot give *o*- or *p*-benzoquinones on two-electron oxidation, and its behaviour is that, in the first stage, of a phenol whose ionization potential is lowered by the second hydroxy group. The e.s.r. spectrum of the *m*-benzene semiquinone radical has been observed.

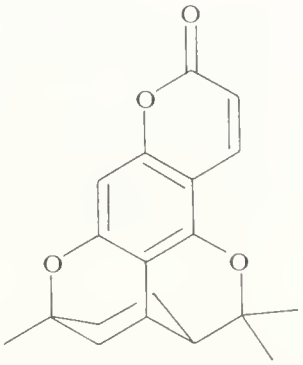
Resorcinol is particularly prone to substitution by electrophiles, reaction occurring at the 2- and (mainly) 4-positions. Preparations of 2- and 4-acylresorcinols are described,[258] and 4,6-di- and 2,4,6-tri-acylresorcinols can be obtained under more forcing conditions. Carboxylation can be achieved simply by heating at 100 °C in aqueous carbonate; β-resorcylic acid (2,4-dihydroxybenzoic acid) and some γ-resorcylic acid (2,6-dihydroxybenzoic acid) are formed. Higher temperatures give the di-acids.

(*i*) *Resorcinol- and phloroglucinol-based meroterpenoids*

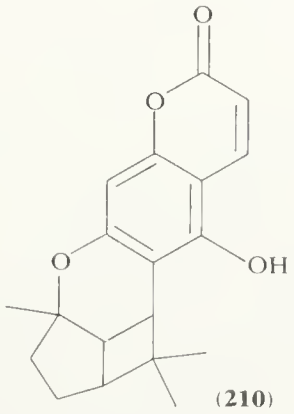
To reiterate what has been said above, the *m*-dihydroxybenzene system arises from polyketide cyclization and is common in Nature. Phenolic compounds of this sort are frequently found conjoined to terpenoid residues; such products have been termed 'meroterpenoids' (Cornforth) and occur with great structural variety. Hemi-, mono-, sesqui-, di-, and other isoprenoid fragments may be involved. In the simplest form, such units comprise acyclic prenyl substituents as in (**208**). Units of this type can be inserted by electrophilic substitution using Lewis acids and prenyl alcohols or halides. Some biogenetically patterned methods have been discussed in Section 4.2.3.3.



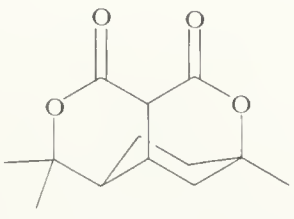
(**208**)



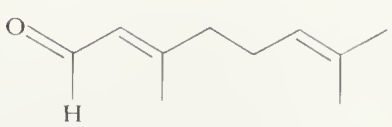
(**209**)



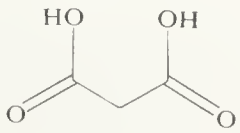
(**210**)



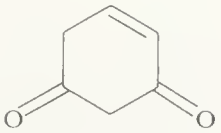
(**211**)



(**212**)

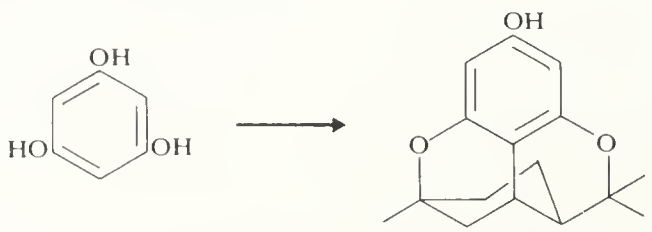


(**213**)



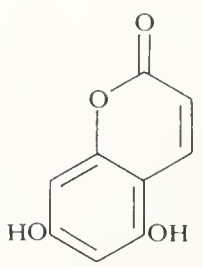
(**214**)

m-Dihydric phenols are nucleophilic enough to react with prenyl aldehydes and acetals in a way which leads to ready synthesis of some otherwise inaccessible structures, *e.g.* the tricyclic terpenoid systems found in deoxybruceol (**209**) and eriobrucinol (**210**), attached to the bicyclic dihydroxycoumarin core. The key to synthetic entry to these systems lay in the recognition of the parallel with citrylidenemalonic acid (**211**), prepared from malonic acid with citral (**212**) under pyridine catalysis.[259] Malonic acid (**213**) has certain structural and reactivity similarities with resorcinol in its dioxo tautomer (**214**) and it was discovered that resorcinol and phloroglucinol (and relatives) would react with citral in pyridine in the same way as malonic acid. For phloroglucinol the product is the 'citran' (**215**) (equation 28).[260a] In the same way, 5,7-dihydroxycoumarin (**216**) gives deoxybruceol (**209**), olivetol (**207**) gives 'citrylidene cannabis' (**217**)[260b] (a minor constituent of Lebanese hashish), and pinocembrin (**218**) gives rubranine (**219**)[260c] (condensation being accompanied by flavanone–chalcone opening). The mechanism of this reaction is indicated by the isolation of chromens (**220**), (**221**) along with (**217**) from the olivetol–citral reaction. This observation suggests that a monochromen may be intermediate and the course of reaction shown in Scheme 133 has been proposed. A resorcinolate anion (although ionization of phenols in pyridine is very limited) appears the most nucleophilic species reasonably present, and is shown in reversible addition with the aldehyde carbonyl group. Base-catalysed dehydration leads to the conjugated dienone (**222**) and electrocyclic closure of this affords the chromen intermediates. Chromen–dienone equilibration has been demonstrated in several reactions, *e.g.* optically active mahanimbine (**223**; arbitrary designation of absolute configuration) when heated in pyridine–D_2O is not only racemized but incorporates deuterium at positions ε to the carbonyl group through enolization of the dienone intermediate (equation 29). Further reaction of chromens to citrans is believed to follow Scheme 134.[260d] The phenolic chromen is subject to base-catalysed tautomerism; if the *exo*-enone (**224**) is trapped intramolecularly by Diels–Alder reaction, the citran is formed. Such a scheme implies stereospecificity in the final step and such control has been shown to apply, *e.g.* in the bicyclizations of (**225**) and (**226**), derived from 6-*trans*- and 6-*cis*-farnesals (equations 30 and 31).[260e]

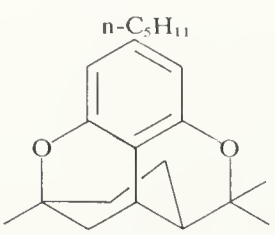


(28)

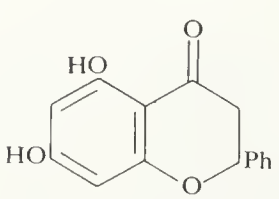
(**215**)



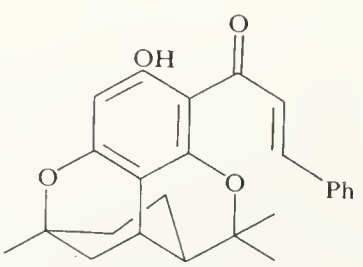
(**216**)



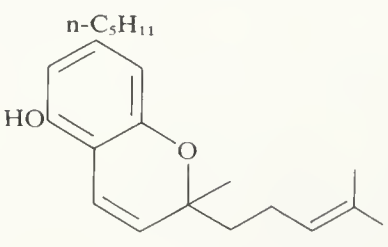
(**217**)



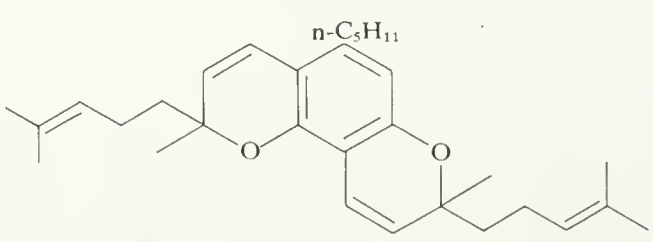
(**218**)



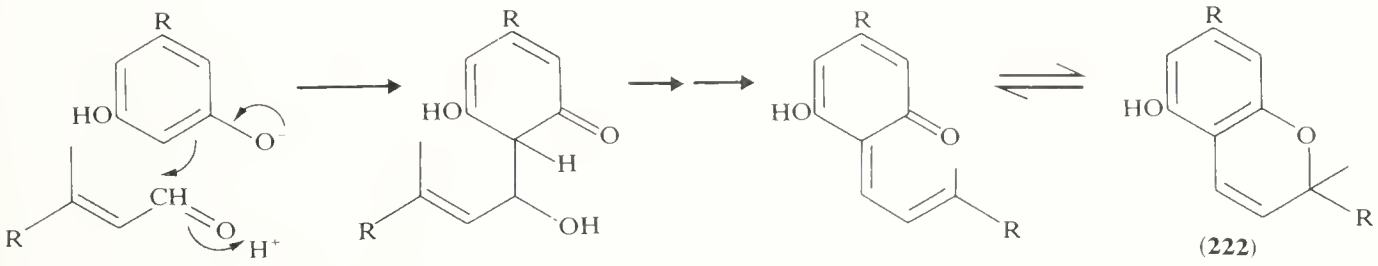
(**219**)



(**220**)

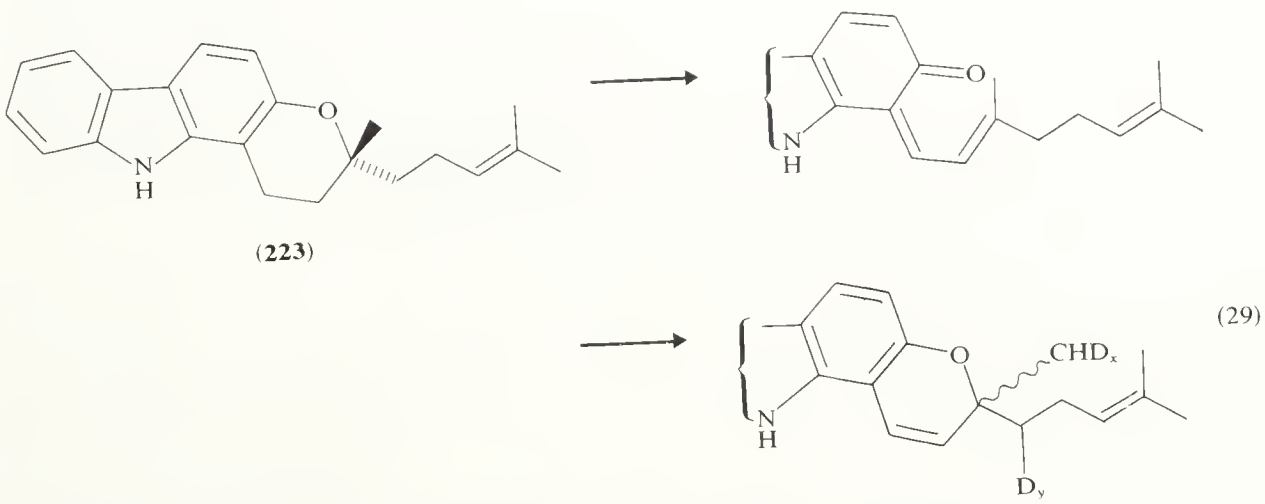


(**221**)



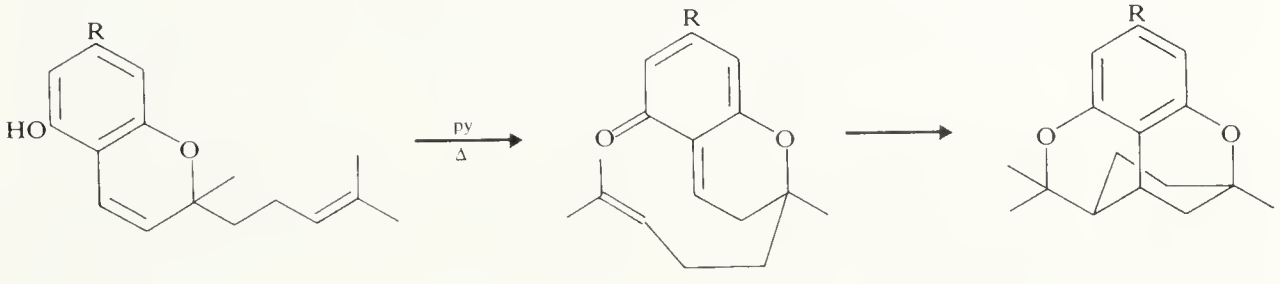
(**222**)

SCHEME 133



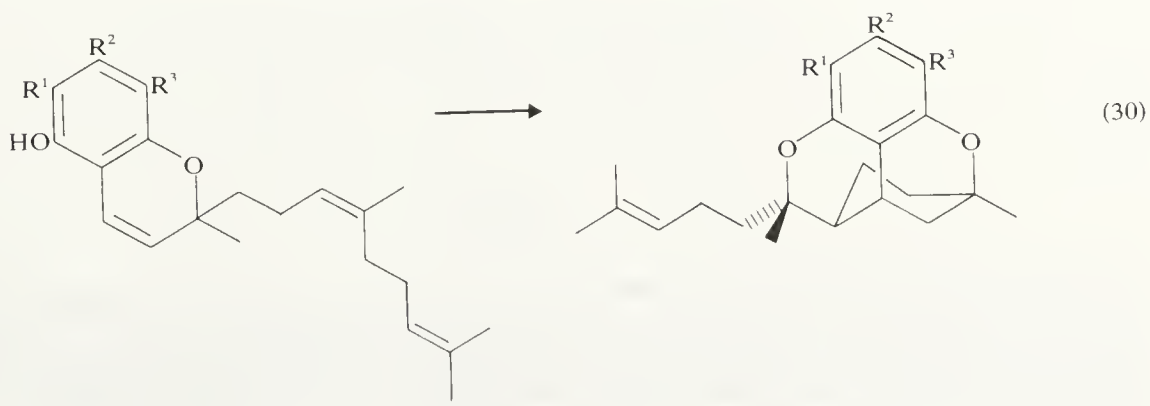
(**223**)

(29)



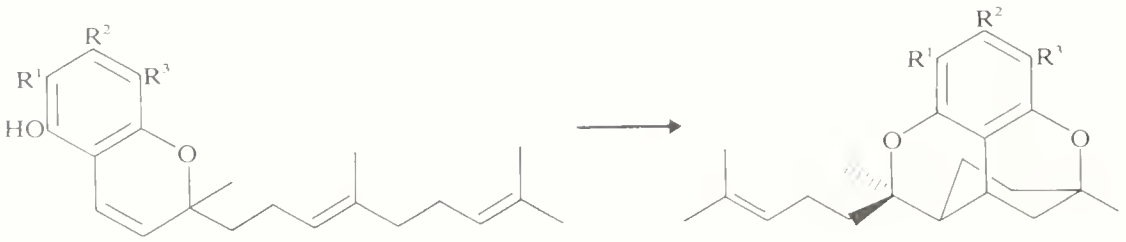
(**224**)

SCHEME 134



(**225**)

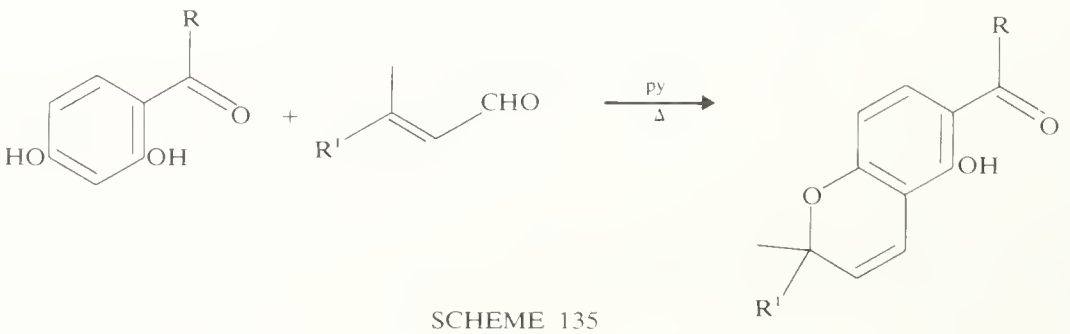
(30)



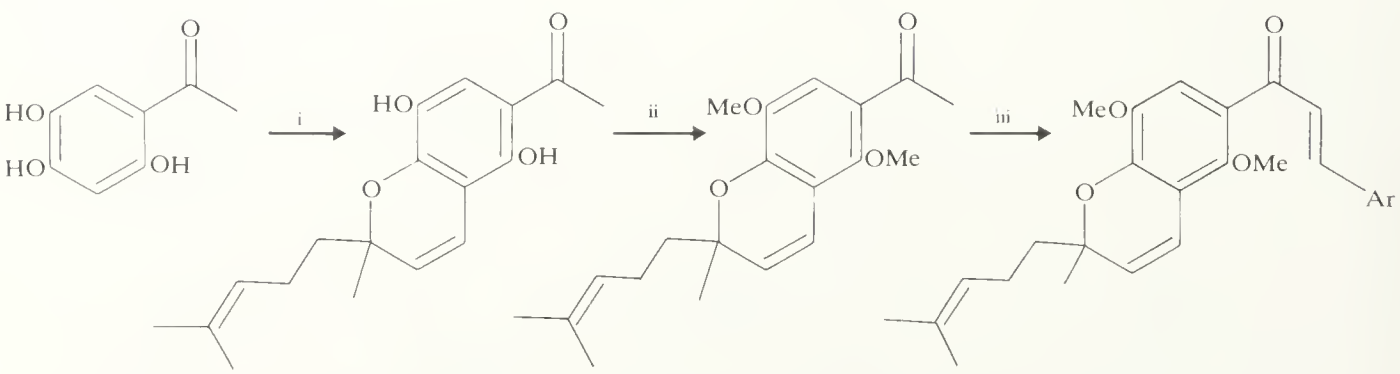
(31)

(**226**)

The chromen intermediates may be obtained as major products when the bicyclization step is slow. This is the case when the second *meta* hydroxy group is involved in chelation, as for example, in resacetophenones, and chromens are obtained even under forcing conditions (Scheme 135). The participating aldehydes include citral, farnesal, phytal, crotonaldehyde, cinnamaldehyde, and 3-methylbut-2-enal. A restricting feature is the lack of stability of some enals in hot pyridine; this can be overcome by employing the corresponding acetals which react equally readily but without resinification. This reaction can be used in synthesis of the methyl ethers of the flemingins-A, -B, and -C, pigments of the East African drug derived from *Flemingia rhodocarpa* (Scheme 136).[260c]



SCHEME 135

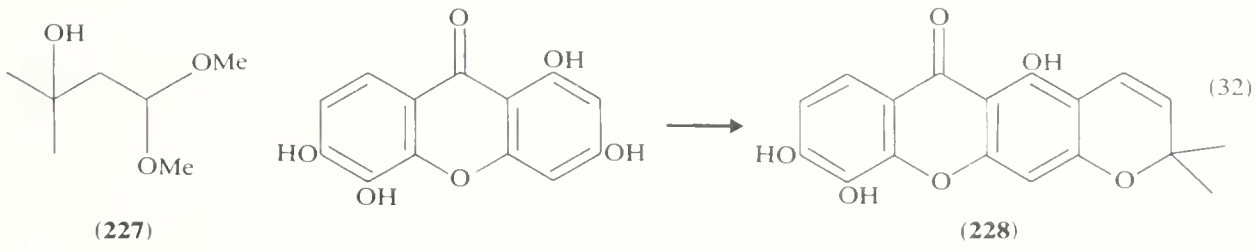


Ar = 2,6-Dimethoxyphenyl, Flemingin B tetramethyl ether
Ar = 2,5-Dimethoxyphenyl, Flemingin C tetramethyl ether
Ar = 2-Methoxyphenyl, Flemingin A trimethyl ether

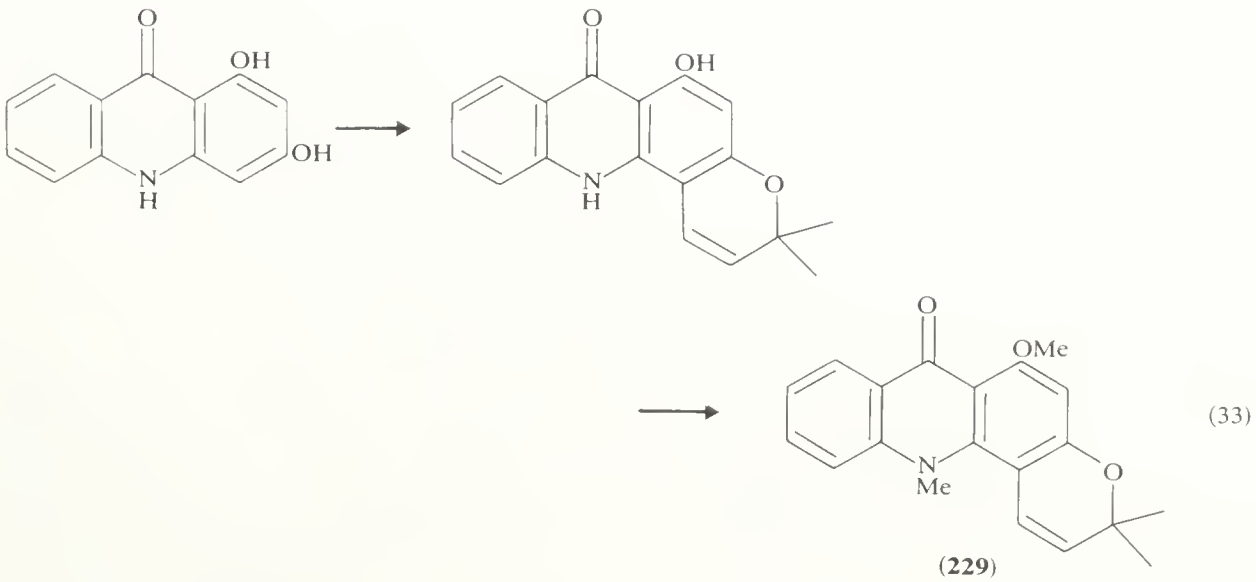
i, Citral, pyridine, Δ; ii, MeI; iii, ArCHO, $^{-}$OH.

SCHEME 136

The frequently encountered dimethylchromen unit can be made most readily with 3-hydroxy-3-methyl-1,1-dimethoxybutane (**227**), more easily prepared and purified than the α,β-unsaturated acetal or aldehyde; this reagent[260f] facilitates synthesis of jacareubin (**228**) from 1,3,5,6-tetrahydroxyxanthone (equation 32) and acronycine (**229**) (an anti-tumour acridone alkaloid) from 1,3-dihydroxyacridone (equation 33).[260g]

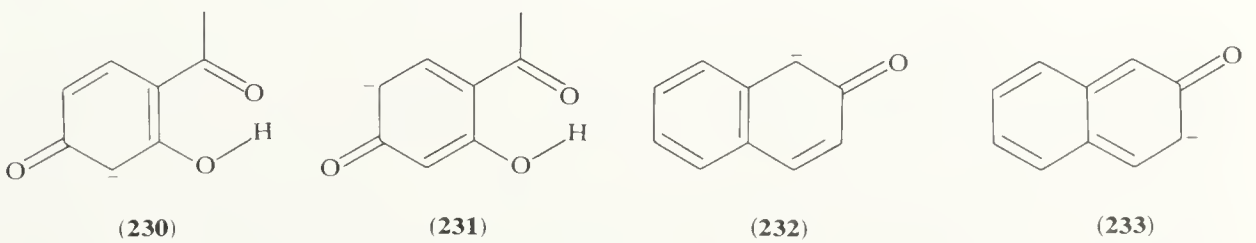


(227) (228) (32)

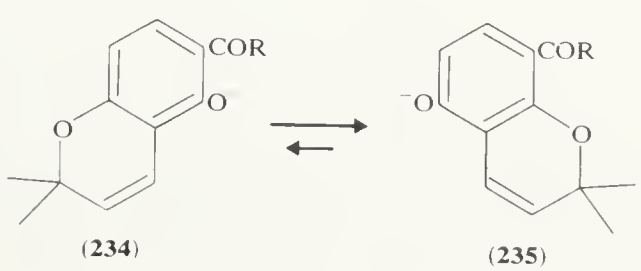


(229) (33)

Marked regioselectivity characterizes certain of these reactions. This selectivity may be ascribed to a degree of bond-fixation in the transition state controlled by the tendency to retain the resonance stabilization of the chelate ring, *e.g.* (**230**) compared with (**231**) or, in the case of a second aromatic ring, (**232**) compared with (**233**). The phenolate anions may show different relative stabilities to those of the parent phenolic chromens. Thus (**234**) is isomerized[261] in base to the more acidic phenol (**235**) (Scheme 137).



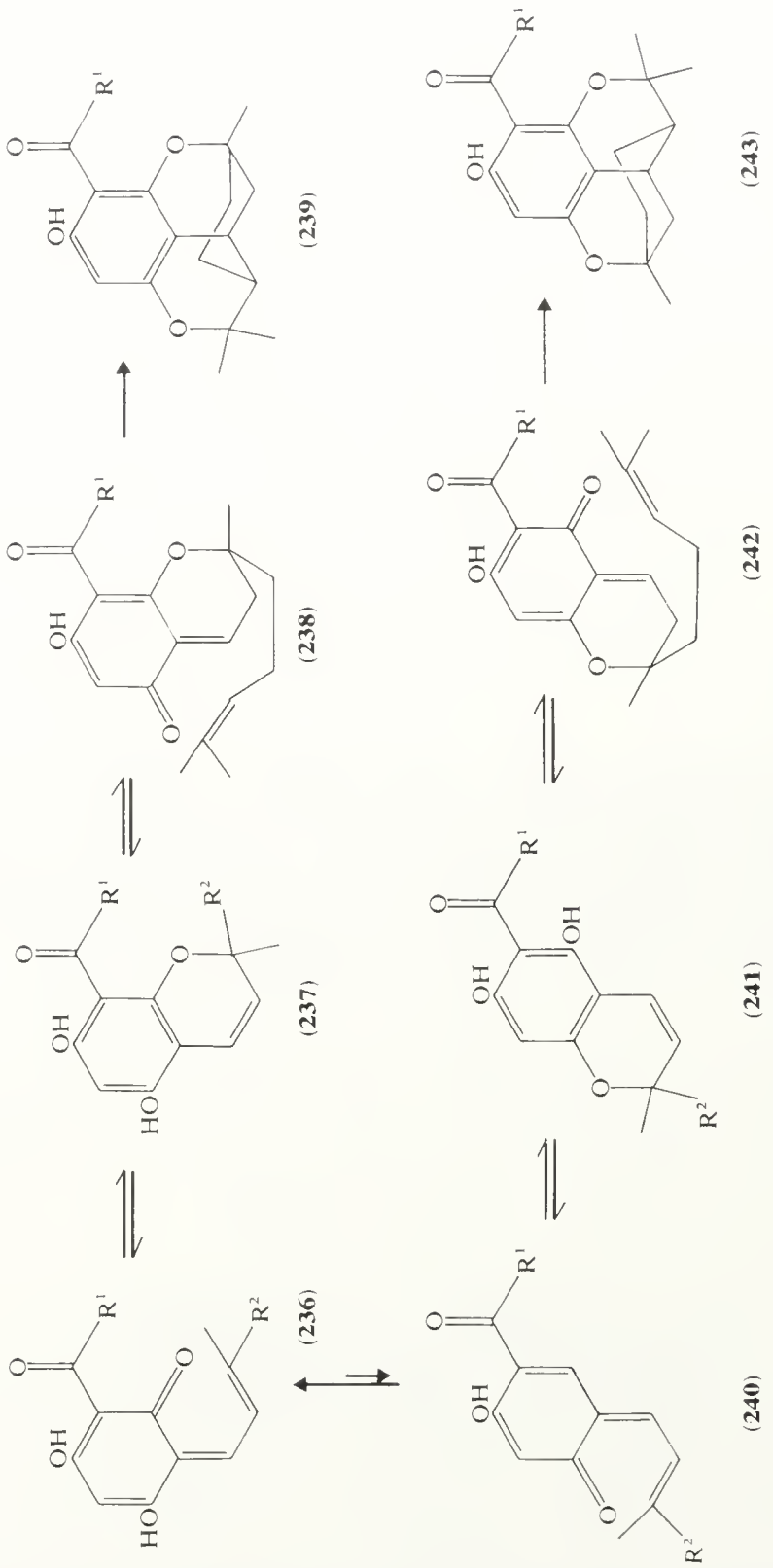
(230) (231) (232) (233)



(234) (235)

SCHEME 137

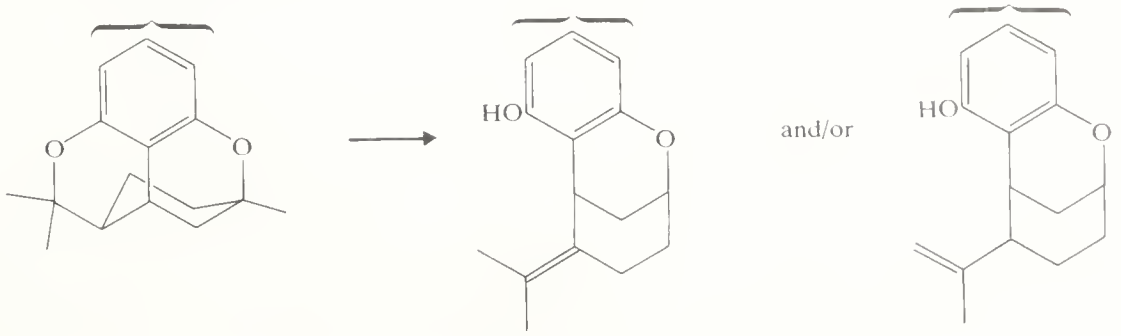
Chromenylation of phloroacetophenone and phloroglucinaldehyde with citral and pyridine at moderate temperatures gives the chromens (**237**) and (**241**), with the former predominating (Scheme 138).[262] However, on further heating in pyridine the major chromen (**237**) re-equilibrates with its isomer, from which citran formation is faster, reflecting the retention of chelate stabilization in (**242**) as opposed to (**238**). Thus the



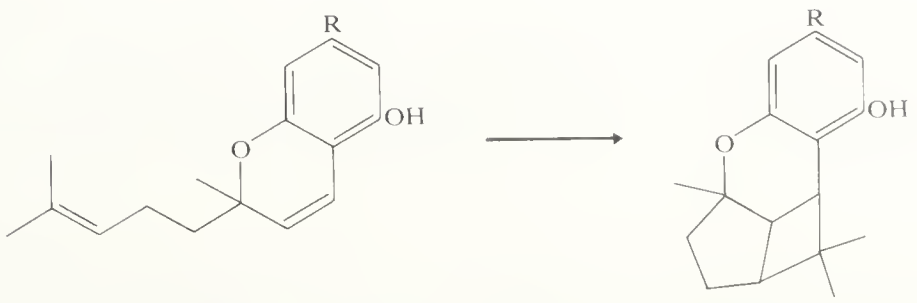
SCHEME 138

bicyclization of (**237**) to (**243**) proceeds with change of orientation. The minor citran (**239**) can be obtained.

Ring opening of citrans by acid, or acid cyclization of chromens, leads to further meroterpenoid types; some modes are illustrated in Scheme 139. Yet another system can be prepared from chromens by [2+2] cycloaddition, *e.g.* cannabicyclol (**245**) from chromen (**244**) (equation 34).[260g]



SCHEME 139



(34)

(**244**) (**245**)

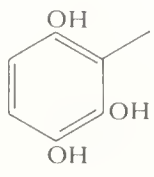
4.2.4.3 Hydroquinone and relatives

p-Dihydroxybenzene or hydroquinone, or quinol, is very readily prepared by reduction of *p*-benzoquinone. It occurs in Nature as its β-glucopyranoside, arbutin, which is present in the leaves of some higher plants, *e.g.* bearberry *Arbutus uva-ursi*; methylarbutin is also found. Hydroquinone was first obtained in 1820 by Pelletier and Caventov from the distillation of quinic acid. The oxidation of hydroquinone is dealt with above. *p*-Benzoquinone products may be further hydroxylated (hydroxy-*p*-benzoquinone has been obtained).[263] Nucleophiles may add in the course of the oxidation, *e.g.* in the presence of bisulphite the 2- and 2,5-sulphonic acids are obtained. 2,2′,5,5′-Tetrahydroxybiphenyl is formed by irradiating an aqueous solution of hydroquinone.[264] As with catechol, oxidation of hydroquinone through a succession of coupling reactions eventually produces humic acid-like products. Substitution by electrophiles does not proceed so readily as with resorcinol but generally takes the expected pathway. Oxidation may, however, intervene, *e.g.* diazo compounds react with hydroquinone to give benzoquinone rather than azo-coupling products. 1,4-Diels–Alder addition has been observed with hydroquinone and maleic anhydride.[265] The antibiotic drosophilin A is tetrachloromonomethyl-hydroquinone.[266]

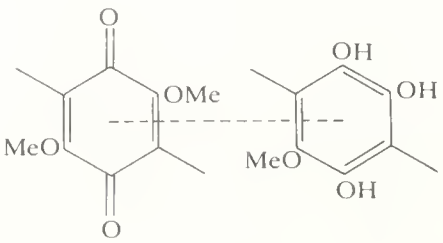
4.2.4.4 Polyhydroxybenzenes

All the possible constitutional isomers of the tri-, tetra-, penta-, and hexa-hydroxybenzenes are known. Many natural compounds contain one or more aromatic

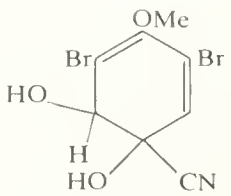
nuclei of these types; when account is taken of full or partial methylation, glucosylation, *etc.*, and of the related quinone forms, an immense variety is encompassed. Natural products found in higher plants, fungi, bacteria, insects, and marine organisms are included. Some unusual compounds of this type[267] are versicolin (**246**), an antifungal antibiotic *ex. Aspergillus versicolor*, the intriguing natural quinhydrone (**247**) from the ascomycete *Nectra coryli*, and aeroplysin-1 (**248**), the cyanohydrin of a 1,2,4-trihydroxybenzene in one of its keto forms, from the sponge *Verongia aerophoba*. The last two compounds are anti-bacterial. The trihydroxybenzenes are the most commonly found in Nature in this group, and pyrogallol (1,2,3-trihydroxybenzene) and phloroglucinol (1,3,5-trihydroxybenzene) (the most important and best studied members) are present with other phenols in wood tar distillates. As expected, polyhydroxybenzenes and their ethers are extremely reactive towards electrophiles. The compounds with *meta* hydroxy groups show many reactions of ketones, and, in some cases, *e.g.* with 1,2,3,4-tetrahydroxybenzene, oxo tautomers have been isolated. Such forms render the phenol susceptible to nucleophilic substitution and reactions such as ammonolysis also proceed fluently. Oxidation also occurs very readily. Most polyhydroxybenzenes are oxidized by air, and solids and solutions become coloured on exposure to it.



(**246**)



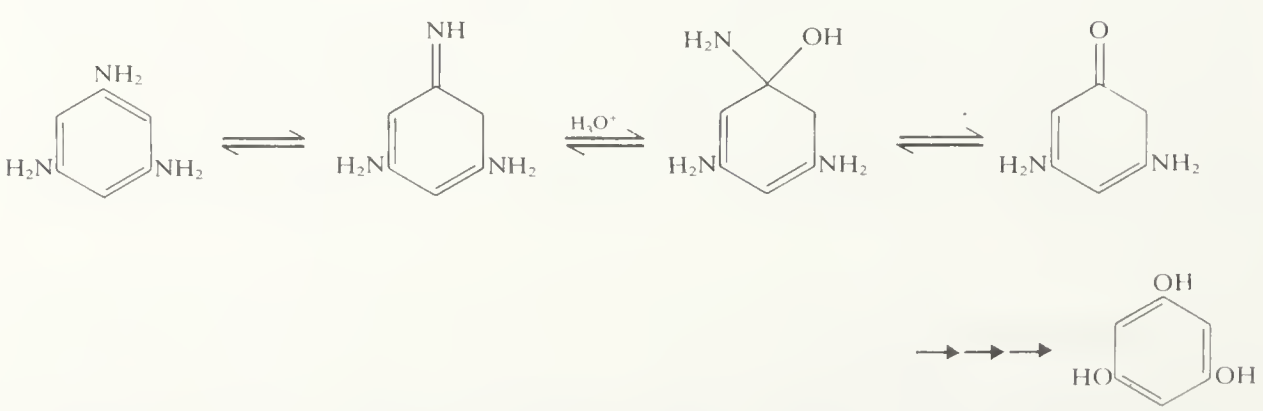
(**247**)



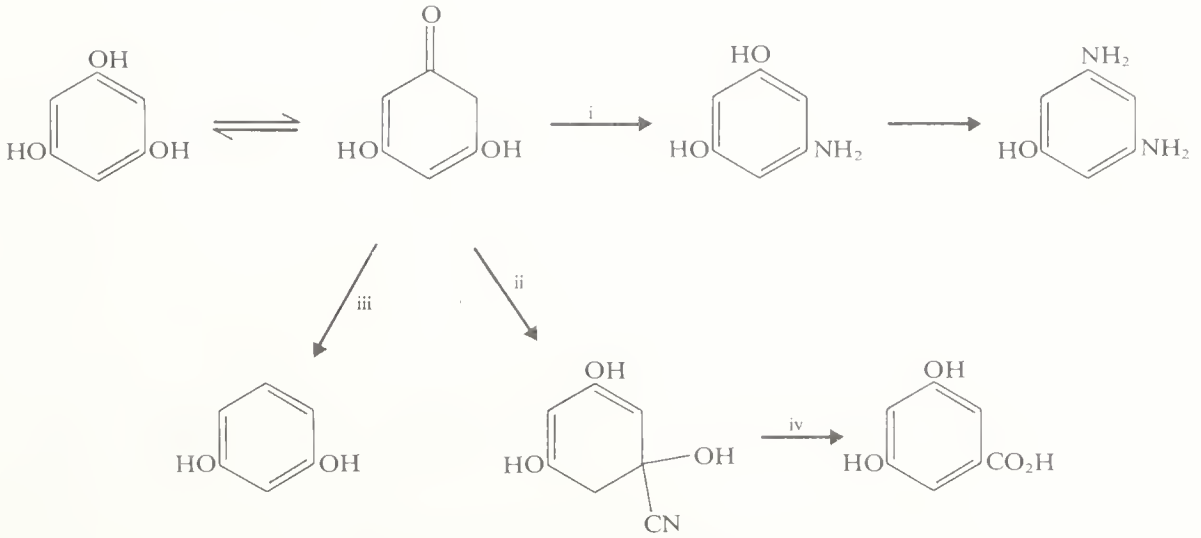
(**248**)

Pyrogallol has been known since 1876 when it was obtained by Scheele from dry distillation of gallic acid from nutgalls. Decarboxylation of gallic acid is still extensively used, and various catalysts, *e.g.* alkaline earth oxides and tertiary bases, have been patented. The rearrangement of 2,2-diacetoxycyclohexa-3,5-dienone, either by heating or by acid catalysis, gives pyrogallol triacetate. Some alkyl derivatives occur naturally, *e.g.* 5-n-propylpyrogallol.

An important industrial process for obtaining phloroglucinol from trinitrotoluene employs dichromate oxidation to the corresponding acid, reductions with iron or tin and hydrochloric acid, and finally hydrolysis of the 1,3,5-triaminobenzene. The last reaction depends on ready imine formation (Scheme 140). Starting from phloroglucinol, various substitutions by nucleophiles can be achieved, and a few are illustrated in Scheme 141. The S_E reactions of phloroglucinol include carboxylation by aqueous bicarbonate at 60 °C, diazo coupling to mono-, di-, and tri-azo compounds, and nitrosation with nitrous acid to trinitrosophloroglucinol.



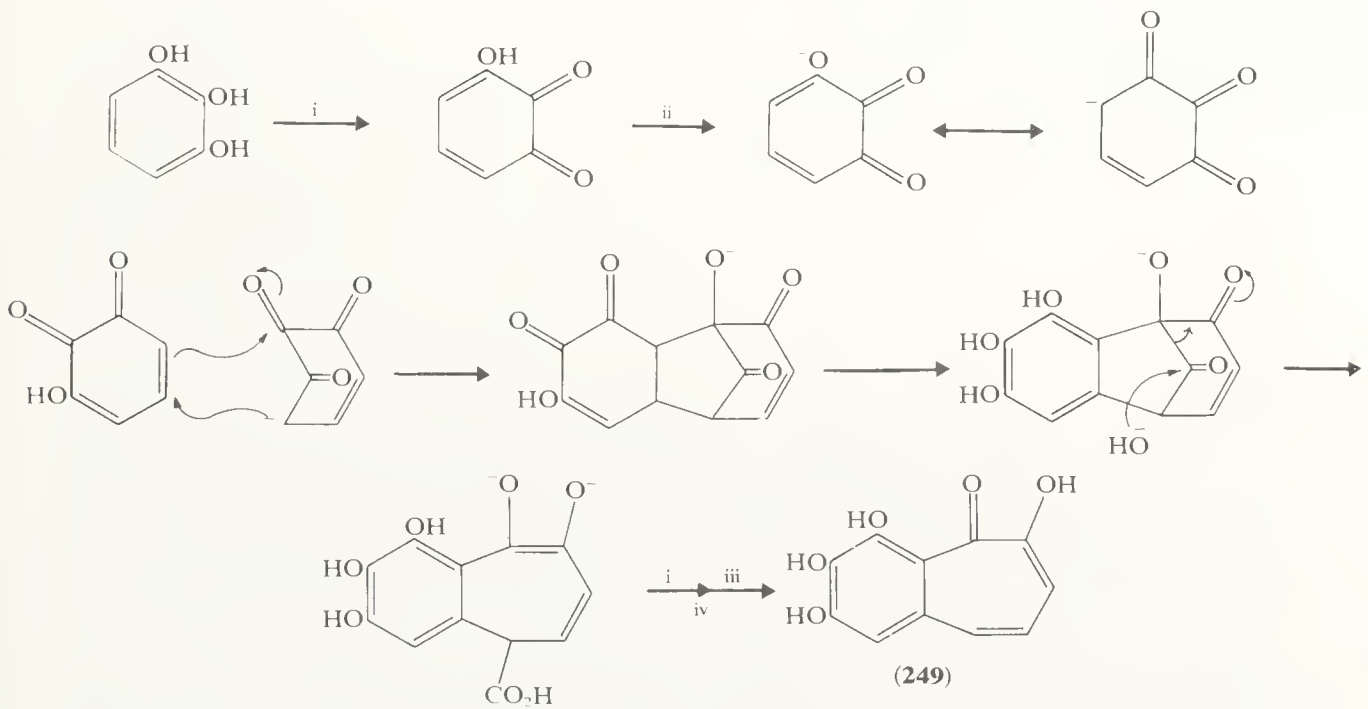
SCHEME 140



i, H_2O, NH_3, Δ; ii, $\bar{C}N$; iii, $^-BH_4$; iv, ^-OH.

SCHEME 141

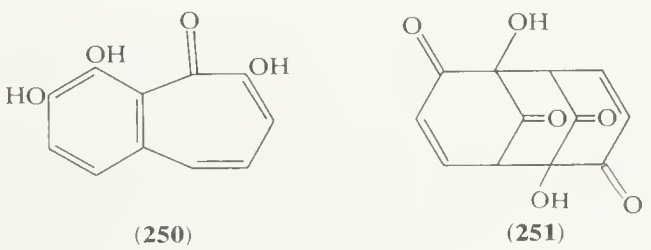
Among oxidation reactions, those of pyrogallol are particularly interesting. Purpurogallin (**249**) is obtained using sodium iodate or other oxidants and the mechanism is shown in Scheme 142.[268] Other benzotropolones are obtained by co-oxidation of pyrogallol with an *o*-benzoquinone or catechol, *e.g.* (**250**). The tricycle (**251**) is obtained from pyrogallol by oxidation with isopentyl nitrite and acetic acid.



(**249**)

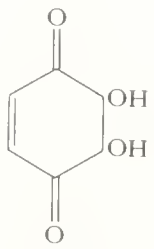
i, −2H; ii, $-H^+$; iii, $-CO_2$; iv, $+2H^+$.

SCHEME 142

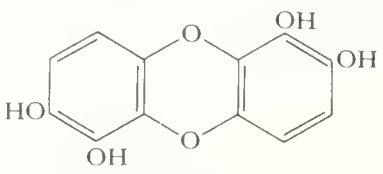


(**250**) (**251**)

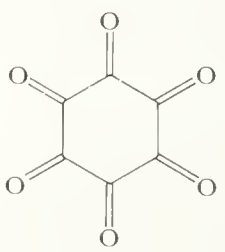
1,2,4-Trihydroxybenzene is usually prepared by Thiele–Winter reductive acetoxylation of benzoquinone, with subsequent hydrolysis. 1,2,3,4-Tetrahydroxybenzene, apionol, is obtained by hydrolysis of 4-aminopyrogallol in acid, or of 2,3-dimethoxyhydroquinone. Acidifying an alkaline solution of apionol at low temperatures leads to the oxo form (**252**) by kinetically preferred *C*-protonation; reversion to the phenolic form is catalysed by acid and negligible oxo form is present at equilibrium.[269] The product of oxidizing hydroquinone with sodium chlorate and osmium tetroxide is not a tautomer of apionol but the dimer (**253**).[270] 1,2,4,5-Tetrahydroxybenzene is produced by reduction of 2,5-dihydroxy-*p*-benzoquinone; the latter can be obtained by oxidation of hydroquinone with hydrogen peroxide in concentrated alkali. 1,2,3,5-Tetrahydroxybenzene is best prepared[271] from hydrogenation of 2,6-dibenzyloxy-*p*-benzoquinone. Pentahydroxybenzene is obtained by hydrolysing diaminopyrogallol in boiling water.[272] Hexahydroxybenzene can be prepared by reduction of tetrahydroxy-*p*-benzoquinone; this quinone is available through self-condensation of glyoxal in aqueous sodium carbonate and bisulphite.[273] Salts of hexahydroxybenzene are produced from carbon monoxide and alkali metals;[274] high yields are possible. In alkali, autoxidation gives the corresponding *p*-benzoquinone, while nitric acid oxidizes it to triquinonyl (**254**). Potassium crotonate is obtained by evaporating a solution of hexahydroxybenzene in potassium hydroxide. Hydrogenation of the hexaol over nickel affords inositols and quercitols, while with platinum catalyst, phloroglucinol is the chief product.



(**252**)



(**253**)



(**254**)

References

1. (a) W. Karrer, 'Konstitution und Vorkommen der organischen Pflanzenstoffe', Birkhauser, Basel, 1958; (b) T. K. Devon and A. I. Scott, 'Handbook of Naturally Occurring Compounds', Academic, New York, 1975, vol. 1; (c) M. W. Miller, 'The Pfizer Handbook of Microbial Metabolites, McGraw-Hill, New York, 1961.
2. (a) R. W. Rickards, in 'Chemistry of Natural Phenolic Compounds', ed. W. D. Ollis, Pergamon, Oxford, 1961, p. 1; (b) A. C. Neish, in 'Biochemistry of Phenolic Compounds', ed. J. B. Harborne, Academic, London, 1964, p. 295; (c) A. J. Birch, in 'Progress in the Chemistry of Organic Natural Products', ed. L. Zechmeister, Springer-Verlag, Vienna, 1957, vol. 14, p. 186.
3. E. Haslam, 'The Shikimate Pathway', Butterworths, London, 1974.
4. S. K. Erickson, J. Schadelin, U. Schmeling, H. H. Schott, V. Ullrich, and H. Staudinger, in 'Chemistry of the Hydroxyl Group', ed. S. Patai, Interscience, New York, 1971, part 2, p. 776.
5. (a) G. J. Kasperek and T. C. Bruice, *J. Amer. Chem. Soc.*, 1972, **94,** 198, and refs. therein; (b) G. J. Kasperek, T. C. Bruice, H. Yagi, N. Kausbisch, and D. M. Jerina, *ibid.*, 7876; (c) K. B. Sharpless and T. C. Flood, *ibid.*, 1971, **93,** 2316.
6. (a) A. Weller, *Prog. Reaction Kinetics*, 1961, **1,** 187; (b) L. Avigal, J. Feitelson, and M. Ottolenghi, *J. Chem. Phys.*, 1969, **50,** 2614.
7. A. Albert and E. P. Serjeant, 'Ionisation Constants of Acids and Bases', Methuen, London, 1962.
8. (a) L. A. Cohen and W. M. Jones, *J. Amer. Chem. Soc.*, 1963, **85,** 3400; (b) N. V. Sidgwick, 'The Organic Chemistry of Nitrogen' Clarendon, Oxford, 1966, p. 400.
9. (a) J. C. Dearden and W. F. Forbes, *Canad. J. Chem.*, 1959, **37,** 1294; (b) D. Harvey and E. G. Penketh, *Analyst*, 1957, **82,** 498.
10. (a) F. Feigl, 'Spot Tests in Organic Chemistry', Elsevier, Amsterdam, 1966; (b) G. Zweig, 'Analytical Methods for Pesticides, Plant Growth Regulators and Food Additives', Academic, New York, 1964.
11. C. H. Rochester, in 'Chemistry of the Hydroxyl Group', ed. S. Patai, Interscience, New York, 1971, part 1, p. 327.

12. (a) W. Lüttke and R. Mecke, *Z. phys. Chem.*, 1951, **196,** 56; (b) A. W. Baker and A. T. Shulgin, *Spectrochim. Acta*, 1964, **20,** 153.
13. (a) K. U. Ingold, *Canad. J. Chem.*, 1962, **40,** 111; (b) R. A. Nyquist, *Spectrochim. Acta*, 1965, **19,** 1655.
14. J. Massicot, J.-P. Marthe, and S. Heitz, *Bull. Soc. chim. France*, 1963, 2712.
15. A. Arone, G. Cardillo, L. Merlini, and R. Mondelli, *Tetrahedron Letters*, 1967, 4201.
16. (a) A. Pelter and P. I. Amenechi, *J. Chem. Soc.* (*C*), 1969, 887; (b) J. H. Bowie, J. Ronayne, and D. H. Williams, *J. Chem. Soc.* (*B*), 1967, 537; (c) H. M. Fales and K. S. Warren, *J. Org. Chem.*, 1967, **32,** 501; (d) A. Pelter, R. Warren, K. K. Chexal, B. K. Handa, and W. Rahman, *Tetrahedron*, 1971, **27,** 1625; (e) T. Anthonsen, *Acta Chem. Scand.*, 1968, **22,** 352.
17. D. T. Witiak, D. B. Patel, and Y. Lin, *J. Amer. Chem. Soc.*, 1967, **89,** 1908.
18. (a) B. Jackson, P. J. Owen, and F. Scheinmann, *J. Chem. Soc.* (*C*), 1971, 3389; (b) R. A. Archer, D. B. Boyd, P. V. Demarco, I. J. Tyminski, and N. L. Allinger, *J. Amer. Chem. Soc.*, 1970, **92,** 5200.
19. D. Davoust, S. Rebuffat, D. Molho, N. Platzer, and J. J. Basselier, *Tetrahedron Letters*, 1976, 2825.
20. D. A. Slack, Ph.D. Thesis, University of Nottingham, 1976.
21. (a) J. B. Stothers, 'Carbon-13 N.m.r. Spectroscopy', Academic, London, 1972; (b) G. C. Levy and G. L. Nelson, 'Carbon-13 Nuclear Magnetic Resonance for Organic Chemists', Wiley-Interscience, New York, 1972; (c) L. Crombie, G. W. Kilbee and D. A. Whiting, *J.C.S. Perkin I*, 1975, 1497 and refs. therein.
22. F. Wehrli, *J.C.S. Chem. Comm.*, 1975, 663.
23. J. M. Brown, *Tetrahedron Letters*, 1964, 2215.
24. (a) D. Y. Curtin and D. H. Dybrig, *J. Amer.Chem. Soc.*, 1962, **84,** 225; (b) N. Kornblum, P. J. Berrigan, and W. J. LeNoble, *ibid.*, 1963, **85,** 1141; (c) N. Kornblum, R. Seltzer, and P. Haberfield, *ibid.*, 1148; (d) N. Kornblum and P. Pink, *Tetrahedron*, 1963, **19,** Suppl. 1, 17; (e) W. J. LeNoble, *J. Amer. Chem. Soc.*, 1963, **85,** 1470; (f) W. J. LeNoble, *J. Phys. Chem.*, 1964, **68,** 2361.
25. (a) J. L. Corbin, H. Hart, and C. R. Wagner, *J. Amer. Chem. Soc.*, 1962, **84,** 1740; H. Hart, J. L. Corbin, C. R. Wagner, and C.-Y. Wu, *ibid.*, 1963, **85,** 3269.
26. A. J. Birch, K. B. Chamberlain, M. A. Haas, and D. J. Thompson, *J.C.S. Perkin I*, 1973, 1882.
27. R. K. Norris and S. Sternhell, *Austral. J. Chem.*, 1966, **19,** 617.
28. E. W. Garbisch, *J. Amer. Chem. Soc.*, 1965, **87,** 4971.
29. (a) K. Maartmann-Moe, *Acta Cryst.*, 1965, **19,** 155; (b) R. J. Highet and T. J. Batterham, *J. Org. Chem.*, 1964, **29,** 475.
30. S. Oae, *Bull. Soc. Chem. Japan*, 1966, **39,** 1961; 1965, **38,** 1381; 1964, **37,** 770.
31. G. W. Kirby and L. Ogunkoya, *J. Chem. Soc.*, 1965, 6914.
32. P. Heinrich, 'Methoden der Organische Chemie, Photochimie II', Houben-Weyl, George Thieme Verlag, Stuttgart, 1975, vol. 4/5b, p. 795.
33. E. E. Schweizer, D. M. Crouse, and D. L. Dalrymple, *Chem. Comm.*, 1969, 354.
34. M. von Strandtmann, M. P. Cohen, and J. Shavel, Jr., *Tetrahedron Letters*, 1965, 3104.
35. (a) L. A. Angello and W. H. Williams, *Ind. Eng. Chem.*, 1960, **52,** 894; (b) R. M. Crawford, *Chem. Eng. News*, 1947, **25,** 235.
36. J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, 1951, **49,** 273.
37. (a) S. Oae, R. Kintani, and W. Tagaki, *Bull. Chem. Soc. Japan*, 1966, **39,** 1212; (b) W. W. Hartmann, *Org. Synth. Coll. Vol. 1*, 1976, 175, 2260.
38. (a) D. F. Detar and A. R. Ballentine, *J. Amer. Chem. Soc.*, 1958, **78,** 3916; (b) E. S. Lewis and J. M. Insole, *ibid.*, 1964, **86,** 32.
39. (a) E. T. Enisov and D. I. Metelitsa, *Russ. Chem. Rev.*, 1968, **37,** 656; (b) J. B. Braunworth, *U.S. Pat.* 2 976 329/1961.
40. A. S. Banciu, *Chem. Proc. Eng.*, 1967, 31.
41. (a) D. I. Metelitsa, *Russ. Chem. Rev.*, 1971, **40,** 563; (b) D. F. Sangster, in 'Chemistry of the Hydroxyl Group', ed. S. Patai, Interscience, New York, 1971, vol. 1, p. 163; (c) R. O. C. Norman and J. R. L. Smith, 'Oxidases and Related Redox Systems', Wiley, New York, 1965, vol. 1, p. 131.
42. C. T. Clark, R. D. Downing, and J. B. Martin, *J. Org. Chem.*, 1962, **27,** 4698.
43. (a) K. Omura and T. Matsuura, *Tetrahedron*, 1968, **24,** 3475; (b) C. Walling and R. A. Johnson, *J. Amer. Chem. Soc.*, 1975, **97,** 363.
44. J. D. Loudon, *Prog. Org. Chem.*, 1961, **5,** 46.
45. (a) P. Kovacic and M. E. Kurz, *J. Amer. Chem. Soc.*, 1965, **87,** 4811; (b) *J. Org. Chem.*, 1966, **31,** 2011, 2459; (c) M. E. Kurz, P. Kovacic, A. K. Bose, and I. Kugajevsky, *J. Amer. Chem. Soc.*, 1968, **90,** 1818; (d) P. Kovacic, C. G. Reid, and M. E. Kurz, *J. Org. Chem.*, 1969, **34,** 3302.
46. R. L. Dannley and G. E. Corbett, *J. Org. Chem.*, 1966, **31,** 153.
47. (a) H. Hart, *Accounts Chem. Res.*, 1971, **4,** 337; (b) H. Hart, C. A. Buehler, and A. J. Waring, in 'Selective Oxidation Processes', ed. R. F. Gould, Advances in Chemistry Series, No. 51, American Chemical Society, Washington, 1965, p. 1.
48. (a) D. H. R. Barton, P. D. Magnus, and M. J. Pearson, *Chem. Comm.*, 1969, 550; (b) C. Walling and R. B. Hodgdon, *J. Amer. Chem. Soc.*, 1958, **80,** 228.
49. R. A. McClelland, R. O. C. Norman, and C. B. Thomas, *J.C.S. Perkin I*, 1972, 562; J. R. Campbell, J. R. Kalman, J. T. Pinhey, and S. Sternhell, *Tetrahedron Letters*, 1972, 1763.
50. (a) K. Elbs, *J. prakt. Chem.*, 1893, **48,** 179; (b) S. M. Sethna, *Chem. Rev.*, 1951, **49,** 91; (c) E. J. Behrman and P. P. Walker, *J. Amer. Chem. Soc.*, 1962, **84,** 3454.
51. (a) G. Sosnovsky and J. H. Brown, *Chem. Rev.*, 1966, **66,** 527; (b) T. G. Brilkina and V. A. Shushunov, *Russ. Chem. Rev.*, 1966, **35,** 613.

52. (a) M. F. Hawthorne, *J. Org. Chem.*, 1957, **22,** 1001; (b) S.-O. Lawesson and N. C. Yang, *J. Amer. Chem. Soc.*, 1959, **81,** 4230.
53. E. C. Taylor, H. W. Altland, R. H. Danforth, G. McGillivray, and A. McKillop, *J. Amer. Chem. Soc.*, 1970, **92,** 3520.
54. (a) M. S. Kharasch, A. Fono, and W. Nudenberg, *J. Org. Chem.*, 1950, **15,** 748; (b) E. S. E. Hawkins, 'Organic Peroxides', Spon, London, 1961, p. 91.
55. C. H. Hassall, *Org. Reactions*, 1957, **9,** 73.
56. (a) W. G. Toland, *J. Amer. Chem. Soc.*, 1961, **83,** 2507; (b) W. W. Kaeding, *J. Org. Chem.*, 1961, **26,** 3144; (c) W. W. Kaeding and A. T. Shulgin, *ibid.*, 1962, **27,** 3551.
58. (a) J. N. Collie, *J. Chem. Soc.*, 1893, **63,** 329; (b) J. N. Collie and T. P. Hilditch, *ibid.*, 1907, **91,** 787.
59. T. Money, *Chem. Rev.*, 1970, **70,** 553.
60. (a) T. M. Harris and C. M. Harris, *J. Org. Chem.*, 1966, **31,** 1032; (b) T. M. Harris and R. L. Carney, *J. Amer. Chem. Soc.*, 1967, **89,** 6734; (c) P. J. Wittek and T. M. Harris, *ibid.*, 1973, **95,** 6865.
61. T. M. Harris and R. L. Carney, *J. Amer. Chem. Soc.*, 1966, **88,** 2053, 5686.
62. (a) T. Money, F. W. Comer, G. R. B. Webster, I. G. Wright, and A. I. Scott, *Tetrahedron*, 1967, **23,** 3435; (b) J. L. Douglas and T. Money, *ibid.*, 1967, **23,** 3545; T. M. Harris and T. T. Howarth, *Canad. J. Chem.*, 1968, **46,** 3739; T. Money, J. L. Douglas, and A. I. Scott, *J. Amer. Chem. Soc.*, 1966, **88,** 624.
63. (a) S. Auricchio, S. Morrocchi, and A. Ricca, *Tetrahedron Letters*, 1974, 2793; (b) H. Stetter and S. Vestner, *Chem. Ber.*, 1964, **97,** 169; (c) G. Bram, *Tetrahedron Letters*, 1967, 4069; (d) U. Schmidt and M. Schwochau, *Monatsh.*, 1967, **98,** 1492.
64. (a) L. Crombie, M. Eskins, and D. E. Games, *Chem. Comm.*, 1968, 1015; (b) L. Crombie, D. E. Games, and M. H. Knight, *ibid.*, 1966, 355.
65. D. A. Griffin and J. Staunton, *J.C.S. Chem. Comm.*, 1975, 675.
66. (a) P. Vogel, B. Willhalm, and H. Prinzbach, *Helv. Chim. Acta*, 1969, **52,** 584; (b) P. J. Abbott, R. M. Acheson, R. F. Flowerday and G. W. Brown, *J.C.S. Perkin I*, 1974, 1177.
67. R. K. Hill and R. M. Carlson, *Tetrahedron Letters*, 1964, 1157.
68. S. Danishefsky and T. Kitahara, *J. Amer. Chem. Soc.*, 1974, **96,** 7807.
69. R. Breslow, M. Oda, and J. Pecoraro, *Tetrahedron Letters*, 1972, 4415, 4419.
70. W. Reppe and H. Vetter, *Annalen*, 1953, **582,** 133.
71. (a) R. H. Shapiro, in 'Steroid Reactions', ed. C. Djerassi, Holden-Day, San Francisco, 1963; (b) B. J. Miller, in 'Mechanisms of Molecular Migrations', ed. B. S. Thyagarajan, Wiley-Interscience, 1968, vol. 1 (c) M. J. Perkins and P. Ward, *ibid.*, 1971, vol. 4, p. 55; (d) H. J. Shine, in 'MTP International Review of Science, Organic Chemistry Series One', Butterworths, London, 1973, Vol. 3, p. 65; (e) R. S. Ward, *Chem. Britain*, 1973, **9,** 444.
72. B. Miller and M. R. Saidi, *Tetrahedron Letters*, 1972, 4391, and refs. therein.
73. J. A. D. Jeffreys, *J. Chem. Soc.*, 1959, 2153.
74. (a) C. A. Weber-Schilling and H.-W. Wanzlick, *Tetrahedron Letters*, 1969, 2345; (b) *Chem. Ber.*, 1971, **104,** 1518.
75. U. Jahnke and H.-W. Wanzlick, *Chem. Ber.*, 1968, **101,** 3744.
76. H.-W. Wanzlick, *Angew. Chem. Internat. Edn.*, 1964, **3,** 401.
77. G. P. Chiusoli and G. Agnès, *Proc. Chem. Soc.*, 1963, 310.
78. H. E. Zimmerman and D. I. Schuster, *J. Amer. Chem. Soc.*, 1962, **84,** 4527.
79. A. Small, *J. Amer. Chem. Soc.*, 1964, **86,** 2091.
80. (a) J. S. Meek, J. S. Fowler, P. A. Monroe, and T. J. Clark, *J. Org. Chem.*, 1968, **33,** 223; (b) J. St. Pyrek and O. Achmatowicz Jr., *Tetrahedron Letters*, 1970, 2651.
81. (a) E. H. White, A. A. Baum, and D. E. Eitel, *Org. Synth.*, 1968, **48,** 102; (b) V. Ya. Pochinok and V. A. Portnyagina, *Chem. Abs.*, 1955, **49,** 982.
82. J. F. W. McOmie, 'Protective Groups in Organic Chemistry', Plenum, London, 1973.
83. J. P. Marsh Jr. and L. Goodman, *J. Org. Chem.*, 1965, **30,** 2491.
84. (a) Ch. Adamek, W. Barz, and J. Berlin, *Phytochemistry*, 1970, **9,** 1735; (b) L. Jurd, *J. Amer. Chem. Soc.*, 1958, **80,** 5531; (c) L. Crombie, P. J. Ham, and D. A. Whiting, *Phytochemistry*, 1973, **12,** 703.
85. (a) F. L. Bach, *J. Org. Chem.*, 1965, **30,** 1300; (b) E. Vowinkel, *Chem. Ber.*, 1966, **99,** 1479.
86. N. Kornblum and A. Scott, *J. Amer. Chem. Soc.*, 1974, **96,** 590.
87. P. Denniff and D. A. Whiting, *J.C.S. Chem. Comm.*, 1976, 712.
88. (a) G. J. H. Rall, M. E. Oberholzer, D. Ferreira, and D. G. Roux, *Tetrahedron Letters*, 1976, 1033; (b) J. P. Yardley and H. Fletcher III, *Synthesis*, 1976, 244; (c) E. J. Corey, J.-L. Gras, and P. Ulrich, *Tetrahedron Letters*, 1976, 809.
89. (a) R. C. Parish and L. M. Stock, *J. Org. Chem.*, 1965, **30,** 927; (b) T. Gramstead and R. N. Haszeldine, *J. Chem. Soc.*, 1957, 4069; (c) A. R. Bader and A. D. Kontowicz, *J. Amer. Chem. Soc.*, 1953, **75,** 5416; (d) S. Neelakantan, R. Padmasini, and T. R. Seshadri, *Tetrahedron*, 1965, **21,** 3531; (e) W. J. Lowrance Jr., *Tetrahedron Letters*, 1971, 3453.
90. T. G. Bonner and P. McNamara, *J. Chem. Soc.* (*B*), 1968, 795.
91. E. Haslam, in Ref. 82, p. 145.
92. D. H. R. Barton, Y. L. Chow, A. Cox, and G. W. Kirby, *J. Chem. Soc.*, 1965, 3571.
93. P. Salomaa, A. Kankaanperä, and K. Pihlaja, in 'Chemistry of the Hydroxyl Group', ed. S. Patai, Interscience, New York, 1971, part 1, p. 481.
94. D. M. Brown, *Adv. Org. Chem.*, 1963, **3,** 75.

95. J. B. Harborne and C. A. Williams, *Z. Naturforsch.*, 1971, **26b,** 490.
96. A. T. Balaban, C. N. Rentea, and M. Mocanu, *Tetrahedron Letters*, 1964, 2049.
97. Th. Severin and I. Ipach, *Synthesis*, 1973, 796.
98. W. J. Musliner and J. W. Bates, *J. Amer. Chem. Soc.*, 1966, **88,** 4271.
99. J. D. Weaver and E. J. Eisenbraun, *Chem. and Ind. (London)*, 1973, 187.
100. J. P. Schaefer and J. Higgins, *J. Org. Chem.*, 1967, **32,** 1607.
101. D. G. Lee, *Chem. Comm.*, 1968, 1554.
102. R. A. Rossi and J. F. Bunnett, *J. Org. Chem.*, 1972, **37,** 3570.
103. (a) S. Oae and R. Kiritani, *Bull. Chem. Soc. Japan*, 1965, **38,** 1138; (b) M. S. Newman and H. A. Karnes, *J. Org. Chem.*, 1966, **31,** 3980; (c) J. E. Cooper and J. M. Paul, *ibid.*, 1970, **35,** 2046.
104. F. M. Dean, 'Naturally Occurring Oxygen Ring Compounds', Butterworths, London, 1963.
105. G. Scott, 'Atmospheric Oxidation and Antioxidants', Elsevier, Amsterdam, 1965.
106. (a) D. H. R. Barton and T. Cohen, 'Festschrift A. Stoll', Birkhauser, Basel, 1957, p. 117; (b) R. G. R. Bacon and H. A. O. Hill, *Quart. Rev.*, 1965, **19,** 95; (c) A. I. Scott, *ibid.*, 1965, **19,** 1; (d) W. I. Taylor and A. R. Battersby, 'Oxidative Coupling of Phenols', Arnold, London, 1967; R. H. Thomson, 'Biochemistry of Phenolic Compounds', Academic, London, 1964, p. 1.
107. L. M. Jackman, *Adv. Org. Chem.*, 1960, **2,** 329.
108. (a) I. C. P. Smith and A. Carrington, *Mol. Phys.*, 1967, **12,** 439; (b) A. Carrington, *Quart. Rev.*, 1963, **17,** 67.
109. (a) J. Harley-Mason and A. H. Laird, *J. Chem. Soc.*, 1958, 1718; (b) C. A. Bishop and L. K. J. Tong, *J. Amer. Chem. Soc.*, 1965, **87,** 501.
110. J. P. Marino and A. Schwartz, *J.C.S. Chem. Comm.*, 1974, 812.
111. E. Adler, *Acta Chem. Scand.*, 1959, **13,** 505; 1960, **14,** 515, 529, 539.
112. (a) H.-J. Teuber and W. Rau, *Chem. Ber.*, 1953, **86,** 1036; (b) A. R. Forrester and R. H. Thomson, *J. Chem. Soc. (C)*, 1966, 1844; (c) A. S. Kende and P. MacGregor, *J. Amer. Chem. Soc.*, 1961, **83,** 4197; (d) J. A. Strickson and M. Leigh, *Tetrahedron*, 1968, **24,** 5145; (e) E. C. Horswill and K. U. Ingold, *Canad. J. Chem.*, 1966, **44,** 263.
113. (a) R. D. Chambers, P. Goggin and W. K. R. Musgrave, *J. Chem. Soc.*, 1959, 1804; (b) D. Bryce-Smith and A. Gilbert, *ibid.*, 1964, 873; (c) M. F. Ansell, B. W. Nash, and D. A. Wilson, *ibid.*, 1963, 3028; (d) G. W. K. Cavill, E. R. Cole, P. T. Gillian, and D. J. McHugh, *ibid.*, 1954, 2785; (e) B. Sklarz, *Quartz. Rev.*, 1967, **21,** 3.
114. D. H. R. Barton, A. G. Brewster, S. V. Ley, and M. N. Rosenfeld, *J.C.S. Chem. Comm.*, 1976, 985.
115. B. Belleau and N. L. Weinberg, *J. Amer. Chem. Soc.*, 1963, **85,** 2525.
116. A. B. Turner, *Quart. Rev.*, 1964, **18,** 347.
117. C. D. Cook, N. G. Nash, and H. R. Flanagan, *J. Amer. Chem. Soc.*, 1955, **77,** 1783.
118. L. K. Dyall and S. Winstein, *J. Amer. Chem. Soc.*, 1972, **94,** 2196.
119. H.-D. Becker, *J. Org. Chem.*, 1965, **30,** 982.
120. (a) C. J. Dixie and I. O. Sutherland, *J.C.S. Chem. Comm.*, 1972, 646; (b) M. Chauhan, F. M. Dean, K. Hindley, and M. Robinson, *Chem. Comm.*, 1971, 1141.
121. G. Cardillo, R. Cricchio, and L. Merlini, *Tetrahedron*, 1968, **24,** 4825.
122. C. L. McIntosh and O. L. Chapman, *Chem. Comm.*, 1971, 771.
123. G. Cardillo, L. Merlini and S. Servi, *Ann. Chim. (Rome)*, 1970, **60,** 564.
124. (a) A. J. Waring, *Adv. Alicyclic Chem.*, 1966, **1,** 129; (b) F. Wessely, *J. Roy. Inst. Chem.*, 1959, 424.
125. W. A. Bubb and S. Sternhell, *Tetrahedron Letters*, 1970, 4499.
126. D. J. Bichan and P. Yates, *Canad. J. Chem.*, 1975, **53,** 2054.
127. D. H. R. Barton, P. D. Magnus, and M. J. Pearson, *J. Chem. Soc. (C)*, 1971, 2231.
128. (a) Y. Yamada, K. Hosaka, H. Sanjoh, and M. Suzuki, *J.C.S. Chem. Comm.*, 1974, 661; (b) Y. Hayashi, S. Shioi, M. Togami, and T. Sakan, *Chem. Letters*, 1973, 651.
129. (a) J. R. Lewis, *Chem. and Ind. (London)*, 1964, 1672; (b) C. H. Hassall and A. I. Scott, in 'Chemistry of Natural Phenolic Compounds', ed. W. D. Ollis, Pergamon, Oxford, 1961.
130. F. Hewgill, T. J. Stone and W. A. Waters, *J. Chem. Soc.*, 1964, 213, 408.
131. (a) K. Dimroth, A. Berndt, C. Reichardt, and H. Perst, *Org. Synth.*, 1970, **49,** 116; (b) E. Muller, K. Ley, and W. Kiedaish, *Chem. Ber.*, 1954, **87,** 1605; (c) K. Dimroth, W. Umbach, and H. Thomas, *ibid.*, 1967, **100,** 132.
132. (a) A. R. Forrester, J. M. Hay, and R. H. Thomson, 'Organic Chemistry of Stable Free Radicals', Academic, London, 1968; (b) E. R. Altwicker, *Chem. Rev.*, 1967, **67,** 475.
133. W. A. Waters, *J. Chem. Soc. (B)*, 1971, 2026.
134. (a) D. H. R. Barton, *Chem. Britain*, 1967, **3,** 330; (b) D. G. Hewitt, *J. Chem. Soc. (C)*, 1971, 1750.
135. J. W. A. Findlay, P. Gupta, and J. R. Lewis, *J. Chem. Soc. (C)*, 1969, 2761.
136. E. A. Shearing and S. Smiles, *J. Chem. Soc.*, 1937, 1931 and previous papers.
137. (a) A. H. Jackson and J. A. Martin, *J. Chem. Soc. (C)*, 1966, 2222; (b) A. C. Waiss, Jr., J. A. Kuhnle, J. J. Windle, and A. K. Wiersema, *Tetrahedron Letters*, 1966, 6251.
138. (a) D. H. R. Barton, Y. L. Chow, A. Cox, and G. W. Kirby, *J. Chem. Soc.*, 1965, 3571; (b) A. M. Choudhury, K. Schofield, and R. S. Ward, *J. Chem. Soc. (C)*, 1970, 2543; (c) I. G. C. Coutts, D. J. Humphreys, and K. Schofield, *ibid.*, 1969, 1982.
139. (a) M. A. Schwartz, R. A. Holton and S. W. Scott, *J. Amer. Chem. Soc.*, 1969, **91,** 2800; (b) R. G. R. Bacon and A. R. Izatt, *J. Chem. Soc. (C)*, 1966, 791; (c) D. Schulte-Frohlinde and F. Erhardt, *Annalen*, 1964, **671,** 92.

140. C. L. Chen, W. J. Connors, and W. M. Shinker, *J. Org. Chem.*, 1969, **34,** 2966.
141. (a) R. A. Anderson, D. T. Dagleish, D. C. Nonhebel, and P. L. Pauson, *J. Chem. Res. (S)*, 1977, 12 *et seq.*; (b) L. R. Mahoney and S. A. Weiner, *J. Amer. Chem. Soc.*, 1972, **94,** 585, 1412.
142. L. Taimr and J. Popišil, *Tetrahedron Letters*, 1971, 2809.
143. S. Tobinaga and E. Kotani, *J. Amer. Chem. Soc.*, 1972, **94,** 309.
144. (a) M. J. S. Dewar and T. Nakaya, *J. Amer. Chem. Soc.*, 1968, **90,** 7134; (b) A. R. Forrester, R. H. Thomson, and S.-O. Woo, *J.C.S. Perkin II*, 1975, 2340.
145. M. A. Schwartz and I. S. Mami, *J. Amer. Chem. Soc.*, 1975, **97,** 1239.
146. V. Balogh, M. Fétizon, and M. Golfier, *J. Org. Chem.*, 1971, **36,** 1339.
147. (a) S. M. Kupchan, C.-K. Kim, and J. T. Lynn, *J.C.S. Chem. Comm.*, 1976, 86; (b) G. E. Gervay, F. McCapra, T. Money, G. M. Sharma, and A. I. Scott, *Chem. Comm.*, 1966, 142; (c) D. H. R. Barton, R. James, G. W. Kirby, D. W. Turner and D. A. Widdowson, *J. Chem. Soc. (C)*, 1968, 1529.
148. K. Korinek and T. F. W. McKillop, *Ann. Reports*, 1971, **68B,** 315.
149. J. M. Bobbitt and R. C. Hallcher, *Chem. Comm.*, 1971, 543.
150. (a) J. R. Falck, L. L. Miller, and F. R. Stermitz, *Tetrahedron*, 1974, **30,** 931; (b) J. M. Bobbitt, I. Noguchi, R. S. Ware, K. N. Chiong, and S. J. Huang, *J. Org. Chem.*, 1975, **40,** 2924.
151. A. I. Scott, P. A. Dodson, F. McCapra, and M. B. Meyers, *J. Amer. Chem. Soc.*, 1963, **85,** 3702.
152. J. M. Bobbitt, I. Noguchi, H. Yagi, and K. H. Weisgraber, *J. Amer. Chem. Soc.*, 1971, **93,** 3551.
153. L. L. Miller, F. R. Stermitz and J. R. Falck, *J. Amer. Chem. Soc.*, 1971, **93,** 5941.
154. V. D. Parker and A. Ronlán, *J. Amer. Chem. Soc.*, 1975, **97,** 4714.
155. T. Kametani and K. Fukumoto, *Accounts Chem. Res.*, 1972, **5,** 212.
156. T. Kametani and M. Koizumi, *J. Chem. Soc. (C)*, 1971, 3976.
157. (a) Z. Horii, C. Iwata, S. Wakawa, and Y. Nakashita, *Chem. Comm.*, 1970, 1039; (b) D. H. Hey, G. H. Jones, and M. J. Perkins, *ibid.*, 1971, 47; (c) S. M. Kupchan, C.-K. Kim, and K. Miyano, *J.C.S. Chem. Comm.*, 1976, 91.
158. H. Dürr, 'Methoden der Organischen Chemie, Photochemie I', Houben-Weyl, George Thieme Verlag, Stuttgart, 1975, vol.4/5a p. 642.
159. J. M. Harkin, K. Weinges and R. Spänig, 'Oxidative Coupling of Phenols', Arnold, London, 1968.
160. (a) K. V. Sarkanen and A. F. A. Wallis, *J.C.S. Perkin I*, 1973, 1869, 1873; (b) S. Tobinaga and E. Kotani, *J. Amer. Chem. Soc.*, 1972, **94,** 309.
161. (a) P. B. D. de la Mare, O. M. H. el Dusouqui, J. G. Tillett, and M. Zeltner, *J. Chem. Soc.*, 1964, 5306; (b) G. Chuchani, H. Diaz, and J. Zabicky, *J. Org. Chem.*, 1966, **31,** 1573, 2330.
162. (a) R. Taylor, 'MTP International Review of Science, Organic Chemistry Series One', Butterworths, London, 1973, vol. 3, p. 2
163. D. A. R. Happer and J. Vaughan, in 'Chemistry of the Hydroxyl Group', ed. S. Patai, Interscience, New York, 1971, p. 393.
164. H. Hart, *J. Amer. Chem. Soc.*, 1950, **72,** 2900.
165. (a) T. Birchall, A. N. Bourns, R. J. Gillespie and P. J. Smith, *Canad. J. Chem.*, 1964, **42,** 1433; (b) D. M. Brouwer, E. L. Mackor, and C. Maclean, in 'Carbonium Ions', ed. G. A. Olah and P. v. R. Schleyer, Wiley-Interscience, New York, 1970, p. 837; (c) G. A. Olah and Y. K. Mo, *J. Amer. Chem. Soc.*, 1972, **94,** 5341.
166. J.-P. Gesson and J.-C. Jacquessy, *J.C.S. Chem. Comm.*, 1976, 652.
167. (a) U. Svanholm and V. D. Parker, *J.C.S. Perkin I*, 1973, 562; (b) T. Watanabe, *Org. Prep. Proceed. Internat.*, 1974, **6,** 107, 117.
168. M. J. Begley, R. V. M. Campbell, L. Crombie, B. Tuck, and D. A. Whiting, *J. Chem. Soc. (C)*, 1971, 3634.
169. G. A. Olah, 'Friedel Crafts and Related Reactions', Interscience, New York, 1963.
170. N. I. Shuikin and E. A. Viktorova, *Russ. Chem. Rev.*, 1960, **29,** 560; A. V. Topchiev, S. V. Zavgorodnii, and Y. M. Paushkin, 'Boron Trifluoride and its Compounds as Catalysts in Organic Chemistry', Pergamon, London, 1959.
171. A. J. Kolka, J. P. Napolitano, A. H. Filbey, and G. G. Ecke, *J. Org. Chem.*, 1957, **22,** 642.
172. (a) G. A. Olah and E. G. Melby, *J. Amer. Chem. Soc.*, 1973, **95,** 4971; (b) P. Beak, J. T. Adams, P. D. Klein, P. A. Szczepanik, D. A. Simpson, and S. G. Smith, *J. Amer. Chem. Soc.*, 1973, **95,** 6027.
173. M. M. Shiryaev and V. N. Klyuev, *Chem. Abs.*, 1972, **76,** 3500.
174. P. Burri and H. Zollinger, *Helv. Chim. Acta*, 1973, **56,** 2204.
175. T. G. Bonner, K. A. Holder, and P. Powell, *J. Organometallic Chem.*, 1974, **77,** C37.
176. M. F. Ansell and B. Gadsby, *J. Chem. Soc.*, 1959, 2994.
177. P. A. Grieco and R. S. Finkelhor, *Tetrahedron Letters*, 1974, 527.
178. (a) L. H. Baekeland, *Ind. Eng. Chem.*, 1909, **1,** 149; (b) L. M. Yeddanapalli and D. J. Francis, *Makromol. Chem.*, 1962, **55,** 74; (c) J. S. Rodia and J. H. Freeman, *J. Org. Chem.*, 1959, **24,** 21.
179. (a) J. F. Walker, 'Formaldehyde', Reinhold, New York, 1944; (b) N. J. L. Megson, 'Phenolic Resin Chemistry', Academic, New York, 1956; (c) R. W. Lenz, 'Organic Chemistry of Synthetic High Polymers', Wiley, New York, 1967.
180. J. Kahovec and J. Popišil, *Coll. Czech. Chem. Comm.*, 1969, **34,** 2843; 1968, **33,** 1709.
181. E. C. M. Coxworth, *Canad. J. Chem.*, 1967, **45,** 1777.
182. W. Barker, A. J. Floyd, J. F. W. McOmie, G. Pope, A. S. Weaving, and J. H. Wild, *J. Chem. Soc.*, 1956, 2010, 2018.
183. M. G. Burdon and J. G. Moffatt, *J. Amer. Chem. Soc.*, 1966, **88,** 5855; T. Durst, *Adv. Org. Chem.*, 1969, **6,** 285.

184. (a) P. Claus, *Monatsh.*, 1971, **102,** 913, 1072; (b) J. P. Marino, K. E. Pfitzner, and R. A. Olofson, *Tetrahedron*, 1971, **27,** 4181; (c) R. A. Olofson and J. P. Marino, *ibid.*, 4195.
185. S. Mageswaran, W. D. Ollis, R. J. Roberts, and I. O. Sutherland, *Tetrahedron Letters*, 1969, 2897.
186. (a) L. Jurd, K. Stevens, and G. Manners, *Tetrahedron*, 1973, **29,** 2347; (b) L. Jurd, G. Manners, and K. Stevens, *J.C.S. Chem. Comm.*, 1972, 992.
187. T. A. Geissman and N. N. Yoshimura, *Tetrahedron Letters*, 1966, 2669.
188. (a) E. C. Taylor, K. Lenard, and Y. Shvo, *J. Amer. Chem. Soc.*, 1966, **88,** 367; (b) R. K. Razdan and G. R. Handrick, *ibid.*, 1970, **92,** 6061; (c) B. Cardillo, L. Merlini, and S. Servi, *Tetrahedron Letters*, 1972, 945; (d) G. Manners, L. Jurd, and K. Stevens, *Tetrahedron*, 1972, **28,** 2949.
189. P. H. Gore, in 'Friedel–Crafts and Related Reactions', ed. G. Olah, Interscience, 1963, vol. 3, part 1, p. 1.
190. V. R. Shah, J. L. Bose, and R. C. Shah, *J. Org. Chem.*, 1960, **25,** 677.
191. (a) S. Sethna and R. Phadke, *Org. Reactions*, 1953, **7,** 2; (b) E. H. Woodruff, *Org. Synth. Coll. Vol. 3*, 1955, 581.
192. W. E. Truce, *Org. Reactions*, 1957, **9,** 37.
193. H. Wynberg, *Chem. Rev.*, 1960, **60,** 169.
194. (a) V. I. Minkin and G. N. Dorofeenko, *Russ. Chem. Rev.*, 1960, **29,** 599; (b) J. Carnduff, *Quart. Rev.*, 1966, **20,** 169.
195. (a) A. S. Lindsey and H. Jeskey, *Chem. Rev.*, 1957, **57,** 583; (b) Y. Yawuhara and T. Nogi, *Chem. and Ind. (London)*, 1969, 77; (c) C. A. Buehler and W. E. Cate, *Org. Synth. Coll. Vol. 2*, 1943, 341.
196. (a) M. S. Newman and A. G. Pinkus, *J. Org. Chem.*, 1954, **19,** 978; (b) V. V. Ershov, A. A. Volodkin and G. N. Bogdanov, *Russ. Chem. Rev.*, 1963, **32,** 75.
197. H. Musso, U. V. Gizycki, U. I. Zahorszky, and D. Bormann, *Annalen*, 1964, **676,** 10.
198. (a) M. J. S. Dewar, in 'Molecular Rearrangements', ed. P. de Mayo, Interscience, New York, 1963, p. 295; (b) M. J. S. Dewar and L. S. Hart, *Tetrahedron*, 1970, **26,** 973.
199. J. R. Norell, *J. Org. Chem.*, 1973, **38,** 1924.
200. N. I. Bruckner and N. L. Bauld, *J. Org. Chem.*, 1972, **37,** 2359.
201. (a) D. Bellus, *Adv. Photochem.*, 1971, **8,** 109; (b) D. Bryce-Smith and A. Gilbert, in 'MTP International Review of Science, Organic Chemistry Series One', Butterworths, London, 1973, vol. 3, p. 131.
202. (a) C. E. Kalmus and D. M. Hercules, *Tetrahedron Letters*, 1972, 1575; (b) J. W. Meyer and G. S. Hammond, *J. Amer. Chem. Soc.*, 1972, **94,** 2219; (c) W. Adam, J. A. de Sanabia, and H. Fischer, *J. Org. Chem.*, 1973, **38,** 2571.
203. J. Hill, *Chem. Comm.*, 1966, 260.
204. V. T. Ramakrishnan and J. Kagan, *J. Org. Chem.*, 1970, **35,** 2898.
205. C. P. Falshaw, S. A. Lane, and W. D. Ollis, *J.C.S. Chem. Comm.*, 1973, 491.
206. D. Y. Curtin and A. R. Stein, *Org. Synth.*, 1966, **46,** 115.
207. (a) B. Miller, *J. Amer. Chem. Soc.*, **92,** 6246; (b) *J. Org. Chem.*, 1970, **35,** 4262; (c) R. Baird and S. Winstein, *J. Amer. Chem. Soc.*, 1963, **85,** 567.
208. G. Casnati, M. Crisafulli, and A. Ricca, *Tetrahedron Letters*, 1965, 243.
209. G. Casiraghi, G. Casnati, M. Cornia, G. Sartori, and K. Ungaro, *J.C.S. Perkin I*, 1974, 2077.
210. J. O. Asgill, L. Crombie, and D. A. Whiting, *J.C.S. Chem. Comm.*, 1978, 59.
211. J. K. MacLeod and B. R. Worth, *Tetrahedron Letters*, 1972, 237, 241.
212. (a) A. V. Topchiev, 'Nitration of Hydrocarbons and Other Organic Compounds', Pergamon, London, 1959; (b) B. C. Challis and A. J. Lawson, *J. Chem. Soc. (B)*, 1971, 770; (c) C. A. Bunton, E. D. Hughes, C. K. Ingold, D. I. H. Jacobs, M. H. Jones, G. J. Minkhoff, and R. I. Reed, *J. Chem. Soc.*, 1950, 2628, 2657.
213. M. J. Zabik and R. I. Schuetz, *J. Org. Chem.*, 1967, **32,** 300.
214. K. Ley and E. Müller, *Chem. Ber.*, 1956, **89,** 1402.
215. J. F. Bunnett, *Quart. Rev.*, 1958, **12,** 1; A. R. Butler, in 'Organic Reaction Mechanisms', ed. B. Capon and C. W. Rees, Wiley, New York, 1971, p. 211.
216. (a) M. R. Crampton, *Adv. Phys. Org. Chem.*, 1969, **7,** 211; (b) E. Buncel, A. R. Norris, and K. E. Russell, *Quart. Rev.*, 1968, **22,** 123.
217. (a) M. R. Crampton and V. Gold, *J. Chem. Soc. (B)*, 1966, 893; (b) K. L. Servis, *J. Amer. Chem. Soc.*, 1967, **89,** 1508; (c) J. W. Larsen, J. H. Fendler, and E. J. Fendler, *ibid.*, 1969, **91,** 5903; (d) A. R. Norris, *Canad. J. Chem.*, 1969, **47,** 2895.
218. K.-A. Kovar, *Arch. Pharm.*, 1974, **307,** 100.
219. R. Foster, 'Organic Charge Transfer Complexes', Academic, London, 1969.
220. R. K. Norris and S. Sternhell, *Austral. J. Chem.*, 1969, **22,** 935.
221. R. Henry, *J. Org. Chem.*, 1958, **23,** 648; K. M. Ibne-Rasa, *J. Amer. Chem. Soc.*, 1962, **84,** 4962.
222. (a) O. Baudisch, *J. Amer. Chem. Soc.*, 1941, **63,** 622; (b) G. E. Cronheim, *J. Org. Chem.*, 1947, **12,** 1, 7, 20; (c) I. Tanimoto, *Bull. Chem. Soc. Japan*, 1970, **43,** 139, 1182.
223. C. W. L. Bevan, J. Hirst, and A. J. Foley, *J. Chem. Soc.*, 1960, 4543.
224. R. Schröter in 'Methoden der Organischen Chemie', Houben-Weyl, George Thieme Verlag. Stuttgart, 1957, vol. XI/I.
225. (a) W. W. Hartman and H. L. Silloway, *Org. Synth. Coll. Vol. 3*, 1955, 82; (b) H. H. Hodgson and E. W. Smith, *J. Chem. Soc.*, 1935, 671.
226. (a) H. E. Heller, E. D. Hughes and C. K. Ingold, *Nature*, 1951, **168,** 909; (b) R. A. Crochet and P. Kovacic, *J.C.S. Chem. Comm.*, 1973, 716.
227. (a) H. Zollinger, 'Azo and Diazo Chemistry', Interscience, New York, 1961; (b) K. H. Saunders, 'The Aromatic Diazo Compounds and their Technical Applications', 2nd eds., Arnold, London, 1949.

228. L. A. Kazitsyna, B. S. Kikot, and A. V. Upadysheva, *Russ. Chem. Rev.*, 1966, **35,** 388.
229. (a) O. Süs, *Annalen*, 1944, **556,** 65, 85; (b) O. Süs, H. Steppan, and R. Dietrich, *ibid.*, 1958, **617,** 20; (c) M. J. S. Dewar and K. Narayanaswami, *J. Amer. Chem. Soc.*, 1964, **86,** 2422; (d) E. Wasserman and R. W. Murray, *ibid.*, 1964, **86,** 4203.
230. N. N. Bubnov, K. A. Bilevitch, L. Poljakova, and O. Yu. Okhlobystin, *J.C.S. Chem. Comm.*, 1972, 1058.
231. R. S. Berger, *Science*, 1972, **177,** 704.
232. (a) P. B. de la Mare and J. Ridd, 'Aromatic Substitution', Butterworths, London, 1969; (b) R. O. C. Norman and R. Taylor, 'Electrophilic Substitution in Benzenoid Compounds', Elsevier, New York, 1965.
233. (a) L. Vollbracht, W. G. B. Huysmans, W. J. Mijs, and H. J. Hageman, *Tetrahedron*, 1968, **24,** 6265; (b) E. Morita and M. W. Dietrich, *Canad. J. Chem.*, 1969, **47,** 1943.
234. A. W. Burgstahler, T. B. Lewis, and M. O. Abdel Rahman, *J. Org. Chem.*, 1966, **31,** 3516.
235. (a) E. M. Kosower, W. J. Cole, G.-S. Wu, D. E. Cardy, and G. Meisters, *J. Org. Chem.*, 1963, **28,** 630; (b) R. O. C. Norman and D. R. Harvey, *J. Chem. Soc.*, 1961, 3604.
236. (a) D. E. Pearson, R. D. Wysong, and C. V. Breder, *J. Org. Chem.*, 1967, **32,** 2358; (b) S. D. Saraf, *Canad. J. Chem.*, 1969, **47,** 2803; (c) E. J. O'Bara, R. B. Balsley, and I. Starer, *J. Org. Chem.*, 1970, **35,** 16; (d) M. V. Sargent, *J.C.S. Perkin I*, 1973, 340.
237. (a) G. H. Woollett and W. W. Johnson, *Org. Synth. Coll. Vol. 2*, 1943, 343; (b) P. Charbier, J. Seydon-Penne and A. M. Fouace, *Compt. rend.*, 1957, **254,** 174; (c) O. O. Orazi, R. A. Corral, and H. E. Bertorello, *J. Org. Chem.*, 1965, **30,** 1101; (d) D. E. Janssen and C. V. Wilson, *Org. Synth. Coll. Vol. 4*, 1963, 547; (e) F. C. Whitmore and E. R. Hanson, *Org. Synth. Coll. Vol. 1*, 1941, p. 326; (f) A. McKillop, J. D. Hunt, M. J. Zelesko, J. S. Fowler, E. C. Taylor, G. McGillivray, and F. Kienzle, *J. Amer. Chem. Soc.*, 1971, **93,** 4841, 4845.
238. (a) R. C. Huston and M. M. Ballard, *Org. Synth. Coll. Vol. 3*, 1943, 97; (b) D. S. Tarbell, J. W. Wilson, and P. E. Fanta, *Org. Synth. Coll. Vol. 3*, 1955, 267.
239. (a) A. Roe, *Org. Reactions*, 1949, **5,** 193; (b) M. M. Boudakian, *J. Org. Chem.*, 1961, **26,** 4641.
240. A. W. Burgstahler, P.-L. Chien, and M. O. Abdel-Rahman, *J. Amer. Chem. Soc.*, 1964, **86,** 5281.
241. (a) P. B. D. de la Mare and B. N. B. Hannan, *Chem. Comm.*, 1971, 1324; (b) P. B. D. de la Mare, A. Singh, J. G. Tillett, and M. Zeltner, *J. Chem. Soc. (B)*, 1971, 1122.
242. (a) N. I. Shuikin and L. A. Erivanskaya, *Russ. Chem. Rev.*, 1960, **29,** 309; (b) P. N. Rylander, 'Catalytic Hydrogenation over Platinum Metals', Academic, New York, 1967, p. 331; (c) A. J. Birch and H. Smith, *Quart. Rev.*, 1958, **12,** 17; (d) J. A. Waters and B. Witkop, *J. Amer. Chem. Soc.*, 1967, **89,** 1022.
243. G. L. Closs and L. E. Closs, *J. Amer. Chem. Soc.*, 1961, **83,** 599.
244. L. A. Paquette, *J. Amer. Chem. Soc.*, 1963, **85,** 3288.
245. (a) J. T. Pinhey and R. D. G. Rigby, *Tetrahedron Letters*, 1969, 1267, 1271; (b) K. Omura and T. Matsuura, *Chem. Comm.*, 1969, 1394, 1516; (c) R. L. Letsinger and J. H. McCain, *J. Amer. Chem. Soc.*, 1966, **88,** 2884.
246. K. S. Brown, Jr., *Chem. Soc. Rev.*, 1975, **4,** 263.
247. M. F. Ansell, A. J. Bignold, A. F. Gosden, V. J. Leslie, and R. A. Murray, *J. Chem. Soc. (C)*, 1971, 1414; M. F. Ansell and R. A. Murray, *ibid.*, 1971, 1429.
248. (a) G. P. Chiusoli and P. Agnes, *Proc. Chem. Soc.*, 1963, 310; (b) R. C. Fuson 'Reactions of Organic Compounds', Wiley, New York, 1962, p. 119.
249. (a) H. H. Wasserman and D. L. Larsen, *J.C.S. Chem. Comm.*, 1972, 253; (b) H. Hart and A. Oko, *ibid.*, 1972, 254.
250. T. Teitei, D. Wells, and W. H. F. Sasse, *Austral. J. Chem.*, 1973, **26,** 2129.
251. H.-D. Becker and T. Bremholt, *Tetrahedron Letters*, 1973, 197.
252. F. P. Dwyer and D. P. Mellor, 'Chelating Agents and Metal Chelates', Academic, New York, 1964, p. 106.
253. (a) R. Stroh, R. Seydel, and W. Hahn, in 'Newer Methods of Preparative Organic Chemistry', ed. W. Foerst, Academic, New York, 1963, vol. 2, p. 337; (b) J. C. Anderson and C. B. Reese, *Proc. Chem. Soc.*, 1960, 217.
254. (a) H. Steinberg, 'Organoboron Chemistry', Interscience, New York, 1964, vol. 1; (b) M. A. Ferreira, M. Moir and R. H. Thomson, *J.C.S. Perkin I*, 1974, 2429.
255. K. Venkataraman, 'Progress in the Chemistry of Organic Natural Products', ed. L. Zechmeister, Springer-Verlag, Berlin, 1959, vol. 17, p. 1.
256. D. E. Pearson, in 'Heterocyclic Compounds', ed. R. C. Elderfield, Wiley, New York, 1957, vol. 6, p. 624.
257. M. Nozaki *et al.*, 'Oxidation of Organic Compounds', A.C.S. Special Publication, American Chemical Society, Washington, 1968, vol. 3, p. 242.
258. A. Russell and J. R. Frye, *Org. Synth. Coll. Vol. 3*, 1955, 281; S. R. Cooper, *ibid.*, p. 761.
259. C. E. Berkoff and L. Crombie, *J. Chem. Soc.*, 1960, 3734.
260. (a) L. Crombie and R. Ponsford, *J. Chem. Soc. (C)*, 1971, 788; (b) *ibid.*, 1971, 796; (c) W. M. Bandaranayake, L. Crombie, and D. A. Whiting, *ibid.*, 1971, 804; (d) D. G. Clarke, L. Crombie, and D. A. Whiting, *J.C.S. Perkin I*, 1974, 1007; (e) *J.C.S. Chem. Comm.*, 1973, 582; (f) W. M. Bandaranayake, L. Crombie, and D. A. Whiting, *J. Chem. Soc.*, (*C*), 1971, 811; (g) W. Bandaranayake, M. J. Begley, D. G. Clarke, L. Crombie, and D. A. Whiting, *J.C.S. Perkin I*, 1974, 998.
261. G. D. Manners and L. Jurd, *J.C.S. Chem. Comm.*, 1976, 448.
262. L. Crombie, D. A. Slack, and D. A. Whiting, *J.C.S. Chem. Comm.*, 1976, 139.
263. (a) W. Flaig and J. C. Salfeld, *Naturwiss.*, 1960, **47,** 516; (b) M. Eigen and P. Matthies, *Chem. Ber.*, 1961, **94,** 3309.

264. H. Joschek and S. I. Miller, *J. Amer. Chem. Soc.*, 1966, **88,** 3273.
265. R. C. Cookson and N. S. Wariyar, *J. Chem. Soc.*, 1957, 327.
266. P. Singh and S. Rangaswami, *Tetrahedron Letters*, 1966, 1229.
267. (a) R. W. Rickards, *J. Antibiot.*, 1971, **24,** 715; (b) M. S. R. Nair and M. Anchel, *Tetrahedron Letters*, 1972, 795; (c) K. Moody, R. H. Thomson, E. Fattorusso, L. Minale, and G. Sodano, *J.C.S. Perkin I*, 1972, 16.
268. (a) L. Horner, K. H. Weber, and W. Dürckheimer, *Chem. Ber.*, 1961, **94,** 2881; (b) J. C. Salfeld and E. Baume, *ibid.*, 1964, **97,** 307; (c) L. Horner, W. Dürchkheimer, K.-H. Weber, and K. Dölling, *ibid.*, 1964, **97,** 312.
269. W. Mayer and R. Weiss, *Angew. Chem.*, 1956, **68,** 680.
270. H. A. Anderson and R. H. Thomson, *J. Chem. Soc. (C)*, 1967, 2152.
271. R. A. Baxter and J. P. Brown, *Chem. and Ind. (London)*, 1967, 1171.
272. A. Einhorn, J. Cobliner, and H. Pfeiffer, *Ber.*, 1904, **37,** 100.
273. A. J. Fatiadi and W. F. Sager, *Org. Synth.*, 1962, **42,** 66, 90.
274. (a) R. Nietzki and T. Benckiser, *Ber.*, 1885, **18,** 1833; (b) W. Buechner and E. Weiss, *Helv. Chim. Acta*, 1964, **47,** 1415.

4.3

Ethers

N. BAGGETT
University of Birmingham

4.3.1 NOMENCLATURE 799
4.3.2 PROPERTIES OF ETHERS 800
4.3.3 GEOMETRY AND BONDING 802
4.3.4 BASICITY AND SOLVENT PROPERTIES 804
4.3.4.1 Basicity and solvation 804
4.3.4.2 Solvation of proton acids 805
4.3.4.3 Solvation of alkali metal derivatives 810
4.3.4.4 Solvation of alkaline earth derivatives 810
4.3.4.5 Solvation of Group III elements 812
4.3.4.6 Solvation of Group IV elements 813
4.3.4.7 Other ether complexes 818
4.3.5 FORMATION OF ETHERS 819
4.3.5.1 Ethers by displacement 819
4.3.5.2 Ethers by addition 823
4.3.5.3 Ethers by reduction 826
4.3.5.4 Ethers by oxidation 827
4.3.5.5 Ethers from other ethers 829
4.3.6 REACTIONS OF ETHERS 832
4.3.6.1 The Wittig rearrangement 835
4.3.6.2 The Claisen rearrangement 837
4.3.6.3 Photochemical reactions 839
4.3.7 REACTIONS OF α-HALOETHERS 841
4.3.8 REACTIONS OF UNSATURATED ETHERS 843
4.3.9 POLYETHERS 845

4.3.1 NOMENCLATURE

Compounds of the type R^1—O—R^2 are called 'ethers' and may be named in a variety of ways[1] using either radicofunctional or substitutive methods. The various systems for naming ethers will be explained and then examples will be given (see Table 1) with a letter in parenthesis denoting the nomenclature system used.

(a) Radicofunctional names for ethers are generated by giving the names of the ligands R^1 and R^2 followed by the word 'ether'.

(b) Substitutive names can be generated by using the name of the group R^1O as a prefix to the name of the hydrocarbon R^2H and adding any necessary locants; the more senior component is selected as parent.

(c) Alternatively, and especially with partial ethers of polyhydroxy compounds, substitutive names can be generated by using the name of the ligand R^1 as a prefix to the name of the polyhydroxy compound R^2OH together with any necessary locants and multiplying prefixes, and an italicized capital *O* to denote substitution on oxygen. This system is particularly useful for carbohydrate derivatives. Introduction of an alkyl group on O-1 of a cyclic sugar gives an acetal not an ether, and these derivatives are named as alkyl glycosides.

(d) A further alternative possibility for naming partial ethers of polyhydroxy compounds is to state the name of the polyhydroxy compound followed by the name of the etherifying radical or radicals with any required locant or multiplying prefix, then by the word 'ether'.

(e) When two identical groups are linked by an ether bridge and they contain a group which takes priority over the ether group for citation as the suffix, then the ether bridge can be indicated by the prefix 'oxy'.

(f) With compounds of the type RO—X—OR, where the two parent compounds RH are identical and they contain a group having priority over the ether group for citation as suffix, the name is derived by the method used for naming assemblies of identical units.

(g) Linear polyethers are conveniently named by the open-chain replacement nomenclature where the structure is envisaged as being derived from a parent by substitution of oxygen atoms for methylene groups. The name is derived by naming the parent molecule and then using the prefix 'oxa', together with any necessary locants and multiplying prefixes, to specify which methylene groups are replaced by oxygen atoms.

(h) Constitutionally symmetrical linear polyethers may be named as derivatives of the central portion of the molecule which is an ether bridge in molecules with an odd number of ether oxygens and a hydrocarbon radical in molecules with an even number of ether oxygen atoms.

TABLE 1

Examples of Ether Nomenclature

$CH_3OC_2H_5$	(a) Ethyl methyl ether
	(b) Methoxyethane
$C_2H_5OC_2H_5$	(a) Diethyl ether
	(b) Ethoxyethane
$C_2H_5OCH{=}CH_2$	(a) Ethyl vinyl ether
	(b) Ethoxyethene
$CH_3OCH(CH_3)_2$	(a) Isopropyl methyl ether
	(b) 2-Methoxypropane
$HOCH_2CH_2OCH_3$	(b) 2-Methoxyethanol
	(d) Ethylene glycol monomethyl ether
CH_2OCH_2Ph	(b) 3-Benzyloxypropane-1,2-diol
|	
CHOH	(c) 1-*O*-Benzylglycerol
|	
CH_2OH	(d) Glycerol 1-benzyl ether
$HOCH_2CH_2OCH_2CH_2OH$	(e) 2,2′-Oxydiethanol
	(g) 3-Oxapentane-1,5-diol
$HOCOCH_2OCH_2CH_2OCH_2COOH$	(f) 2,2′-(Ethylenedioxy)diacetic acid
	(g) 3,6-Dioxaoctanedioic acid
$HO(CH_2)_2O(CH_2)_2O(CH_2)_2O(CH_2)_2O(CH_2)_2OH$	(g) 3,6,9,12-Tetraoxatetradecane-1,14-diol
$C_2H_5O(CH_2)_2O(CH_2)_2O(CH_2)_2OC_2H_5$	(g) 3,6,9,12-Tetraoxatetradecane
	(h) 1,2-Bis-(2′-ethoxyethoxy)ethane
$C_2H_5O(CH_2)_2O(CH_2)_2O(CH_2)_2O(CH_2)_2OC_2H_5$	(g) 3,6,9,12,15-Pentaoxaheptadecane
	(h) Bis-(2′-ethoxy-2-ethoxy)ethyl ether

4.3.2 PROPERTIES OF ETHERS

The simple ethers are colourless compounds with a characteristic smell. The first member of the ether homologous series, dimethyl ether, is a gas and the lower ethers are

liquids at room temperature. The boiling point of an ether is usually similar to that of the alkane from which it can be formally derived, by substitution of an oxygen atom for a methylene group, and significantly lower than that of the isomeric primary alcohol (see Table 2).

TABLE 2

Some Ethers, Alkanes, and Alcohols, and their Boiling Points (°C)

Ethers	*Alkanes*	*Alcohols*
Dimethyl ether (−25)	Propane (−45)	Ethanol (78.5)
Diethyl ether (35)	Pentane (36)	Butan-1-ol (118)
1,2-Dimethoxyethane (85)	Hexane (68)	Butane-1,4-diol (235)
1,2-Diethoxyethane (123)	Octane (125)	Hexane-1,6-diol (250)

The relatively high boiling point of the alcohol in each trio is believed to be due to association of alcohol molecules in the liquid phase by intermolecular hydrogen bonding which cannot occur with ethers or alkanes, although ethers can participate with protic compounds in intermolecular hydrogen bonding (see Section 4.3.4.2). Ethers can also form ether-soluble complexes with a number of Lewis acids, they dissolve a variety of organic compounds, and they are unreactive under various reaction conditions. These properties make ethers useful solvents for organic reactions. Some ethers with low molecular weight, *e.g.* dimethyl ether, or with several ether groups, *e.g.* 1,2-dimethoxyethane, are soluble in water but the higher simple ethers are immiscible with water and are extensively used for solvent extraction in organic chemistry. The solvent properties of some ethers and methods for their purification have been surveyed.[2]

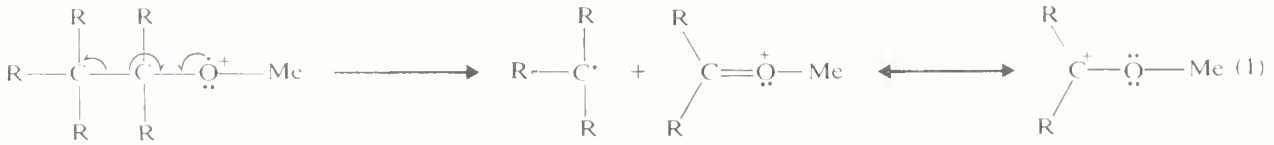
Probably the most commonly known property of diethyl ether is its ability to cause anaesthesia. It has been widely used as a general anaesthetic since it was first used for this purpose by a Boston dentist in 1848. In concentrations in air or oxygen between 3.6–6.5% by volume, inhalation of diethyl ether causes anaesthesia but concentrations greater than 10% are usually fatal. The ether anaesthetics act on the central nervous system and are believed to interfere with transmission of nerve impulses.

A serious disadvantage associated with mixtures of diethyl ether and oxygen used in anaesthesia is that the mixtures are dangerously explosive and this hazard has prompted a search for new anaesthetics which are less explosive. The search has led to discovery of new fluoroether anaesthetics such as 2,2-dichloro-1,1-difluoroethyl methyl ether (methoxyflurane) and 2,2,2-trifluoroethyl vinyl ether (fluroxene).[3] Other fluoroethers have been proposed as anaesthetics[4] but a warning about possible mutagenic effects of α-haloethers has been given.[5]

The ether functional group does not give characteristic absorption bands in the visible or ultraviolet spectral regions but does usually give a strong absorption in the infrared region between 1250–1060 cm^{-1}, due to asymmetric stretching. This i.r. band can be obscured by absorption due to C—C stretching. Therefore the presence of an ether group in a compound containing oxygen is usually inferred indirectly from the electromagnetic spectra if characteristic absorption bands for other oxygen functional groups, *e.g.* OH and C=O, are absent.

Mass spectrometry is uniquely useful in identification, structure determination, and analysis of ethers.[6] Ethers and the alcohols with which they are constitutionally isomeric generally give similar spectra; the molecular ion intensity is usually small and there are prominent peaks at *m/e* 31, 45, and 59. The most striking effect of a heteroatom on the observed fragmentation pattern is to promote cleavage of the bond adjacent to the heteroatom to leave resonance-stabilized ions. Thus when an electron is lost from the heteroatom on electron impact the resulting radical ion can fragment, by cleavage of a C—C bond to the β-carbon atom, to give a resonance-stabilized oxocarbonium ion (equation 1). This fragmentation, which is called β-cleavage, is especially common in methyl ethers. In dimethyl ether, which has no C—C bonds, a C—H bond is broken to give the same type of ion. Cleavage of the C—O bond, called α-cleavage, can also occur,

especially in constitutionally symmetrical and non-branched ethers (equation 2). A combination of α- and β-cleavage with rearrangement is also common with higher ethers but this cannot of course occur with methyl ethers (see equation 3).



(1)

(2)

(3)

In photoelectron spectroscopy, ionization by removal of an electron from lone pairs such as those on oxygen in ethers produces sharp bands which can be unambiguously identified. Electrons in the highest-occupied molecular orbital or in inner orbitals can be removed, each giving rise to a band in the spectrum, and ionization potentials for the various types of electrons can be determined.[7]

The stability of the ether linkage under a variety of reaction conditions (see Section 4.3.6), coupled with its facile synthesis under mild conditions, makes the ether group a useful blocking group in structure determination. Much of our current knowledge of the ring structure of carbohydrates is due to the study of methylated sugars. To illustrate the utility of methyl ethers in structural studies in the carbohydrate group one can cite the observation that oxidation of tetra-*O*-methylglucose with nitric acid gives 2,3,4-trimethoxyglutaric acid, from which it follows that there are at least three contiguous methyl ether groups in the methylated sugar and therefore at least three contiguous free hydroxy groups in the original glucose. This evidence was used to exclude the originally-assumed five-membered ring structure for free sugars and glycosides.[8]

As pointed out above, ethers are generally more volatile than the parent alcohol, and this property has also been extremely valuable in analysis of sugar mixtures obtained during structure determination of polysaccharides. Generally, carbohydrates are not sufficiently volatile to be amenable to vapour-phase chromatography but after etherification, particularly trimethylsilylation, the mixtures of carbohydrate derivatives are sufficiently volatile to be analysed by this method, which has now largely replaced the traditional paper-chromatographic methods of separation. When vapour-phase chromatography and mass spectral analysis are combined they afford an extremely powerful tool for the investigation of mixtures of sugar ethers obtained during polysaccharide structure elucidation.[9]

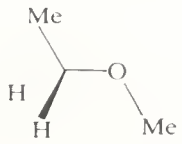
4.3.3 GEOMETRY AND BONDING

The geometries of a number of ethers, including simple ethers, have been determined by diffraction methods and the COC bond angle has been observed to fall in the range $110 \pm 3°$, which is similar to the CCC bond angle in alkanes ($112.6 \pm 0.2°$), whereas the C—O bond length (142.6 ± 0.5 pm) in ethers is somewhat shorter than the C—C bond length (153.7 ± 0.5 pm) in alkanes.

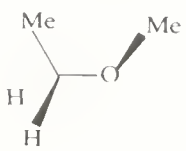
The conformational consequences of replacement of a methylene group by an ether oxygen have been reviewed by Dale,[10] who has concluded that not only the valency angle but also the preferred conformations and the torsional barriers are strikingly preserved.

Methyl ethyl ether and diethyl ether crystallize in the extended (antiperiplanar)

conformation and comparisons of i.r. spectra suggest that the extended conformation is also preferred in the liquid. Additional bands for the liquid in the near i.r. are interpreted as being due to small amounts of *gauche* (synclinal) conformations. The preference for the *anti* conformation (**1**) of vicinal C—O and C—C bonds in ethers over the *gauche* conformation (**2**) has been estimated as 3.8 kJ mol^{-1}, which is slightly larger than the value for the preference of the *anti* conformation of two vicinal C—C bonds in alkanes.

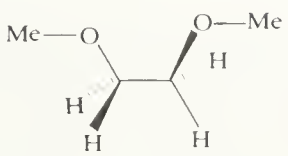


(**1**)

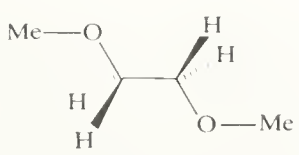


(**2**)

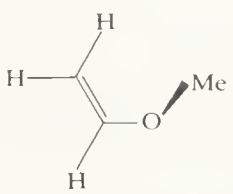
Crystalline 1,2-dimethoxyethane (at −196°C) has a *gauche* conformation about the C—C bond and *anti* conformations at the C—O bonds (**3**) and this is also the preferred conformation in the liquid. The *gauche* conformation is some 1.7 kJ mol^{-1} more stable than the *anti* conformation (**4**). This preference for a *gauche* conformation is also observed with ethane-1,2-diol, where intramolecular hydrogen bonding can be invoked as an explanation. The origin of the observed preference for *gauche* conformations of 1,2-dioxyethane units in ethers is obscure and is not predicted by theoretical calculation. Methyl vinyl ether is also reported[11] to prefer a *gauche* conformation (**5**).



(**3**)



(**4**)



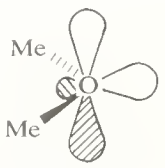
(**5**)

Possibly because of the conformation similarities between ethers and alkanes it has become customary to assume sp^3 hybridization of the oxygen atom with the C—O bonds involving σ overlap of sp^3 hybrid orbitals from the carbon and oxygen atoms, and for the two lone pairs of electrons on the ether oxygen to be depicted as occupying the remaining tetrahedrally-directed localized sp^3 orbitals which are sterically equivalent to the electron pairs forming bonds to hydrogen in the corresponding alkane. Thus dimethyl ether would be represented as in (**6**) with the C—O bonds polarized because of greater electronegativity of oxygen than carbon.

(**6**)

There has been some speculation about the 'size' of the lone pairs[12] and if steric repulsions between vicinal groups determine torsion barriers then, because of the somewhat lower barrier to torsion about the C—O bond in dimethyl ether compared with that about the C—C bond in propane (11.4 *vs.* 13.8 kJ mol^{-1}),[13] despite the shorter C—O bond length in the ether compared with the C—C bond length in propane (142.6 *vs.* 153.7 pm), one can reach the conclusion that the steric requirements of the lone pairs on oxygen are less than those of the methylene hydrogens. There is now some doubt as to whether torsion barriers are determined solely by repulsive forces and so the above conclusion about the 'size' of lone pairs on ethers is not necessarily valid.

The picture of the distribution of electron density around the oxygen atom in dimethyl ether which emerges from molecular orbital calculations[14] is of two sterically and energetically non-equivalent lone pairs. The occupied molecular orbital of lower energy is of σ type with *s* character, having its axis in the plane of the carbon and oxygen atoms, and the higher-energy lone pair orbital is of π type and is orthogonal to the plane of the oxygen and carbon atoms, as in (**7**).



(**7**)

The experimental resolution of the dichotomy about the distribution of the lone pair electrons is not simple because any interaction between the lone pairs and some reagent used to probe the geometry may produce a change in that geometry. However, photoelectron spectroscopy provides a measure of the energies of the lone-pair electrons without involving coordination of the ether to some reagent. This method shows that the lone pairs on oxygen are of different energy,[7] consistent with the representation (**7**).

Preliminary results from force-field calculations of molecular structure, in which electronic effects are taken into account indirectly, indicated that structures of ethers could be calculated without any special difficulty, but it is now apparent that the electron density about the oxygen atom is not adequately described by a sphere centred on the nucleus and that explicit consideration of the lone pairs is necessary.[15]

4.3.4 BASICITY AND SOLVENT PROPERTIES

4.3.4.1 Basicity and solvation

The central feature of much of the chemistry of ethers is their ability to act as bases and form coordination complexes with a wide variety of acids. This interaction involves one or both of the lone pairs of electrons on oxygen and ethers are therefore classified as n-donors. The extent to which charge is transferred and the 'strength' of the complex vary widely, and this variation may be used as a basis for the classification of complexes as either 'strong' or 'weak'. 'Strong' complexes contain, in their electronic ground state, a dative covalent bond between the oxygen atom of the ether and the acceptor molecule. In some cases the interaction with the ether causes ionization of the acid with transfer of a cation to give an oxonium salt, but in other cases strong complexation does not involve oxonium salt formation. 'Strong' complexes can generally be treated in terms of the Brønsted–Lowry or Lewis theories of acids and bases and the equilibrium constant for the reaction, if it can be measured, provides an estimate of the strength of the interaction. In 'weak' complexes the interaction between the ether donor and the acceptor molecule is not strong enough to give isolable complexes. Nevertheless, there has been considerable

interest in weak interactions because they perturb the ground state of the ether molecule only slightly and hence the extent of interaction is a measure of the donor ability of the ether in its ground state. In contrast, with strong interaction there is a change in hybridization and the energies associated with this change in hybridization may not be the same for all ethers.

Mulliken[16] has developed a theory of complexation to include formation of 'weak' complexes in which the interaction between donors and acceptors can be considered as involving resonance between 'dative bond' and 'no bond' structures. The former structures are only minor contributors and the latter are major contributors to the ground-state structure of weak complexes.

Weak complexation can result in absorption of electromagnetic radiation in regions where neither donor nor acceptor absorb. The absorption of energy is believed to be associated with donation of an electron and transfer of charge to the acceptor and consequently these complexes are termed 'charge transfer complexes' (see Section 4.3.4.7).

Oxygen is relatively small, being in the first row of the Periodic Table; therefore the oxygen atom presents a region of high electron density which is difficult to polarize. Ethers can therefore be classified as 'hard' bases.[17] 'Hard' bases generally interact more strongly with 'hard' acids (*e.g.* H^+, Li^+, Mg^{2+}, BF_3) and less strongly with 'soft' acids. Therefore a second possibility for classification of complexes with ethers would be in terms of the 'hardness' of the acceptors.

A third possible classification, which is the one used in this chapter, is to classify the acceptors by their positions in the Periodic Table. In this classification the individual categories may include both 'strong' and 'weak' complexes with both 'hard' and 'soft' acids. Generally, for complexes with elements in the same group, the 'hardness' of the acid and the 'strength' of the complex decrease on going down the group.

The chemical and physical properties of both interacting species may be modified on complexation of various materials by ethers. In general, this modification of properties results in a deviation from ideal behaviour and this deviation can be used to estimate the stoichiometry of the complexation process between particular donor–acceptor pairs. Thus, for example, if the deviation from ideality is plotted as a function of composition of the mixture and an extremum is observed for the mixture with equimolar concentration of ether and acceptor, the occurrence of a 1 : 1 complex can be inferred.

Furthermore, deviation in physical properties from ideal behaviour can be used to compare relative donor abilities of a series of ethers towards a common acceptor or the relative acceptor abilities of a range of acceptors towards a common ether. Since generally only a small fraction of the molecules will be in complexed form, it would be necessary to determine the degree of association before obtaining the molar magnitude of the measured property, but it is not necessary to do this to establish qualitatively relative donor or acceptor properties. In the absence of changing steric effects, the degree of association parallels the strength of interaction.

A number of physical properties have been used to detect complexation with ethers[18] and some of these will be indicated in particular cases in the following sections.

Differences in lone pair ionization potentials for ethers provide a direct measure of donor ability and therefore basicity in the Lewis sense.[19] The values for this property, given in Table 3, show that the ionization potential decreases and therefore basicity increases with increasing substitution, consistent with inductive donation of electron density by alkyl groups. A correlation between inner-shell ionization potential and proton affinity of bases, including ethers, has been observed.[20]

4.3.4.2 Solvation of proton acids

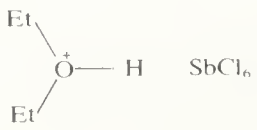
It has been known[21] for a long time from conductivity measurements that ethers are protonated in concentrated sulphuric acid and a number of crystalline 1 : 1 and 2 : 1 complexes of ethers with sulphuric acid have been isolated. The initial van't Hoff *i* factor

TABLE 3

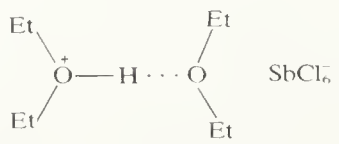
Some Lone-pair Ionization Potentials for Ethers

Compound	*Ionization potentials* (eV)
MeOMe	9.94±0.01
EtOEt	9.50±0.01
Pr^iOPr^i	9.32±0.01
Bu^tOBu^t	8.94±0.01
Methanol	10.85±0.02
Ethanol	10.46±0.02

of 2.0 for the depression of freezing point of sulphuric acid by diethyl ether suggests a 1 : 1 complex in solution and similar results are obtained with other ethers.[22] Careful addition of some ethers to nitric acid gives isolable complexes which are considered to have the structure $R_2OH^+ NO_3^-$ because their i.r. spectra shows peaks diagnostic for nitrate ion.[23] The complex halogen acids HMX_n, where M represents a metal and X a halogen, generally form crystalline complexes with ethers. The complexes show high electrical conductivity in liquid sulphur dioxide, indicative of oxonium salt structure, *e.g.* (**8**). The simplest etherates of this type contain one ether molecule per acidic hydrogen, and are generally white or pale yellow in colour.[24] They are most conveniently prepared by passing the hydrogen halide into a suspension of the 1 : 1 ether–metal halide complex in an inert liquid. These simple complexes generally react readily with a second molecule of ether to give new, intensely coloured complexes, with an ether-to-acid proton ratio of 2 : 1. They are believed[24] to possess ionic structures having a complex anion and a cation made up of the dialkyloxonium ion hydrogen-bonded to a second ether molecule (see **9**). Complex haloacid dietherates can often be prepared by dissolving the appropriate metal in an ether solution of dry hydrogen halide or by mixing the anhydrous metal halide and hydrogen halide in the ether.



(**8**)



(**9**)

In some cases, complexes with more than two molecules of ether per acidic proton have been observed. The ether in complex acid etherates can be exchanged for a different, usually less volatile, ether. Complex acid etherates play an important role in the analytical method involving solvent extraction with ether of metals which form complex haloacids.[25] The ^1H n.m.r. spectra of dialkyloxonium salts have been observed using the acid system HSO_3F–SbF_5–SO_3 at low temperature; the expected splitting of the proton on oxygen by the adjacent hydrogens is observed.[26]

There is ample experimental evidence that ethers behave as bases and interact with protons to give dialkyloxonium ions, but experiments to establish the basicity of ethers relative to each other and to other types of base have not been uniformly successful.

The aqueous pH scale is the traditional standard of reference for determination of pK_a values for acid–base equilibria, but, unlike many amines, ethers are not sufficiently basic to manifest this property simply on solution in water and therefore cannot be studied with a pH meter. Ethers are only protonated in moderately or strongly acidic solutions, and the salts obtained are readily hydrolysed. A theoretical framework for relating ionization equilibria in strongly acidic media by extension of the pH range using indicator-based acidity functions was established by Hammett,[27] but, despite considerable effort over the intervening years, the basic strengths of ethers are poorly defined. Aliphatic ethers do not

have suitable indicator properties and it is consequently not possible to determine the ratio of base to conjugate acid by spectrophotometry in dilute solution; when more concentrated solutions are used, the accuracy of the method is limited by problems of correcting for medium effects.

A further complication is that H_0 values may be inaccurate where relatively high concentrations of ethers are used because the ether co-solvent may have a large effect on the observed concentration ratio of protonated to free indicator by selectively increasing the solubility of the free base form.

TABLE 4
Some pK_a Values for Diethyl Ether

$-pK_a$	*Method*	*Ref.*
0.30	Competitive indicator	a
0.47	Conductivity	b
3.53	Vapour pressure	c
3.59	Solvent extraction	d
4.14	Solvent extraction	e
5.1	Heat of protonation	f
5.7	Titration	g
6.2	N.m.r. spectroscopy	h
10.2	Conductivity	i

[a] C. F. Wells, *Trans. Faraday Soc.*, 1967, **63,** 147. [b] U. Haldna and H. Kuura, *Org. Reactivity*, 1966, **3,** 340. [c] D. Jaqnes and J. A. Leisten, *J. Chem. Soc.*, 1964, 2683. [d] E. M. Arnett and C. Y. Wu, *J. Amer. Chem. Soc.*, 1962, **84,** 1680. [e] U. Haldna and H. Laaneste, *Org. Reactivity*, 1966, **3,** 61. [f] E. M. Arnett, R. P. Quirk, and J. J. Burke, *J. Amer. Chem. Soc.*, 1970, **92,** 1260. [g] J. T. Edward, *Chem. and Ind. (London)*, 1963, 489. [h] J. T. Edward, J. B. Leane, and I. C. Wang, *Canad. J. Chem.*, 1962, **40,** 1521. [i] L. M. Quarterman, H. H. Hyman and J. J. Katz, *J. Phys. Chem.*, 1961, **65,** 90.

Because of these difficulties, the pK_a values for ethers obtained using different methods for the determination of the ratio of conjugate acid to free base vary considerably. The range of values obtained for diethyl ether is illustrated in Table 4. Clearly, because of the wide variation, most of these pK_a values do not represent the true thermodynamic pK_a value but rather the measured H_0 value for the medium in which the ether is half protonated. Despite the variation it might seem likely that pK_a values for a group of similar compounds determined by the same method will reasonably represent the relative order of basicity, but experience has shown that even this assumption is not always valid. Thus, for example, the relative basicities of water, dibutyl ether, and butyl alcohol are found[28] to be $BuOH > HOH > Bu_2O$ above 50 °C, $BuOH > Bu_2O > HOH$ between 1 and 50 °C, and $Bu_2O > BuOH > HOH$ below 1 °C. It is therefore necessary to treat values for relative basicities with some reserve.

Bunnett and Olsen[29] have suggested one way to circumvent the problems associated with concentration by use of a linear free energy relationship to determine the thermodynamic pK_a value of a base from indicator ratios by extrapolation. In this treatment, the ϕ parameter expresses the response of the equilibrium to changing acid concentration. A negative ϕ value means that $\log [BH^+]/[B]$ increases more rapidly than $-H_0$ does. This approach has been applied[30] to ethers using an n.m.r. spectroscopic method to obtain ionization ratios and the pK_a values and ϕ values obtained are shown in Table 5 along with comparative values for methanol and dimethyl sulphide.

A possible rationalization of these results can be seen in the expected requirements for stabilization of a cation by solvent. The necessity for solvent stabilization will increase when the charge is more localized, that is, when the size and polarizibility of the protonated atom is small. Therefore oxonium ions require more effective solvation than sulphonium ions. When the extent of ionization in aqueous sulphuric acid mixtures is plotted against H_0 the lines for dimethyl ether and dimethyl sulphide cross at 67%

TABLE 5

Basicity of Some Ethers

Ether	pK_a	ϕ	$(H_0)_{1/2}$
MeOMe	−2.52	0.82	−8.58
MeOEt	−2.60	0.77	−7.60
MeOPr^i	−2.60	0.75	−7.09
EtOEt	−2.42	0.77	−7.05
Methanol	−1.98	0.85	−6.89
Dimethyl sulphide	−6.95	−0.26	−5.73

sulphuric acid concentration, and in dilute solution the ether is a stronger base than the sulphide, whereas the reverse is true in concentrated acid solutions. Furthermore, the effectiveness of solvation will increase with the number of hydrogens at the protonation site through hydrogen bonding to solvent. Thus protonated ethers are more sensitive to solvent change than alcohols. Simple consideration of inductive effects would lead one to expect that ethers would be more basic than alcohols, but the reverse is found to be the case in water, presumably because of more effective solvation of the protonated alcohols.

An alternative approach to consideration of basicity which avoids problems due to solvents is to determine the proton affinity of each compound in the gas phase. The proton affinity is the exothermicity of the reaction summarized in equation (4) and provides a direct measure of the Brønsted base strength.

$$B + H^+ \rightarrow BH^+ \tag{4}$$

Proton affinity values are available from ion cyclotron resonance spectroscopy, although they are apparently difficult to obtain since those for oxygen bases have recently[31] been modified by nearly 42 kJ mol^{-1} from the original values.[32] These values are shown in Table 6.

TABLE 6

Values for Proton Affinity, PA, Heat of Ionization, ΔH_i in Fluorosulphuric Acid, and Core Electron Ionization Potentials, ΔE_B, in kJ mol^{-1}, for Some Bases

Compound	*PA*	$\Delta H_i(HSO_3F)$	$-\Delta E_B$
Dimethyl ether	823	76	126
Diethyl ether	844	82	175
Methanol	790	72	76
Ethanol	807	78	106
Water	748	69	0
Dimethyl sulphide	849	76	—
Ammonia	865	181	—

Furthermore, a striking linear correlation between proton affinity and core electron ionization potential, as measured by photoelectron spectroscopy, has been observed.[20] This is presumably because ionization of a core electron and addition of a proton can both be considered as an addition of positive charge to the same region of the molecule. Thus photoelectron spectroscopy provides a third measure of relative basicity of ethers in the gas phase and values of some core electron ionization potentials are also shown in Table 6.

The proton affinity and heat of ionization figures show decreasing basicity in the series $Et_2O > EtOH > HOH$ and that diethyl ether is a stronger base than dimethyl ether, consistent with inductive donation of electrons from alkyl groups to stabilize the oxonium ion and a larger effect with larger alkyl groups. The ionization potentials show increasing basicity with increasing substitution, which is also consistent with more effective inductive stabilization by larger alkyl groups.

In view of the difficulties encountered in obtaining reliable measures of base strength in terms of pK_a values which are related to the free energy of ionization (ΔG_i°), it has been proposed[30] that the corresponding enthalpy change (ΔH_i), which can be obtained by solution calorimetry, can be used to give a guide to relative basicity. Justification for this approach comes from the observation of a linear correlation of ΔH_i in fluorosulphuric acid with the corresponding pK_a values in water for many amines. The $\Delta H_i(FSO_3H)$ values for some bases, including ethers, are shown in Table 6.

Hydrogen bonding of ethers with relatively weak Brønsted acids has been extensively studied, particularly by spectroscopic methods, to determine basicity of ethers.[33] I.r. spectroscopy has been used to probe the association of an acid HA with an ether, which causes a shift to longer wavelength in the vibrational stretching frequency and a shift to shorter wavelength in the bending frequency of the HA bond. The interaction of alcohols and phenols with ethers is complicated by self-association of the hydroxyl compound, but this complication can be minimized by working in dilute solution. A particularly useful system for study is one comprising mixtures of MeOD with ethers, because the O—D band at 2689 cm^{-1} occurs in an otherwise transparent region of the spectrum. Carbon acids such as acetylenes and polyhaloalkanes can also show hydrogen bonding to ethers.[34] For example, X-ray analysis of the solid diethyl ether–bromodichloromethane complex shows C—H · · · O bonds in the crystal. Again the i.r. spectroscopic study of hydrogen bonding of carbon acids to ethers is facilitated by deuteration of the acid.

Some representative values of shifts in stretching frequency of three acids in some ethers are shown in Table 7. Apart from the MeOD–Bu^n_2O system, there is a trend towards increasing donor ability with increasing substitution in the ether, which is consistent with inductive donation of electron density from alkyl groups to the oxygen.

TABLE 7

Some Shifts in Stretching Frequency (cm^{-1}) due to Hydrogen Bonding

$\Delta\nu$	Et_2O	Pr^n_2O	Bu^n_2O	Pr^i_2O
O—D in MeOD	106	117	101	130
O—H in PhOH	228	282	292	308
C—D in $CDCl_3$	20.0	20.9	21.6	25.3

Whilst the principal method of study of hydrogen bonding has been vibrational spectroscopy, n.m.r. spectroscopy has been increasingly used in the last 20 years. The n.m.r. signal for the hydrogen nucleus is very sensitive to changes in the electronic environment of the nucleus and hydrogen bonding, even when very weak, is easily detected. Donation of electron density from ether oxygen to the hydrogen of HA in hydrogen bonding results in increased shielding of the acidic hydrogen, and deshielding of the α-hydrogens of the ether. A linear correlation between the strength of the hydrogen bond and the chemical shift of the bonded proton has been observed.[35]

The stoichiometry of complexation has been inferred from the study of freezing point diagrams for chloroform–diethyl ether mixtures. This study indicates both A_2B and B_2A type complexes, and it was proposed that both lone pairs on oxygen can be simultaneously involved in hydrogen bonding. From an analysis of the second virial coefficient for diethyl ether–chloroform mixtures the enthalpy of formation for the hydrogen bond is estimated as $\Delta H^\circ_{form} = -25.2$ kJ mol^{-1}, and the values for other ethers are fairly constant within the range -20 ± 5 kJ mol^{-1}.

Formation of hydrogen bonds is an exothermic process and the energies of hydrogen-bond interactions between proton donors and electron donors can be estimated directly by calorimetry after making suitable correction. Thus the heat of mixing of butanol and dibutyl ether, after correcting for alcohol dissociation, is found to be -17.7 kJ mol^{-1}, which is in good agreement with the values quoted above.

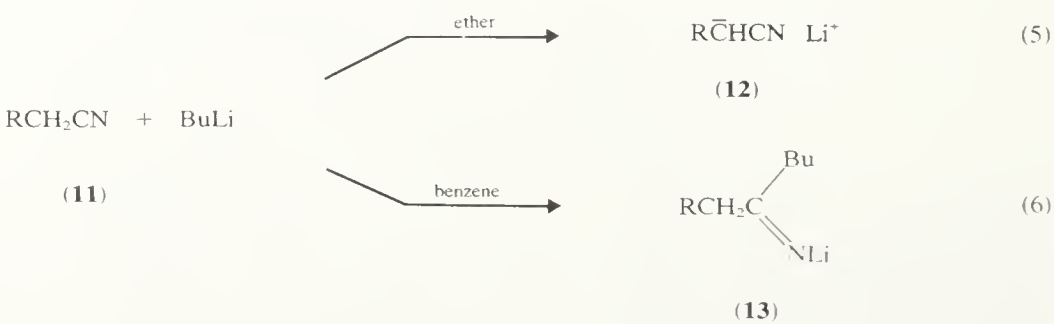
4.3.4.3 Solvation of alkali metal derivatives

A number of cases of solvation of alkali metal cations has been reported, particularly with the smaller lithium and sodium ions,[36] which are 'harder' acids than potassium or caesium ions. For example, a solid adduct $MeLi{\cdot}Et_2O$ has been isolated, and also the high solubility of lithium perchlorate (44 mole % at 25 °C) in diethyl ether and the electrical conductivity of the solution have been interpreted in terms of metallo-oxonium ion formation. The addition of diethyl ether to a solution of sodium tetraethylaluminium in toluene gives a marked increase in conductivity, consistent with the formation of sodio-diethyloxonium ions. Electron spin resonance studies on the preparation of sodium naphthalene in ether solution suggest that sodium naphthalene exists mainly as ion pairs in diethyl ether solution but as solvated ions in glycol ether solution.

Lithium tetrahydridoaluminate(III) and lithium tetrahydridoborate(III) form stable monoetherates and the former gives an unstable dietherate with diethyl ether. This complexation accounts for the relatively high solubility of these reagents in ether.

A particularly sensitive probe of ion pair equilibria involving alkali metal derivatives in solution is provided by the n.m.r. signal for the metal because the chemical shift is principally determined by the surrounding molecules. The lithium nucleus is particularly convenient for study, and it is observed that organolithium derivatives show progressive upfield shifts on going from cyclopentane solvent to ether and then 1,2-dimethoxyethane, suggesting more extensive ionization throughout this series of solvents.[37] The cyclic polyethers called crown ethers (see Section 4.4.5.2) are very much more effective than acyclic ethers for solvating alkali metal ions.[38]

One practical consequence of variation with solvent of the strength of complexation, and hence the degree of ionization of carbon–metal bonds in organometallic reagents, is a tendency for the properties of these reagents to vary with solvent. Thus[39] butyl-lithium in ether abstracts a proton from mesitylacetonitrile (**11**) to give (equation 5) the lithium salt of the nitrile (**12**), whereas in benzene solution the reagent adds to give (equation 6) the imine derivative (**13**).



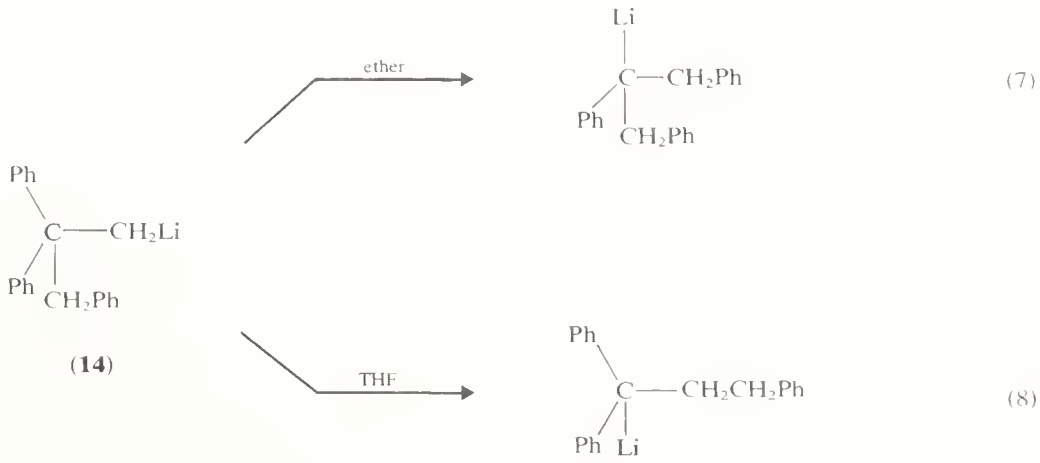
(5)

(6)

The stereochemical integrity of (*Z*)- and (*E*)-1-lithio-1-phenylbut-1-ene in hexane is dramatically affected by addition of 1% of ether. The rates of isomerization with different added ethers are found to be in the following order: 1,2-dimethoxyethane > tetrahydrofuran > diethyl ether, and it is proposed that the isomerization occurs *via* ionization of the C—Li bond.[40] Furthermore, the rearrangement products of 1-lithio-2,2,3-triphenylpropane (**14**) are found to depend on the solvent used (equations 7 and 8). This difference is interpreted as being due (i) to formation in diethyl ether of tight ion pairs, in which phenyl migration occurs and (ii) to formation of loose ion pairs, with benzyl group migration, in THF.[41]

4.3.4.4 Solvation of alkaline earth derivatives

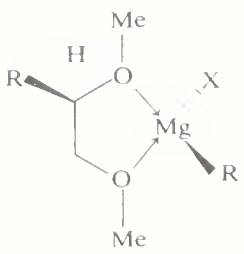
The Grignard reagents, which are generally prepared as solutions in ethers, are versatile reagents in organic synthesis but the detailed nature of the reagent and the mechanism of reaction are only recently emerging.



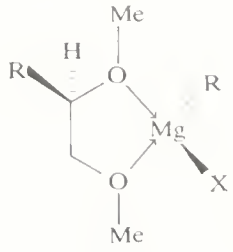
It was a common belief that ether solvents were essential for the preparation of Grignard reagents, particularly with less reactive halides, but this is now known not to be the case. However, Grignard reagents prepared in hydrocarbon solvents have rather different properties from Grignard reagents prepared in ether solvents;[42] radicals are more liable to be formed in hydrocarbon solvents. Evidently, polarization of the C—Mg bond is assisted by coordination of the magnesium with ethers. Ethylmagnesium bromide and phenylmagnesium bromide both crystallize with two molecules of diethyl ether coordinated to the magnesium in a tetrahedral arrangement. It is now believed[43] that, under the usual reaction conditions of relatively low concentrations in ether, the Grignard reagents are generally mainly composed of RMgX species with little association at concentrations below 0.1 M; only small (*ca.* 5%) equilibrium concentrations of R_2Mg and MgX_2 are present *via* the Schlenk equilibrium. All three magnesium species are solvated, normally with two ether molecules. At higher concentrations the magnesium moieties may dimerize through halogen bridges, and the equilibrium between monomeric and dimeric forms is governed by the nature of the halide and the ether; dimerization is less extensive in more basic ethers. Apparently, the more basic the ether, the more effectively it can compete with halide as a coordinating ligand.

The rate of formation of Grignard reagents depends on the ether used as solvent, the following order of reactivity being observed: cyclic ethers > Et_2O > Bu^n_2O > Pr^i_2O > aryl alkyl ethers. Furthermore, the rate of C—Mg bond exchange is also dependent on solvent, being faster in THF than in diethyl ether.[44]

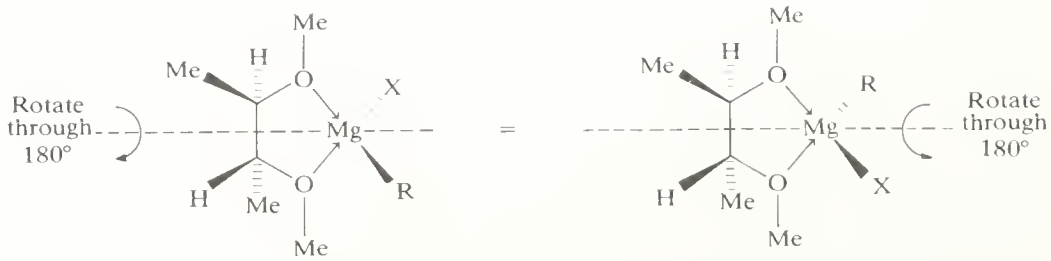
Solvation of a Grignard reagent with a chiral ether will give a chiral solvate which can, in principle, be used in asymmetric synthesis, and indeed a number of successful applications have been reported.[45] The reported enantioselectivity is generally low for reactions in monodentate chiral ethers and polydentate ethers such as hexa-*O*-methyl-D-mannitol and penta-*O*-methyl-D-arabinitol. The chiral bidentate ether (2*R*,3*R*)-2,3-dimethoxybutane has been used with moderate success, but the highest optical yield so far recorded in this type of reaction is 50% in the reaction between methylmagnesium iodide and cyclohexyl phenyl ketone in the presence of methyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-α-D-glucopyranoside with benzene as co-solvent.[46] The interpretation of these results is quite complex because of the number of isomeric solvates possible. Even with a bis-ether, where there is only one chelation site, diastereoisomeric solvates are possible if the ether is asymmetric, *e.g.* (**15**) and (**16**), because the magnesium becomes a chiral centre. The rate of exchange of the C—Mg bond depends on the nature of the solvent but should be rapid on the time scale appropriate to chemical reaction so that there should be relatively rapid stereomutation of the stereoisomeric solvates. Problems associated with diastereoisomeric solvates can be avoided by using a chiral bis-ether containing a C_2 axis such as (2*R*,3*R*)-2,3-dimethoxybutane because, in this solvate (**17**), exchange of the R and X ligands give a structure superimposable on the original by rotation through 180° about a line through the magnesium and the centre of the C-2—C-3 bond. This



(15)



(16)



Identical (17)

simplification has been overlooked.[45] Another difficulty in interpreting addition to aldehydes arises from the observation that bromomagnesium salts of racemic secondary alcohols can undergo asymmetric equilibration in chiral ether solvents, so that the observed enantioselectivity may be due, at least in part, to post-addition asymmetric equilibration.

4.3.4.5 Solvation of Group III elements

The trihalides of boron and aluminium are coordinatively unsaturated and their chemistry is dominated by complexation with Lewis bases including ethers, usually to give 1:1 complexes. The bonding in these complexes is believed to involve a dative bond between oxygen and the metal. The B—O bond in boron trifluoride dimethyl etherate is 150 pm in length.[47]

Complexes of boron trihalides with ethers may decompose, with formation of alkyl halides as in equation (9) (see also Section 4.3.6), but the greater strength of the B—F bond stabilizes boron trifluoride complexes and, for example, boron trifluoride etherates can be distilled without cleavage of the ether.

$$R_2OBX_3 \rightarrow ROBX_2 + RX \tag{9}$$

Contrary to expectation based on the relative electronegativities of halogens, the order of acceptor strengths is $BBr_3 > BCl_3 > BF_3$. The dissociation constants for boron trifluoride etherates give a measure of donor ability of ethers in the order $Pr^i_2O < Et_2O < Me_2O < THF$, which is different from the basicity order, suggesting that the stability of the complexes is determined by steric effects rather than inductive effects in this case.[48] The order of acceptor power of trimethyl derivatives of metals in Group III is B < Al > Ga > In > Tl. Ether complexes of trialkylaluminiums are generally stable and distillable. The strength of the dative bond in this case is sufficient to overcome quite serious steric hindrance and, for example, tri-t-butylaluminium forms a stable diethyl etherate.[49] Alkylaluminium derivatives are extensively used as components of catalysts for stereoselective polymerization of alkenes, and complexation of these reagents with ether has been widely studied, particularly by n.m.r. spectroscopy.[50]

4.3.4.6 Solvation of Group IV elements

Whilst the carbon atoms in stable organic compounds generally have filled electron shells and therefore do not behave as Lewis acids towards the relatively weakly basic ethers, carbenium ions are electron deficient and are strong acids and would be expected to interact with ethers to give trialkyloxonium ions, as in equation (10).

$$R_2O + R^+ \rightarrow R_3O^+ \qquad (10)$$

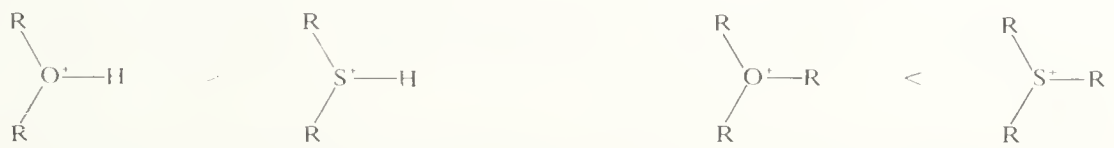
Unlike amines, sulphides, and selenides, which react with alkyl halides to give the corresponding onium salts, as in equation (11), ethers do not generally react to give trialkyloxonium salts.

(11)

(**18**)

Y = Halide; X = NR, S, Se; $X \neq O$

The greater basicity of ethers, compared with sulphides, shows that oxonium salts with hydrogen as ligands are thermodynamically more stable than the corresponding sulphonium salts, at least in solvents which accept hydrogen bonds (see Section 4.3.4.2), whereas the reverse order of stability is observed with trialkyl-oxonium and -sulphonium ions:



This difference can be rationalized because ethers are 'harder' bases than sulphides and carbenium ions are 'softer' acids than protons and, generally, hard acids react preferentially with hard bases and soft acids with soft bases.[17]

When the halide ion is trapped as a complex anion of low polarizability, trialkyloxonium salts of the type (**18**) where X = O can be isolated, as in equation (12).

(12)

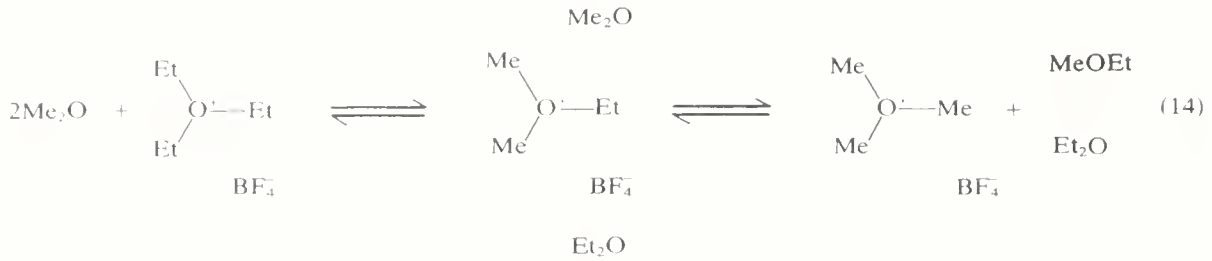
The stability of the salt depends on the nature of the anion and decreases in the following order:[51] $SbCl_6^- > BF_4^- > FeCl_4^- > AlCl_4^- > SnCl_6^{2-}$.

Trialkyloxonium salts are powerful alkylating agents and alkylate halide ions, thus explaining why oxonium ions are not obtained by the scheme shown in equation (11). Using low-temperature n.m.r. spectroscopy, oxonium ions of the type (**18**), where Y^- is not a complex anion (*e.g.* bromide ion), have been observed[52] at −80 °C.

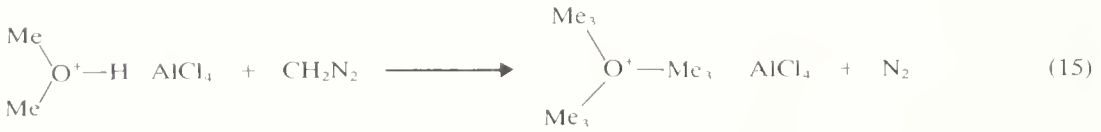
Methyl fluorosulphonate can be used[53] to alkylate ethers, as in equation (13).

$$Me_2O + MeOSO_2F \rightarrow Me_3O^+ \ ^-OSO_2F \qquad (13)$$

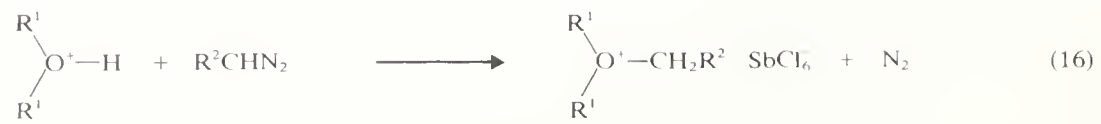
Tertiary oxonium salts can be used to alkylate ethers because an equilibrium is established between various oxonium salts. This reaction (equation 14) has been recommended for the synthesis of trimethyloxonium tetrafluoroborate.[54] Ether complexes of acids react with diazoalkanes to give trialkyloxonium ions[55] (equations 15 and 16).



(14)

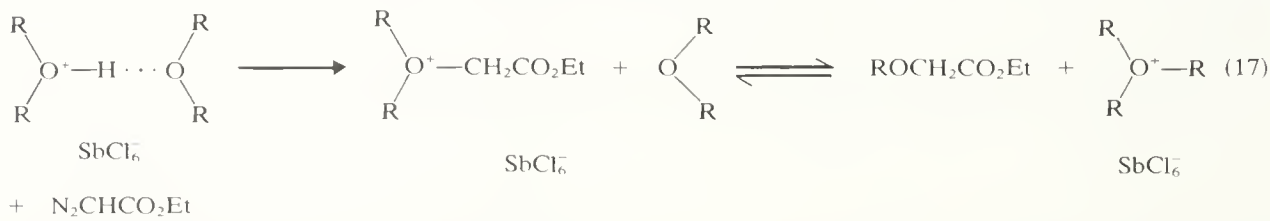


(15)



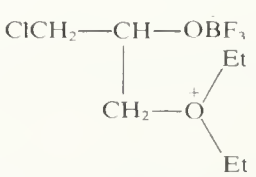
(16)

Dialkyloxonium salts normally crystallize as etherates containing a hydrogen bond (see Section 4.3.4.2) and these react towards diazoalkanes as though they were ether-free salts to give trialkyloxonium salts. With diazoacetic ester they react differently,[56] as in equation (17), presumably because the ethoxycarbonyl group tends to destabilize the first-formed

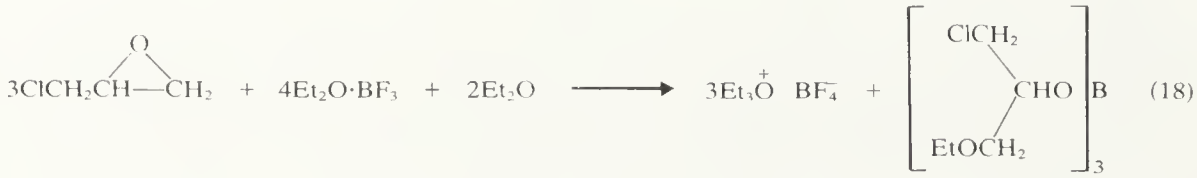


(17)

trialkyloxonium salt. Intermediate formation of reactive oxonium ions, *e.g.* (**19**), which then alkylate an ether molecule, is probably involved in the most convenient method[57] for synthesis of trialkyloxonium salts from epichlorohydrin and boron trifluoride etherate (equation 18). Adducts of trialkyl phosphates or phosphonates with $SbCl_5$ are strong



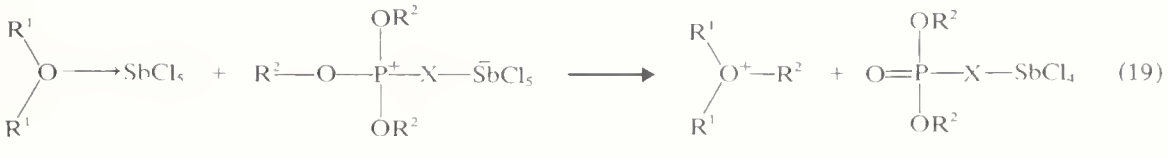
(**19**)



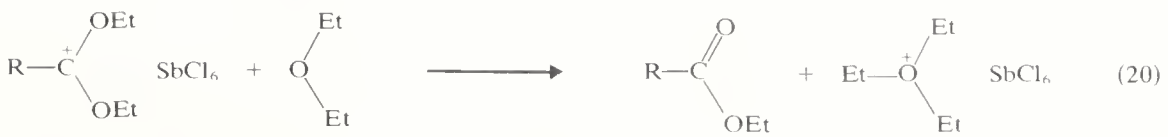
(18)

alkylating agents and alkylate $SbCl_5$ etherates (equation 19) to give trialkyloxonium salts.[58]

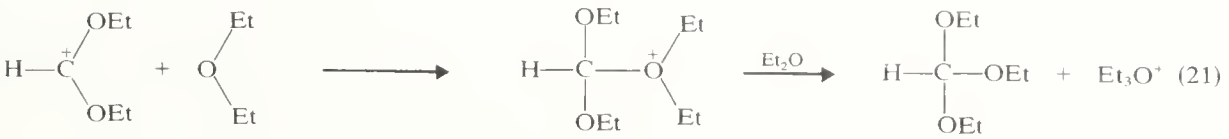
Dialkyloxycarbenium salts can be used to alkylate ethers, as in equation (20), but the reactions may involve reactive trialkyloxonium ions as intermediates[59] (equation 21). Trialkyloxonium salts are reactive species and are normally readily decomposed by water



(19)



(20)



(21)

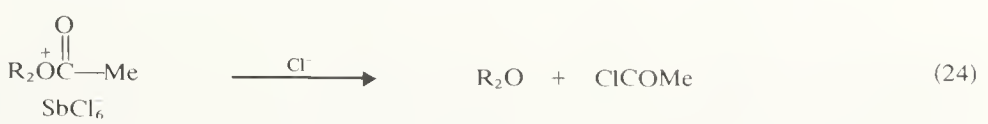
but can be obtained as sparingly soluble salts by precipitation from aqueous solution[60] (see equation 22). Ethers also coordinate with incipient acylium cations. Thus in the

(22)

presence of antimony pentachloride, to complex the halide, acyl halides react with dialkyl ethers but the acyldialkyloxonium salts are only stable at low temperatures.[61] Generally, O—alkyl cleavage occurs as in equation (23). This reaction is the basis of the

(23)

cleavage reaction of ethers with acyl halides catalysed by inorganic halides, *e.g.* $ZnCl_2$, $AlCl_3$, $FeCl_3$, BF_3.[62] Alternatively, O—acyl cleavage can occur and this is the favoured mode in reactions with nucleophiles, as in equation (24).[61]



(24)

Intramolecular solvation of a carbenium ion intermediate by an ether function can have a dramatic effect on the rate of solvolysis reactions. Thus in the solvolysis of ω-methoxyalkyl *p*-bromobenzenesulphonates, a markedly greater rate of reaction for butyl substrates compared with others was observed,[63] as shown in Table 8.

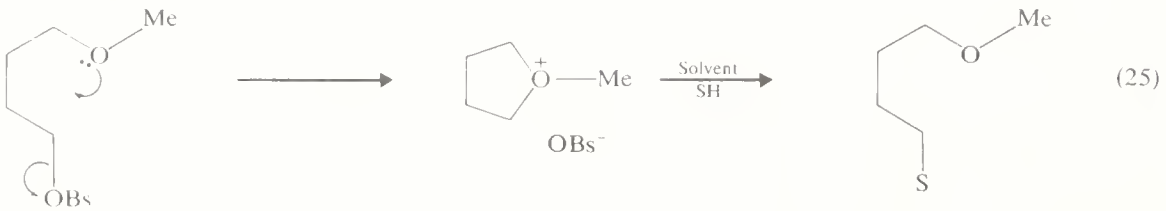
TABLE 8

Relative Rates of Solvolysis of Some Alkoxyalkyl Sulphonates

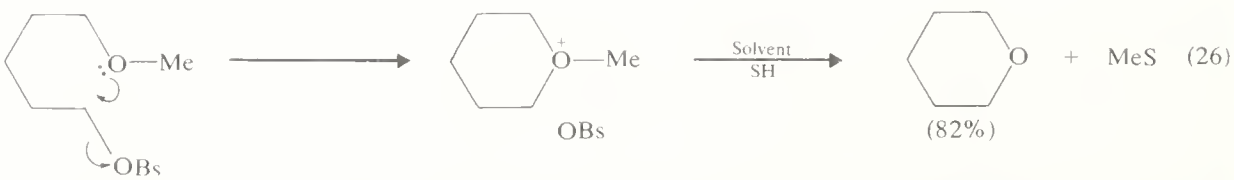
Compound $MeO(CH_2)_nOBs$[b]	*Relative rate of solvolysis*[a] EtOH (75 °C)	MeCOOH (25 °C)
$n = 2$	0.25	0.28
$n = 3$	0.67	0.63
$n = 4$	20.4	657.0
$n = 5$	2.84	123.0
$n = 6$	1.19	1.16

[a] Relative to the rate for C_4H_9OBs in each solvent (temperature). [b] Bs = *p*-bromobenzenesulphonate.

These results were interpreted[64] in terms of neighbouring group participation involving the formation of cyclic oxonium ion intermediates which undergo reaction to products by ring cleavage in the case of tetrahydrofuranium ions (equation 25), but by demethylation in the case of acetolysis *via* the tetrahydropyranium ion (equation 26).

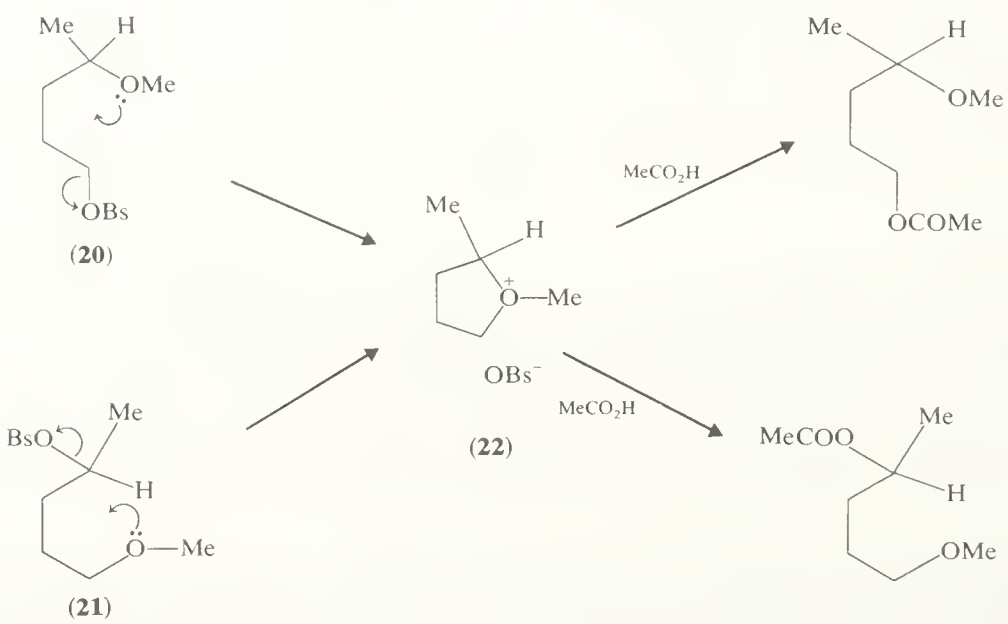


(25)



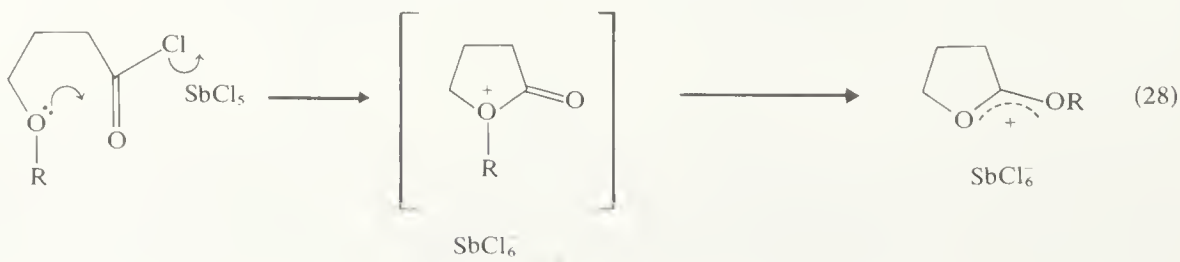
(26)

Other aspects of neighbouring group participation, including alkoxyl group participation, have been reviewed.[65] Further evidence for a cyclic oxonium ion intermediate, *e.g.* (**22**), comes from the observation that the same mixture of products is obtained from acetolysis of the isomeric sulphonates (**20**) and (**21**) shown in equation (27).[66]



(27)

The action of $FeCl_3$ on ω-methoxyalkyl halides gives cyclic ethers by demethylation.[67] The essential difference between this case and the previous one, where predominant ring opening was observed after O-5 participation, is that the product of ring opening is the same as the starting material and can be reconverted into the oxonium ion under the reaction conditions, whereas the demethylation reaction is essentially irreversible. The reaction of $SbCl_5$ with γ-alkoxybutyryl chloride gives a dialkoxycarbenium ion, presumably *via* a cyclic acyldialkyloxonium ion as in equation (28).[68]

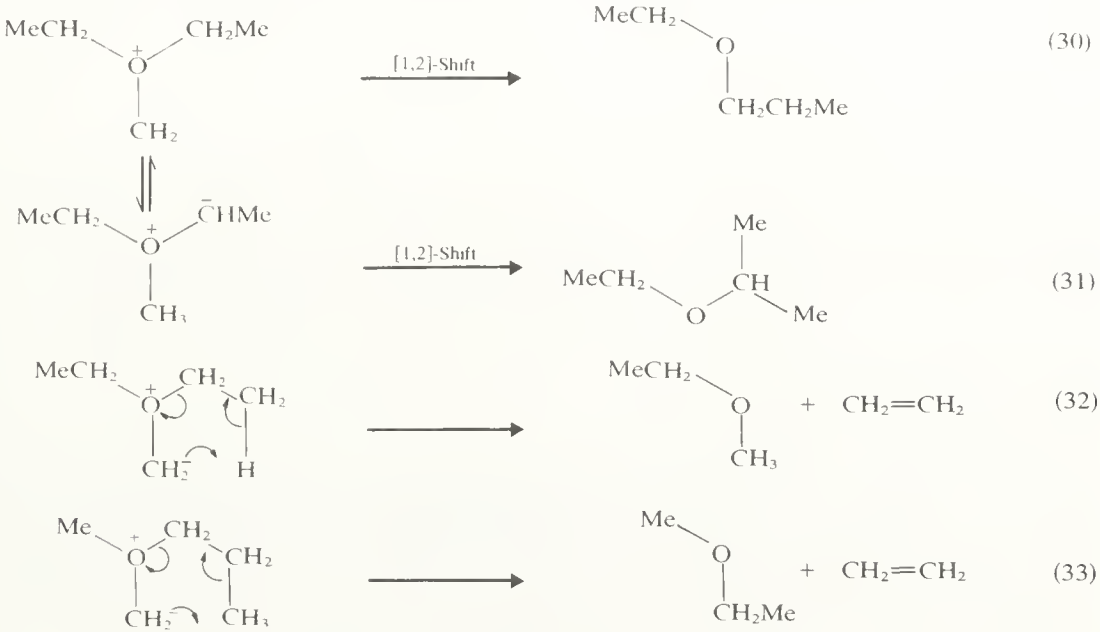


(28)

Singlet carbenes are electron-deficient species which can interact with the basic oxygen in ethers to give oxonium ylides, particularly when the carbene carries electron-withdrawing groups as in equation (29). Oxonium ylides have been postulated as intermediates in reactions of ethers with carbenes.[69] The major reaction of singlet methylene

(29)

with saturated ethers is almost random insertion into all types of C—H bonds to give other ethers, and minor reactions are displacement leading to methyl ethers and alkenes or insertion into the C—O bonds.[70] Methyl ethyl ether is a minor product from the photolysis of diazomethane in methyl propyl ether.[71] Mechanisms involving ylide intermediates have been suggested for some of these reactions,[72] as in equations (30)–(33), which are similar to those postulated in Wittig rearrangements (see Section 4.3.6.1).



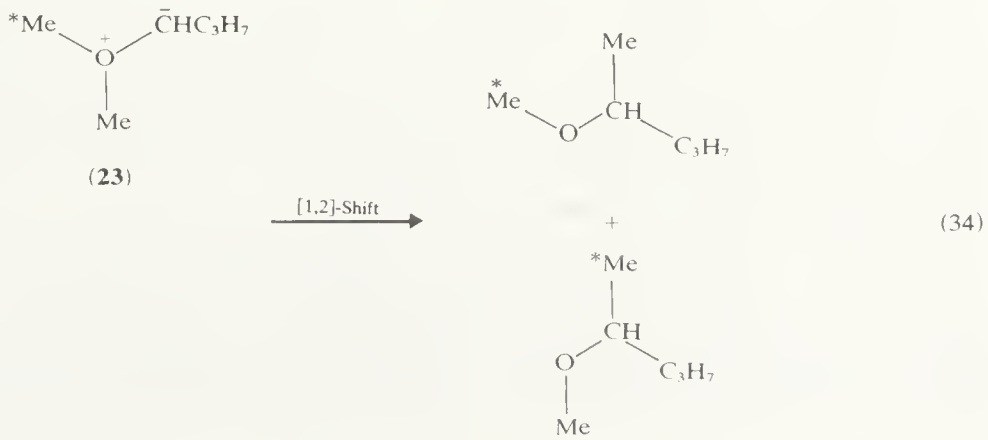
(30)

(31)

(32)

(33)

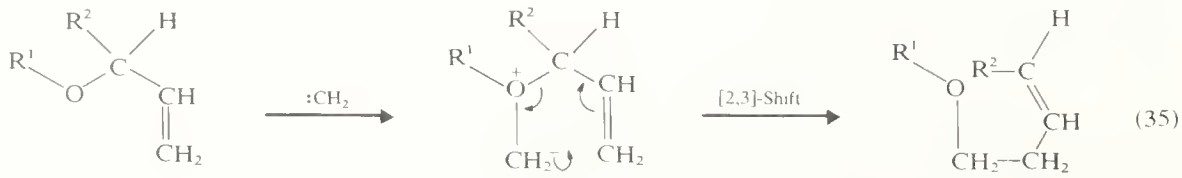
However, evidence contrary to an ylide mechanism, as in equation (30), comes from the observation[73] that the ethyl propyl ether obtained from reaction of $^{14}CH_2$**:** with diethyl ether has the γ-carbon labelled whereas α-carbon labelling would result from the ylide mechanism. Furthermore, the 2-methoxypentane obtained by methylene insertion into the α-C—H bond of methoxy-labelled 1-methoxybutane has retained most of the original label in the methoxy group, which is incompatible with reaction *via* the ylide (**23**) in which the rate of migration of the labelled and unlabelled methyl groups should be similar (see equation 34).



(**23**)

(34)

The cleavage of O—alkyl bonds is more marked in reactions of ethers with alkoxycarbonylcarbenes compared with the methylene reaction.[74] In this case the proposed ylide intermediate would be stabilized by the adjacent carbonyl group. Thus thermolysis of ethyl diazoacetate in dibutyl ether gave ethyl butoxyacetate in 9% yield as well as the products of insertion into the various C—H bonds in 23% yield.[75] Evidence for an ylide mechanism in the formation of C—O insertion products from thermolysis of methyl diazoacetate in benzyl ethers has been obtained from observation of CIDNP signals during the reaction.[76] In reaction of carbenes with allyl ethers, both addition to the double bond and insertion into the O—allyl bond with accompanying allylic inversion is observed.[77] The latter reaction can be rationalized as a [2,3]-shift in the initially formed ylide, similar to that proposed for Wittig rearrangements (see Section 4.3.6.1), as shown in equation (35). However, the rate of reaction of 3-methoxycyclohexene with $:CCl_2$ is about



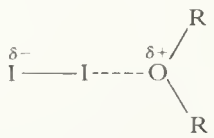
(35)

5 times slower than that of cyclohexene and the product results by addition of $:CCl_2$ in the *trans* position relative to the methoxyl, suggesting that in this case an ylide intermediate is not involved.[78]

Tin(IV) tetrachloride complexes strongly with ethers to give dietherates, in contrast to silicon and germanium tetrachlorides which do not[79] show this tendency.

4.3.4.7 Other ether complexes

Apart from hydrogen-bonded complexes, by far the most commonly studied complexes of ethers are those with iodine. Investigations of these complexes has been central to the development of theories of electron donor–acceptor interaction.[80] A solution of iodine in ether is brown rather than the characteristic violet colour of iodine itself and this colour change is due to a change in the absorption spectrum of iodine which is believed to indicate formation of an electron donor–acceptor complex of type (**24**).

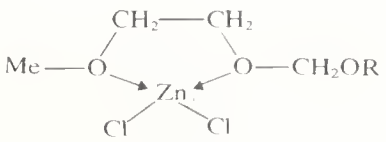


(**24**)

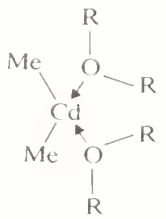
The shift in wavelength of the absorption maximum on complexation gives a measure of the strength of the complex. Furthermore, an intense new absorption band appears in the ultraviolet region where neither component absorbs, called a charge-transfer band.[81] The greater the donor ability of the ether, the longer is the wavelength of the charge-transfer band. Complexes of ethers with other acceptors such as sulphur dioxide[82] and cyanogen iodide[83] have also been extensively studied.[81]

Despite the widely held belief that ethers, which are relatively weakly basic, have poor coordinating ability towards transition metal derivatives, a large number of ether complexes of this class have been prepared, particularly with cyclic ethers.[84] This type of complexation can have important practical application. Thus complexation of ethers to titanium tetrachloride induces downfield shifts of the ^1H n.m.r. signals for protons near the ether oxygen which can be useful in the structural elucidation of ethers.[85] This reagent is very much cheaper than the lanthanide shift reagents which are commonly used. Ether

complexes of zinc and cadmium are well known and this type of complex, *e.g.* (**25**) and (**26**), has been postulated to explain the facile cleavage with zinc chloride of the acetal group in 2-methoxyethoxymethyl derivatives of alcohols[86] and the enhanced rate of self-exchange of dimethylcadmium in ether solvents.[87]



(**25**)



(**26**)

The extraction of metals from aqueous solutions by ether has been extensively studied because of potential preparative or analytical applications. Thus uranyl nitrate, which forms both $UO_2(NO_3)_2 \cdot 3H_2O \cdot Et_2O$ and $UO_2(NO_3)_2 \cdot 2H_2O \cdot 2Et_2O$, is extracted from aqueous solution more effectively by diethyl ether than by higher branched ethers.[88]

4.3.5 FORMATION OF ETHERS

There are several accounts of formation of ethers, the most extensive being that by Meerwein[89] in German. A monograph devoted to the chemistry of the ether linkage contains a chapter[90] on formation of ethers, Buehler and Pearson[91] give a useful account of this subject, and further examples of synthetic methods can be found in books devoted to synthesis.[92] In the following sections some examples of syntheses of ethers will be discussed. The reactions are grouped together into categories depending on the changes in the oxidation level of the carbon forming the new C—O bond. In some cases the classification is rather arbitrary. Obviously, the synthesis of any compound may be considered as a reaction of another compound. Because the two C—O bonds in an ether are usually established at different points in a synthetic sequence, most syntheses of ethers can be considered as reactions of alcohols or derivatives thereof (see Chapter 4.1).

4.3.5.1 Ethers by displacement

One of the most widely used methods for synthesis of constitutionally unsymmetrical ethers, the reaction of alkoxides with alkyl halides as in equation (36), was introduced by Williamson[93] and has since been considerably modified to give improved yields.

$$R^1O^- + R^2X \rightarrow R^1OR^2 + X^- \qquad (36)$$

In the original method, X^- was a halide ion but sulphonate, sulphate ester, or carboxylate leaving groups can be used. For *O*-alkylation of simple alcohols an excess of the alcohol is often used as solvent, but, generally with higher molecular weight alcohols, a solvent is necessary. Refluxing the alcohol with sodium or potassium metal in high-boiling hydrocarbon solvents such as toluene or xylene was a popular method for preparation of the alkoxide, presumably because the molten metal presents a clean surface for reaction with the alcohol, but the alkoxides have only limited solubility in these solvents. Liquid ammonia and ethers are better solvents than hydrocarbons for alkali metal salts, but the most effective solvents for these nucleophilic displacements, especially with methyl and benzyl halides, where base-promoted β-elimination is not a problem, are the dipolar aprotic solvents such as DMF and DMSO. These last-named solvents are particularly useful in the facile formation of ethers of polyhydric alcohols such as polysaccharides.[94] Various bases including alkali metals, sodamide, and sodium hydride have been commonly used for the preparation of alkoxides, with sodium hydride becoming increasingly

popular since it has become readily available in powder form. A useful variation, when DMSO is used as solvent, is to react sodium hydride with the solvent to give the corresponding carbanion, which is a powerful base.[95] The Haworth methylation procedure,[96] using dimethyl sulphate and sodium hydroxide in water, has been particularly valuable in the development of carbohydrate chemistry but is no longer widely used. This method is not very satisfactory for etherification of aliphatic alcohols but can be used for phenols. The fact that the method can be applied to carbohydrates is presumably due to their somewhat greater acidity compared with aliphatic alcohols.

Alkoxides are powerful bases and base-promoted elimination often competes with ether formation, particularly when using secondary or tertiary alkyl halides. To avoid strongly basic conditions, Purdie[97] advocated the use of silver oxide to promote *O*-alkylation reactions. Whilst silver oxide is a weaker base than, for example, sodium hydroxide, and therefore less effective in generating the alkoxide, it can provide electrophilic catalysis to the ionization of the C—halogen bond in the alkyl halide. Again, modern variants of the Purdie method involve dipolar aprotic solvents.[98] Similar electrophilic catalysis is presumably involved in the recently reported synthesis of ethers in high yields using mercury salts.[99] The Purdie method has been applied[100] to the synthesis of the optically pure ethyl ether of 1-phenylethanol, whereas attempted alkylation of this chiral alcohol by the Williamson method gives partially racemized product. Alkylation of thallium alkoxides (equation 37) has been recommended[101] as a useful modification of the Williamson

$$R^1OH \xrightarrow[C_6H_6]{TlOEt} R^1OTl \xrightarrow[MeCN]{R^2X} R^1—O—R^2 \qquad (37)$$

method for use with chiral readily racemized alcohols. Thus no racemization or epimerization is observed on alkylation of lactic, malic, or tartaric acid. The reaction proceeds readily at low temperature with primary alkyl halides and with primary or secondary non-benzylic hydroxy groups.

In the Williamson ether synthesis and its variants, the rate and course of the reaction, which may involve S_N1 or S_N2 type mechanisms (see Section 3.3.3), are influenced by the substrate structure including the nature of the leaving group and also by the solvent and temperature. Using ethoxide in ethanol as nucleophile the rates of reaction and extents of elimination are generally lower with sulphonates than with iodides or bromides, whereas sulphonates generally undergo solvolysis in ethanol faster than iodides or bromides. Competing elimination is more pronounced with secondary and tertiary halides (or sulphonates) than with simple primary halides. Branching or aryl substitution in the β-position of the halide promotes elimination and the Williamson method is therefore not a suitable method for etherification using β-aryl ethyl halides. Increasing substitution in the alkoxide is associated with increasing basicity and consequently more extensive elimination. Thus, for example, 1-bromo-octadecane gives predominantly alkene *via* elimination with potassium t-butoxide and predominantly ether *via* substitution with the weaker base sodium methoxide.[102] Furthermore, sulphonates of primary alcohols, which give almost exclusive substitution with potassium t-butoxide in t-butyl alcohol, undergo more rapid reaction and give up to 20% of elimination using the same base in DMSO because this solvent increases the basicity of the reagent.[103] From a practical point of view, in the synthesis of constitutionally unsymmetrical ethers by the Williamson and related methods, the preferred strategy is to use the alkoxide of the more substituted alcohol with the halide or sulphonate of the less substituted group to minimize elimination.

Two mechanisms for displacements of alkyl carboxylates can be envisaged; the normal reaction involves nucleophilic attack on the carbonyl group with acyl–oxygen bond fission to give a new alkoxide and exchanged ester (equation 38), but a second possibility, which is like the normal reaction of sulphonates, involves nucleophilic attack at the alkyl carbon with alkyl–oxygen bond fission to give an ether and the acid anion (equation 39). The former reaction is reversible and the latter is irreversible. A good yield of dimethyl ether

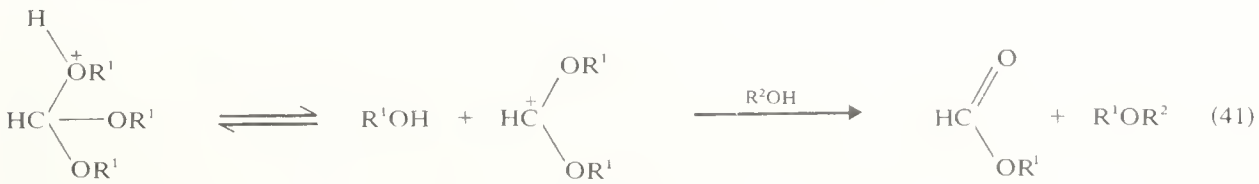
has been obtained by this method,[104] *e.g.* equation (40), but it has not been generally applied to the synthesis of mixed alkyl ethers presumably because ether exchange by the reversible reaction could give rise to mixtures of products.

$$R^1CO_2R^2 + R^3O^- \rightleftharpoons R^1CO_2R^3 + R^2O^- \quad (38)$$

$$R^1CO_2R^2 + R^3O^- \rightarrow R^3OR^2 + R^1CO_2^- \quad (39)$$

$$HCO_2Me + MeO^- \rightarrow Me_2O + HCO_2^- \quad (40)$$

Orthoesters of carboxylic acids can be used to alkylate alcohols under acid conditions; thus reaction of 3β-hydroxysteroids with trialkyl orthoformate and perchloric acid gives 3β-alkoxysteroids in good yield. The reaction presumably involves alkylation of the alcohol by an intermediate dialkoxycarbenium ion which is an ambident electrophile (see equation 41; *cf.* equation 20).



(41)

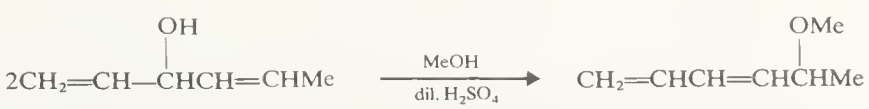
$$R^1OH + R^2\text{—}\overset{+}{O}H_2 \rightarrow R^1\text{—}O\text{—}R^2 + H_2O + H^+ \quad (42)$$

In the presence of acid catalysts, two molecules of alcohol can condense to give an ether (see equation 42). The role of the acid is to convert one of the hydroxy groups into a better leaving group. This synthesis is the most common method for preparing constitutionally symmetrical ethers from primary alcohols[105] (equation 43). Various acids have been used including sulphuric acid, phosphoric acid, and ion exchange resins. The reaction is particularly suitable for the synthesis of mixed ethers if R^1 and R^2 are primary and tertiary groups, respectively,[106] as in equation (44). Mesomeric stabilization of the cationic intermediate allows etherification to proceed under mild conditions[107] (equations 45 and 46). Rearrangements are encountered during acid-promoted etherification,[108] *e.g.* equation (46). Addition of triphenylacetic acid dissolved in 100% sulphuric acid to methanol gives[109] triphenylmethyl methyl ether rather than the ester (equation 47).

$$2EtOH \xrightarrow[140\,^\circ C]{\text{Conc. } H_2SO_4} EtOEt \quad (95\%) \quad (43)$$

$$EtOH + Bu^tOH \xrightarrow[70\,^\circ C]{15\%\ H_2SO_4} Bu^tOEt \quad (95\%) \quad (44)$$

$$2Ph_2CHOH \xrightarrow[75\,^\circ C]{85\%\ H_3PO_4} Ph_2CHOCHPh_2 \quad (90\%) \quad (45)$$



(46)

$$Ph_3CCOOH \xrightarrow[\text{ii, MeOH}]{\text{i, 100\% } H_2SO_4} Ph_3COMe + CO \quad (47)$$

Acidic hydroxy groups such as the enediol group in ascorbic acid react readily with diazomethane to give methyl ethers.[110] When diazomethane and alcohol mixtures are photolysed, the major products are ethers, formed by insertion of carbene into the O—H bond, and branched alcohols, formed by insertion into C—H bonds.[111] From t-butyl alcohol the major products are t-butyl methyl ether and 2-methylbutan-2-ol and the

O—H bond is found to be some 11 times more reactive than the C—H bond.[112] From competition studies it was established that the order of reactivity of alcohols towards insertion into the O—H bond is methanol > ethanol > isopropyl alcohol > t-butyl alcohol.[112] This order parallels the order of acidity of the OH group. Lewis acids promote the formation of ethers from diazomethane and alcohols. The most generally useful catalysts for this reaction are fluoroboric acid and boron trifluoride etherate, with which good to excellent yields of methyl ethers of simple primary and unhindered secondary alcohols are obtained.[113,114] Formation of ethyl ethers with diazoethane is less satisfactory.

Boron trifluoride etherate also catalyses the formation of ethers from diazoketones and alcohols (equation 48), in competition with formation of esters *via* the Wolff rearrangement.[115] Conflicting claims have appeared that copper catalysts promote formation of esters[116] by Wolff rearrangement (equation 49) or ethers[117] (equation 50), but the weight of evidence is in favour of the latter claim.

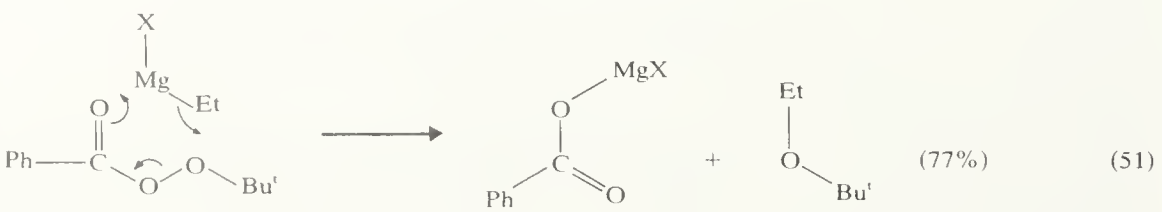
$$PhCOCHN_2 + MeOH \xrightarrow{BF_3\cdot Et_2O} PhCOCH_2OMe \quad (79\%) \qquad (48)$$

$$PhCOCHN_2 + MeOH \xrightarrow{CuO} PhCH_2COOMe \qquad (49)$$

$$PhCOCHN_2 + MeOH \xrightarrow{Cu\ bronze} PhCOCH_2OMe \quad (55\%) \qquad (50)$$

Reaction of diphenyldiazomethane with alcohols to give benzhydryl ethers proceeds without catalysts[118] and this facile synthesis, coupled with the ready removal of the protecting group, makes the benzhydryl group a potentially useful blocking group for hydroxy functions where other labile functional groups are present. Difluoromethyl ethers are obtainable from reaction of difluorocarbene with alcohols,[119] but other dihalomethyl ethers are not obtained by this method presumably because of their greater reactivity.

All methods for synthesis of ethers so far considered in this section have involved formation of the C—O bond in the ether by nucleophilic attack of oxygen on to electron-deficient carbon. Nucleophilic attack of carbanionoid reagents on to electron-deficient oxygen is another route to ethers. Thus reaction of Grignard reagents with peroxides or peresters gives ethers. Reaction of Grignard reagents from primary or secondary bromides with di-t-butyl peroxide gave t-butyl alkyl ethers, but the yields were not good.[120] Much better yields are obtainable from reaction of Grignard reagents with t-butyl perbenzoate under mild conditions in a reaction formulated as in equation (51). Di-t-butyl ether is obtained in 44% yield by this method.[121]



(51)

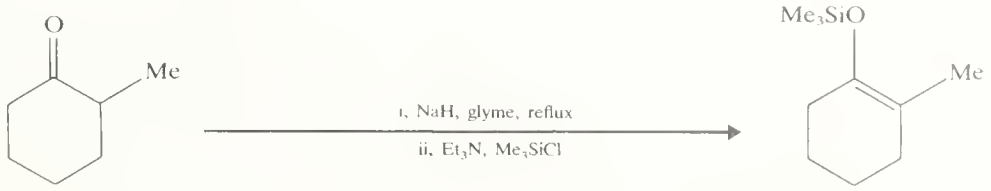
Silyl ethers are finding increasing use as protecting groups or reaction intermediates in organic chemistry.[122] These ethers are generally made[123] by displacements as shown in equations (52)–(54). In some cases, such as the chlorosilane in equations (52) and (53), the reagents used are analogous to those used for synthesis of carbon ethers but in other cases, *e.g.* the displacement of ammonia from hexamethyldisilazane in equation (54), the corresponding reaction in carbon chemistry is not a viable route to ethers.

$$C_4H_9OH + Me_3SiCl \longrightarrow C_4H_9OSiMe_3 \quad (76\%) + HCl \qquad (52)$$

$$HC{\equiv}CCH_2OH + Me_3SiCl \xrightarrow{C_6H_5N} HC{\equiv}CCH_2OSiMe_3 \quad (76\%) + C_6H_6NCl \qquad (53)$$

$$2CH_2{=}CHCH_2OH + Me_3SiNHSiMe_3 \longrightarrow 2CH_2{=}CHCH_2OSiMe_3 \quad (80\%) + NH_3 \qquad (54)$$

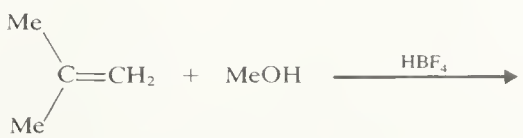
Whilst enol forms of β-carbonyl compounds can be *O*-alkylated to give enol ethers with diazoalkanes, enolate anions tend to be alkylated on carbon rather than oxygen. In contrast, trialkylsilylation of enolate anions gives good yields of silyl enol ethers[124] which are versatile synthetic intermediates (see Section 4.3.7). With constitutionally unsymmetrical ketones this reaction gives predominantly the more substituted enol ether (equation 55) in contrast to the synthesis of enamines where the less substituted product is preferred. Because of their greater resistance to hydrolysis, t-butyldimethylsilyl enol ethers are easier to handle than the trimethylsilyl derivatives.[125] The *N,O*-bis(trialkylsilyl)amides are among the most powerful silyl donors and can be used for direct silylation of carbonyl compounds[126] to give enol ethers.



(55)

4.3.5.2 Ethers by addition

Alcohols can be added to alkenes under acidic conditions to give ethers. The reaction, which involves protonation of the alkene to give a carbenium ion followed by nucleophilic addition of the alcohol, requires the use of an acid with a weakly nucleophilic conjugate base and obeys Markownikov's rule, *e.g.*[127] equation (56). The reason for the requirement



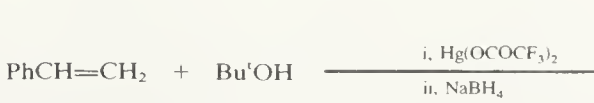
(56)

that the conjugate base of the acid should be weakly nucleophilic is that alcohols are weakly nucleophilic and in the second stage of the reaction there is a competition between the alcohol and the acid anion for the carbenium ion intermediate. As in other reactions involving carbenium ions, rearrangement of the alkene fragment is possible, as in equation (57). Excellent yields of ethers have been obtained from a variation of this reaction, which

(57)

also follows Markownikov's rule, involving solvomercuration of the alkene in alcohol solvent followed by demercuration, as in equations (58)–(60). Mercuric acetate is ineffective in promoting solvomercuration with tertiary alcohols, but mercuric trifluoroacetate

(58)



(59)

(60)

may be used with all types of alcohol.[128] The intermediate is demercurated with sodium borohydride under alkaline conditions. Rearrangement of the carbon skeleton is not observed even with substrates that are prone to rearrange, as in equation (58), but some anti-Markownikov addition occurs with branched alkenes or tertiary alcohols (see equation 60).

The intermediate obtained from solvomercuration of vinyl acetate with an alcohol and mercuric acetate readily loses mercuric acetate to give a vinyl ether[129] (equation 61), and similarly transvinylation of vinyl ethers can be achieved with mercuric acetate and an alcohol[130] (equation 62).

$$\begin{aligned} ROH + AcOCH{=}CH_2 &\longrightarrow \begin{matrix} RO \\ \diagdown \\ CHCH_2HgOAc \\ \diagup \\ AcO \end{matrix} \longrightarrow ROCH{=}CH_2 \\ + Hg(OAc)_2 & \qquad\qquad\qquad\qquad + Hg(OAc)_2 \end{aligned} \tag{61}$$

$$Me(CH_2)_{11}OH + EtOCH{=}CH_2 \xrightarrow{Hg(OAc)_2} Me(CH_2)_{11}OCH{=}CH_2 + EtOH \tag{62}$$

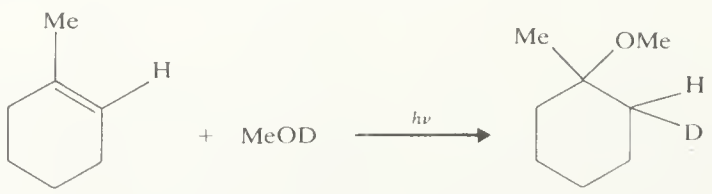
A novel two-step procedure for synthesis of ethers involves addition of the alcohol to the alkene in the presence of *N*-bromosuccinimide to give a β-bromoether followed by reduction with tributyltin hydride,[131] as in equation (63). The regioselectivity in the alkoxyhalogenation step is that expected for an ionic reaction and the product is that predicted by Markownikov's rule. This synthesis may be useful where the strongly basic conditions of classical procedures must be avoided.

$$CR^1_2{=}CR^1_2 \xrightarrow[\text{N-Br}]{R^2OH} CR^1_2Br{-}CR^1_2OR^2 \xrightarrow{Bu_3SnH} CHR^1_2CR^1_2OR^2 \tag{63}$$

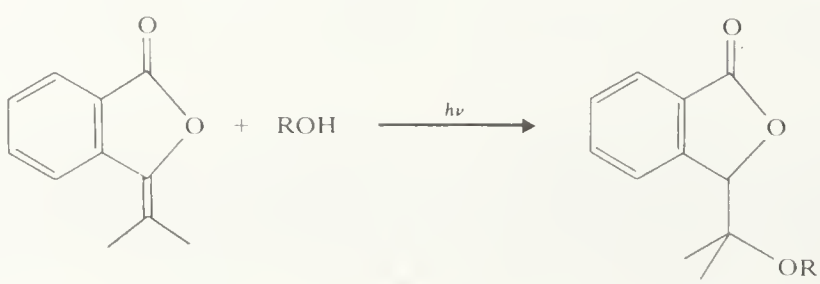
In contrast to radical-induced addition of thiols to alkenes giving thioethers, the corresponding radical-induced addition of alcohols to alkenes is not a viable route to ethers. Polymerization is the major reaction and the principal low-molecular weight products are secondary or tertiary alcohols.[132] The reason for this difference in reaction between thiols and alcohols lies in the differences in bond energy; H—O bonds are stronger than H—C bonds, which are stronger than H—S bonds. Therefore, in free radical reactions with thiols, hydrogen abstraction from H—S bonds is preferred whereas with alcohols there is preferential abstraction of hydrogen from H—C bonds rather than from H—O bonds and, furthermore, polymerization is preferred to chain transfer.

Catalysts, containing molybdenum and vanadium derivatives, for the addition of alcohols to alkenes under pressure have been patented[133] but the low yield (25%) obtained from the addition of methanol to 2-methylprop-1-ene coupled with the need for an autoclave will probably prevent this from becoming a general laboratory method for synthesis of ethers.

Photoinitiated addition of alcohols to alkenes can be achieved, but this is believed to be an ionic rather than a radical reaction. The reaction follows Markownikov's rule and with MeOD leads to incorporation of deuterium, as in equation (64). With seven- and six-membered cyclic alkenes the reaction is believed to involve formation of a strained *trans*-olefin of enhanced basicity which is protonated by the alcohol to give a carbenium ion which either adds alcohol or rearranges.[134] Other examples, *e.g.* equation (65), involve addition to systems where the intermediacy of strained double bonds cannot be invoked.



(64)

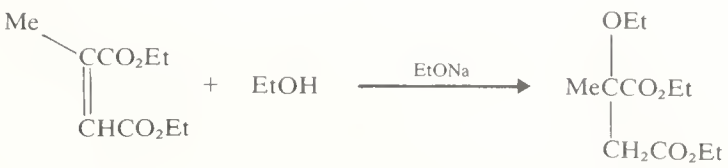


(65)

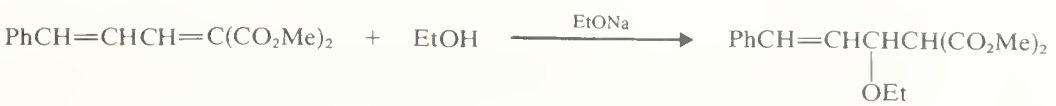
The presence of electron-withdrawing groups adjacent to a double bond facilitates nucleophilic addition of alcohols to give ethers. Conjugation to carbonyl or cyano groups[135] or substitution by fluorine[136] are effective activating influences, *e.g.* equations (66)–(71).

$$ROH + CH_2{=}CHCN \xrightarrow{ROMetal} ROCH_2CH_2CN \quad (66)$$

(67)



(68)



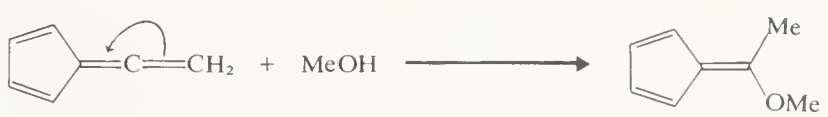
(69)

$$CF_2{=}CFCl + MeOH \xrightarrow{MeONa} MeOCF_2CFClH \quad (70)$$

$$CF_2{=}C(CF_3)_2 + MeOH \longrightarrow MeOCF_2CH(CF_3)_2 \quad (71)$$

The orientation of addition is consistent with attack of the alkoxide ion on the double bond to give the more stabilized carbanion which is then protonated by the medium. In the cyanoethylation reaction (equation 66) the order of reactivity of various alkoxides dissolved in their parent alcohol is[137] $Pr^iO^- > EtO^- > MeO^-$, in parallel with the basicity order, and identical rates were obtained with lithium, sodium, or potassium derivatives of the same alcohol, supporting the hypothesis that attack of alkoxide ion is the first step. In the example shown in equation (68), both ends of the double bond carry activating groups and addition of ethoxide occurs at the more substituted end. However, in equation (69), attack of the nucleophile has occurred at the less substituted β-position rather than at the more substituted, but similarly conjugated, γ-position. In the case of addition to constitutionally unsymmetrical fluoroalkenes[136] the nucleophile attacks a CF_2 group and, in the example shown in equation (71), the perfluoroalkene is so reactive towards nucleophilic attack that a basic catalyst is not required.

Enol ethers may be obtained by base-promoted addition of alcohols to allenes or alkynes,[138] as in equations (72) and (73).



(72)

$$Me(CH_2)_{11}OH + HC{\equiv}CH \longrightarrow Me(CH_2)_{11}OCH{=}CH_2 \quad (73)$$

In the mercuric ion catalysed addition of an alcohol to an alkyne, which would give an enol ether, two molecules of alcohol usually add to give an acetal (equation 74). However, subsequent elimination of one molecule of alcohol gives[139] the enol ether, as in the synthesis of the anaesthetic fluoroxene shown in equation (75).

$$CF_3CH_2OH + HC{\equiv}CH \xrightarrow[BF_3]{HgO} CH_3CH(OCH_2CF_3)_2 \quad (74)$$

$$CH_3CH(OCH_2CF_3)_2 \xrightarrow[240\text{–}280\,^\circ C]{clay} CH_2{=}CHOCH_2CF_3 + CF_3CH_2OH \quad (75)$$

4.3.5.3 Ethers by reduction

A number of reagents are available to reduce acetals or hemiacetals to ethers, as illustrated in equations (76)–(81). These reagents are acidic and the reaction may be

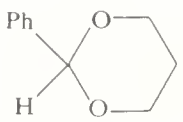
$$(C_6H_{11}O)_2CMe_2 \xrightarrow[HCl]{H_2,\ Rh/Al_2O_3} C_6H_{11}OCHMe_2 \quad (76)^{140}$$

$$Me_2CHCHO + MeOH \xrightarrow[HCl]{H_2,\ PtO} Me_2CHCH_2OMe \quad (77)^{141}$$

$$PhCHO \xrightarrow{H_2,\ Co(CO)_8} PhCH_2OCH_2Ph \quad (78)^{142}$$

$$Me_2CHCH_2CH(OEt)_2 \xrightarrow{Bu^i_2AlH} Me_2CHCH_2CH_2OEt \quad (79)^{143}$$

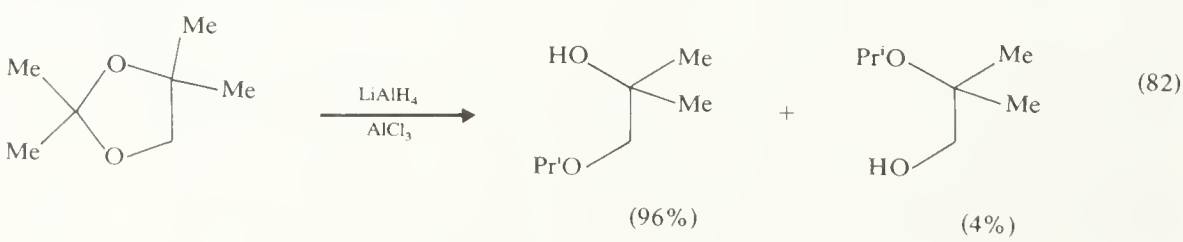
$$PhCH(OEt)_2 \xrightarrow[ZnCl_2]{Et_3SiH} PhCH_2OEt \quad (80)^{144}$$



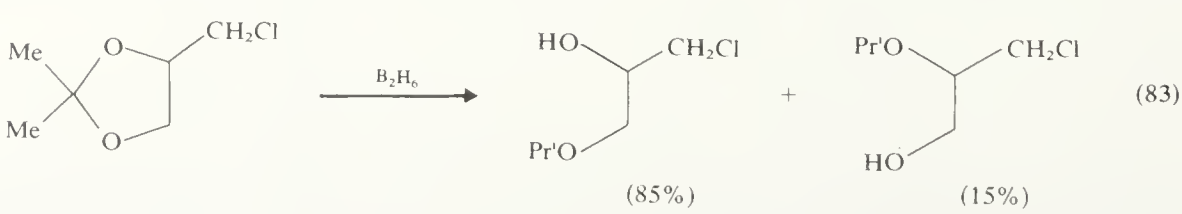
$$\xrightarrow{B_2H_6} PhCH_2OCH_2CH_2CH_2OH \quad (81)^{145}$$

considered to involve reduction of an intermediate alkyloxycarbenium ion derived by acid-catalysed loss of alcohol or water from the acetal or hemiacetal, respectively. Because the simple ethers obtainable from this type of reaction are generally readily available by other simpler or cheaper means, the method is only suitable for special applications. One recent example involves simultaneous reduction of an acetal and hydroboration of a triple bond.[146]

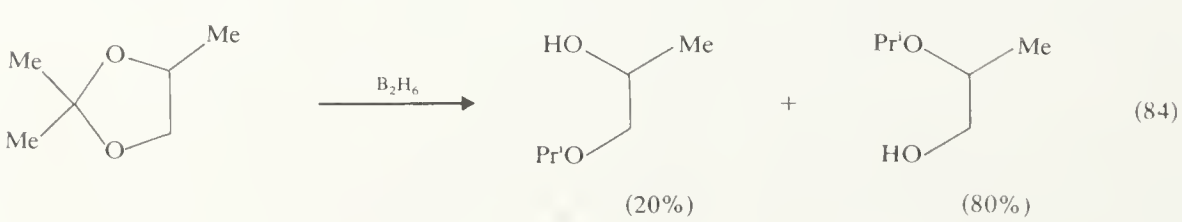
The method is particularly suitable for the synthesis of certain partially substituted derivatives of polyols including methylated sugars by reduction of cyclic acetals, *e.g.* equations (82)–(85), because of the marked regioselectivity observed in formation of cyclic acetals of polyols and sugars. The direction of opening of constitutionally unsymmetrical acetals depends on stereochemical as well as constitutional influences,[145,147] as illustrated in equations (82)–(85).



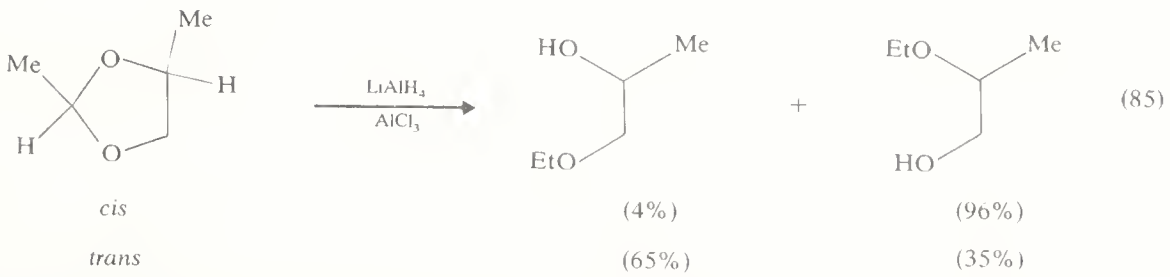
(82)



(83)



(84)



(85)

cis (4%) (96%)

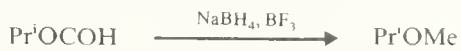
trans (65%) (35%)

Under the usual reaction conditions, acetals are sufficiently resistant to cleavage by Grignard reagents to permit their use as protecting groups. Under more vigorous conditions acetals are cleaved to ethers but the low yields of recovered product limit the applicability of the method.[148] However, intramolecular reactions of this type are potentially useful routes to cyclopropyl ethers,[149] as in equation (86).

(86)

Good yields of cyclic ethers have been reported in the cleavage of 1-aryloxytetrahydropyrans with Grignard reagents and titanium tetrachloride.[150] However, the applicability of the method to synthesis of mixed aliphatic ethers is limited by the inaccessibility of mixed aryl alkyl acetals.

Reduction of esters with a complex hydride usually gives alcohols, but ethers can be obtained using certain hydrides, the combination of boron trifluoride and sodium borohydride being most satisfactory (equation 87). The yields are higher with increased branching in the alkyl group; thus a 70% yield of 24-t-butoxy-5β-cholane was obtained by reduction of 5-β-cholanic t-butyl ester.[151]



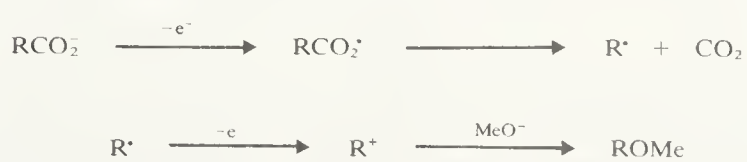
(87)

A method for reduction of esters to ethers which is complementary to the above method, because it gives best yields of ethers from primary alkyl esters, involves reaction with trichlorosilane under radical conditions, as in equation (88). The hydrocarbon arising by fission of the alkyl–oxygen bond is the principal by-product and the yield of this by-product increases with increasing substitution in the alkyl group.[152]

(88)

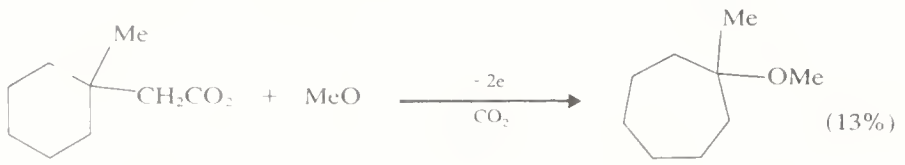
4.3.5.4 Ethers by oxidation

In the Kolbé anodic decarboxylation of carboxylic acids, methanol is frequently used as solvent and methyl ethers can be formed as by-products.[153] The ethers are believed to arise by oxidation of electrolytically produced radicals to carbenium ions, which then react with the alcohol solvent as in equation (89). With simple aliphatic acids and platinum



(89)

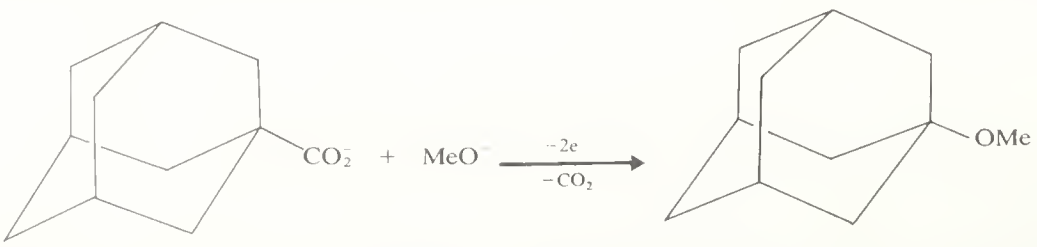
anodes the ether is only a minor product, but yields of ether increase as carbenium ion stabilizing groups are introduced into the α-position of the acid and when elimination is not possible, *cf.* equations (90) and (91). Ether products are also favoured by using carbon anodes and higher voltages.[154] The intermediacy of carbenium ions in the reaction is supported by the observation of rearranged products arising from Wagner–Meerwein shifts in the intermediate ion, *e.g.* equation (90).



(90)

$$Ph_2CHCO_2^- + MeO^- \xrightarrow[-CO_2]{-2e^-} PhCHOMe \quad (80\%) \qquad (91)$$

The principal interest in this type of reaction has been as a route to unstable or 'hot' carbenium ions. These ions generally do not undergo selective reaction to give single products and therefore the preparative value of this method is limited to special cases, such as equation (92).[155] A further limitation is the possible oxidation of the alcohol which essentially limits the applicability of the method to synthesis of methyl ethers.



(92)

Electrochemical methoxylation of alkenes in methanol can be used for the synthesis of ethers; the type of product and yield obtained depends on the supporting electrolyte, the anode material, and the substrate structure.[156] With strongly basic electrolytes and platinum anodes, alkenes conjugated to aryl or alkoxyl groups give good yields of glycol dimethyl ethers[157] or β-methoxyacetals,[158] respectively, as in equations (93)–(96). With

$$PhCH{=}CH_2 + 2MeO^- \xrightarrow[\text{Pt anode}]{-2e^-} PhCH(OMe)CH_2OMe \qquad (93)$$

$$PhCH{=}CHPh + 2MeO^- \xrightarrow[\text{Pt anode}]{-2e^-} PhCH(OMe)CH(OMe)Ph \qquad (94)$$

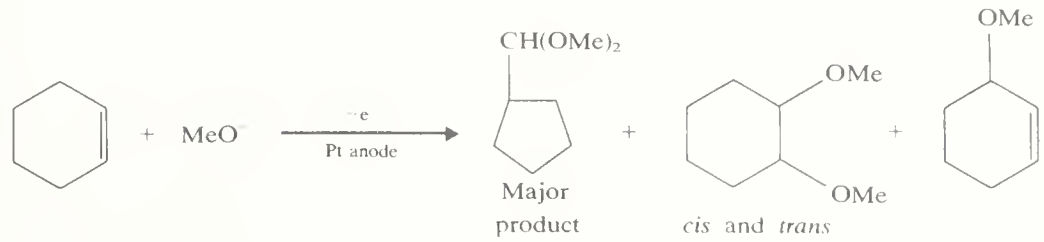
$$PhCH{=}CHCH{=}CHPh + 2MeO^- \xrightarrow[\text{Pt anode}]{-2e^-} PhCH(OMe)CH{=}CHCH(OMe)Ph \qquad (95)$$

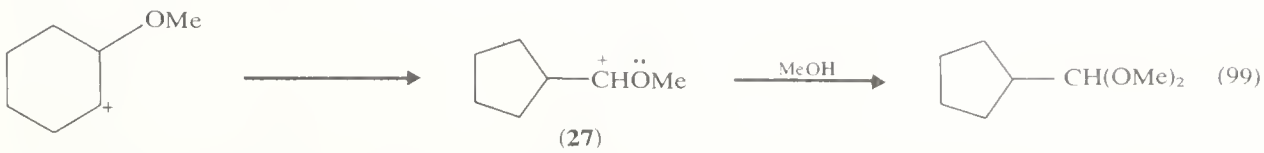
$$ROCH{=}CH_2 + 2MeO^- \xrightarrow[\text{Pt anode}]{-2e^-} ROCH(OMe)CH_2OMe \qquad (96)$$

these substrates, which can stabilize a cationic intermediate, the reaction involves loss of an electron from the double bond to give a radical cation, addition of methoxide, loss of another electron, and, finally, addition of a second methoxide ion. Both (*Z*)- and (*E*)-1,2-diphenylethylene give a mixture of diastereoisomeric products, but the major product in each case is the one that would arise by *syn* addition (equation 94). With conjugated dienes under these conditions 1,4-addition is also observed, *e.g.* equation (95). Arylcyclopropanes behave in a similar way to the above alkenes and undergo anodic methoxylation to give excellent yields of 1,3-dimethoxy derivatives,[159] *e.g.* equation (97).

(97)

Under these anodic methoxylation conditions, simple alkenes other than ethylene give a mixture of dimethoxy compounds and allyl ethers[160] (equation 98). The observed skeletal rearrangement is expected for a reaction involving carbenium ions because of the extra stability of the resonance-stabilized cation (**27**) (equation 99). The addition of lithium perchlorate — or other ions which are readily discharged to give radicals — to the electrolyte promotes the conversion to allyl ethers. The formation of allyl ethers is therefore believed to involve abstraction of hydrogen from the allylic position by anodically produced radicals followed by oxidation to the allylic carbenium ion, which reacts with solvent.

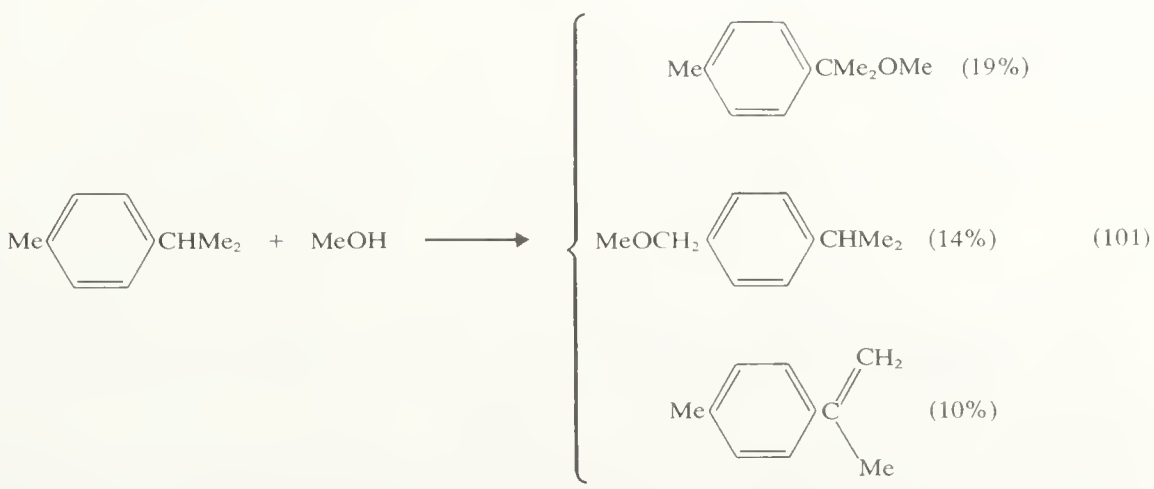




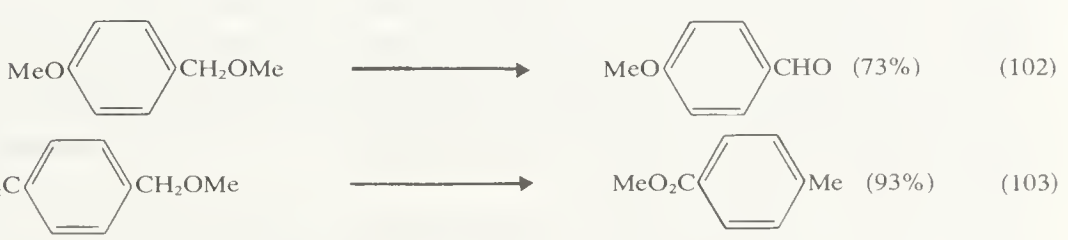
(**27**)

Using a graphite anode and an electrolyte containing iodide or perchlorate ions as well as methoxide, conjugated alkenes give predominantly methoxy dimers,[161] *e.g.* equation (100). The effect of the anode on the course of this reaction contrasts with that observed in the Kolbé reaction, where a platinum anode favours coupling and a carbon anode favours the formation of products derived from carbenium ions.

Electrochemical oxidation in alcoholic media of benzylic C—H groups to give ethers has been achieved, *e.g.* equation (101); the yields are generally low and the corresponding alkenes are also obtained.[162]



In electrochemical syntheses of benzyl ethers, two types of wasteful reaction of the ether have been recognized.[163] The ether may be further oxidized at the anode, particularly when the benzene ring carries an electron-releasing group, *e.g.* equation (102), or reductively cleaved at the cathode, particularly when the benzene ring carries an electron-withdrawing group, *e.g.* equation (103).

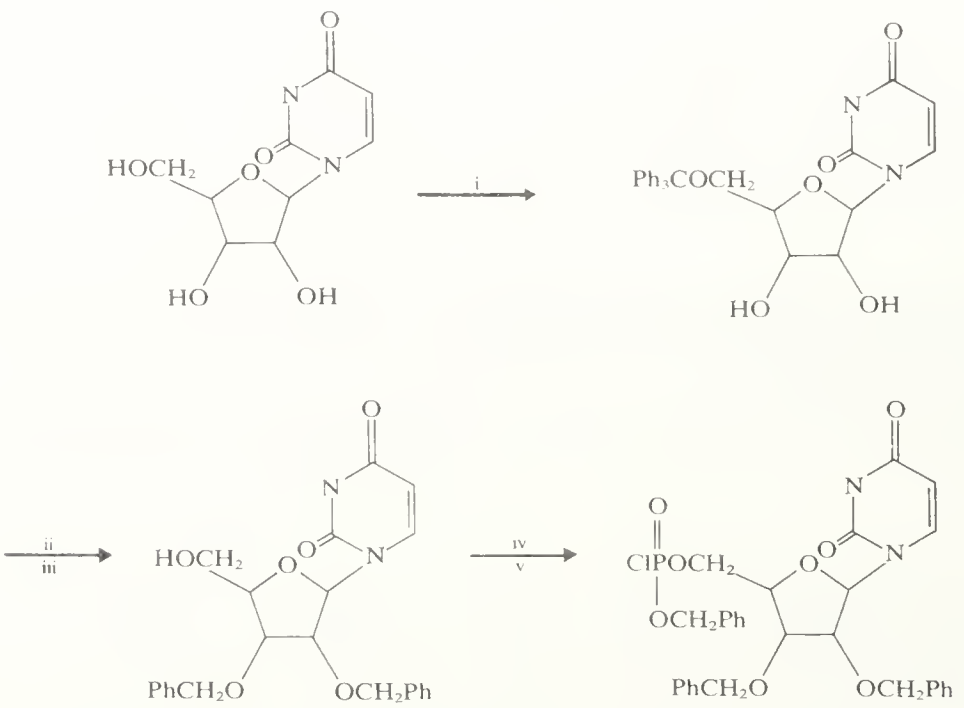


4.3.5.5 Ethers from other ethers

The chemical stability of the ether linkage allows various degradative methods to be used in structural studies without affecting the ether links and a wide range of synthetic

procedures to be used to elaborate simple ethers into more complex structures. For example, the resistance of ether groups to cleavage and migration during hydrolysis, reduction, and derivatization is an important factor in making methylation analysis one of the most reliable methods for determination of polysaccharide structures.[164] However, this resistance to cleavage limits the use of ether groups for blocking hydroxy functions during synthetic sequences to special cases.[165] One such special case is when the final product is sufficiently stable to withstand relatively vigorous deblocking conditions. Some ether groups which can be widely applied to blocking because of their facile removal are benzyl, other arylmethyl, and silyl ethers (see Chapter 13).

Some key steps in the synthesis[166] of uridine 5′-phosphate derivatives, shown in Scheme 1, illustrate the use of arylmethyl blocking groups. Selective reaction of the primary



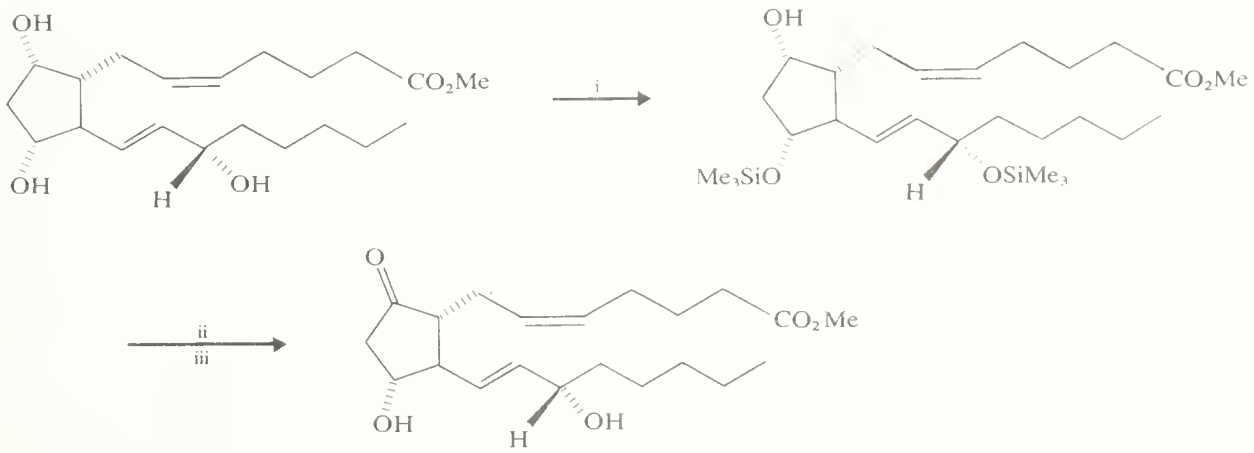
i, Ph_3CCl, C_5H_5N; ii, $PhCH_2Cl$, KOH; iii, HBr, AcOH; iv, $PhCH_2OP(O)OP(O)(OPh)_2$. 2,6-lutidine; v, *N*-chlorosuccinimide.

SCHEME 1

hydroxy group of uridine can be achieved by reaction with triphenylmethyl chloride whereupon benzylation gives the 2′,3′-di-*O*-benzyl-5′-triphenylmethyl derivative. Selective removal of the triphenylmethyl group without affecting the benzyl groups is accomplished by brief treatment with hydrogen bromide in acetic acid. After esterification of the exposed hydroxy group, during which the benzyl ether groups are unaffected, the benzyl groups are finally removed by hydrogenolysis. Silyl ether groups are being increasingly used for blocking in this type of synthesis.[167] Silyl ether blocking groups have also been used to achieve the required regioselectivity in the conversion of F- into E-prostaglandins, as shown in Scheme 2. The methyl ester of the F-prostaglandin is converted regioselectively into its 11,15-bis(trimethylsilyl) ether which can be oxidized without affecting the ether groups, and then the product is desilylated to give the methyl ester of the E-prostaglandin in fair yield.[168]

Other groups which are widely used for blocking hydroxyls and which are often named as ethers, such as tetrahydropyran-2-yl, 4-alkoxytetrahydropyran-4-yl, and 2-methoxyethoxymethyl, are readily hydrolysed because they are acetals rather than ethers.

In the examples mentioned so far in this section the ether group is generally present in the molecule simply as an inert appendage that plays no role in the reactions until the final deblocking step and, whilst further examples could be cited covering most types of



i, Me_3SiNEt_2; ii, CrO_3, C_5H_5N; iii, AcOH.

SCHEME 2

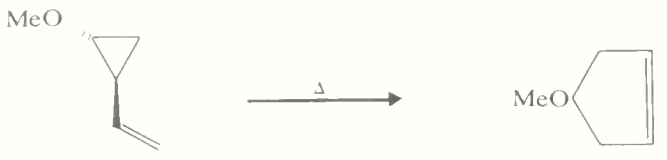
reaction in most branches of chemistry, such cases will not be considered further. In the remainder of this section attention will be focused on reactions in which the ether group already present is close to the reacting site and plays an important role in the reaction.

An ether function may influence the reactions of the molecule in which it is located because the ether group can, by virtue of its electronic characteristics, alter the stability of the initial state, the transition state, or the final state of the reaction and thereby influence either the rate or the equilibrium of that reaction. The effect of an ether group on reactivity will be considered in more detail in Section 4.3.6, but generally the presence of the ether oxygen stabilizes a carbenium ion or a free radical at the α-position. Therefore reactions which involve generation of these transient species at the α-position of an ether will be facilitated. Some photochemical reactions, and reactions of α-haloethers and unsaturated ethers leading to other ethers, fall within the scope of this section but will be considered separately in Sections 4.3.6, 4.3.7, and 4.3.8, respectively.

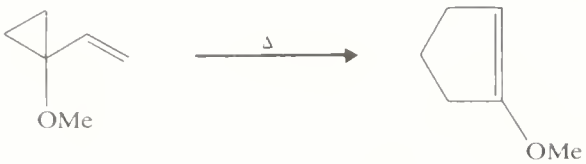
Some reactions have been mentioned already, in the sections devoted to solvation by ethers, where the presence of an ether group has an important effect on reactivity of another group within the molecule. Thus in the solvolysis of alkoxyalkyl halides the ether group can cause a dramatic increase in reactivity, and in reactions of carbenes with some ethers the ether groups can influence the position of attack of the carbene (see Section 4.3.4.6). Chelation of zinc chloride to the ether oxygen in 2-methoxyethoxymethyl acetals is important in the facile cleavage of these derivatives (see Section 4.3.4.7).

The presence of an alkoxy substituent at the migrating terminus greatly facilitates [1,3]-sigmatropic rearrangements of carbon atoms. Thus a 7-alkoxy substituent in norbornadiene strikingly alters the thermal rearrangement;[169] the reaction rate is some 10^6 times faster and the 7-substituted compound rearranges only to isomeric cycloheptatrienes (equation 104), whereas the parent compound gives a mixture of different products. In both examples shown in equations (105) and (106) the methoxy group increases the rate of rearrangement, the effect being more marked in the former case.[170] Similarly, substitution of alkoxy groups at the migrating carbon atom enhances the rate of the methylenecyclopropane rearrangement,[171] *e.g.* equation (107). The rate enhancement observed in these rearrangements is believed to be due to stabilization of diradical intermediates by the ether oxygen.

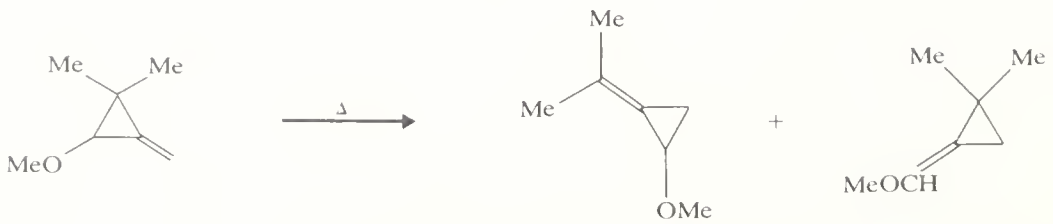
(104)



(105)

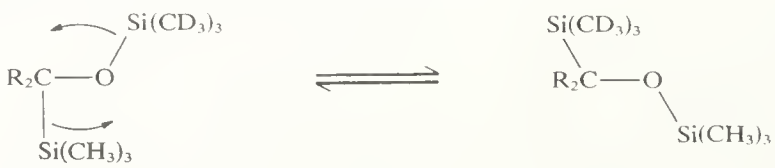


(106)



(107)

Recently a new class of rearrangement, termed a dyotropic rearrangement, has been recognized. The rearrangement involves simultaneous exchange of groups on adjacent atoms and has been achieved[172] with silyl ethers, as in equation (108). The carbon ether analogue of this reaction is forbidden by orbital symmetry and therefore the reaction is not likely to be generally applicable to ethers.



(108)

4.3.6 REACTIONS OF ETHERS

The feature of ethers which is most important in determining the chemical and physical properties of this class of compound is the presence of the oxygen atom with its lone pair of electrons. The ability of ethers to donate electron density from these lone pairs to a variety of acceptors is discussed in Sections 4.3.4.2–4.3.4.7. In this section the effect of the oxygen atom on electron availability within the ether molecule, and therefore reactivity, will be considered.

Because of the greater electronegativity of the oxygen atom compared with carbon, the C—O bond will be polarized and alkoxy groups will attract electrons inductively. The effect of this inductive withdrawal of electron density is most marked at the α-carbon atom and rapidly diminishes with distance through space or along a saturated chain of atoms. The direction of the effect is such as to destabilize a carbenium ion intermediate and therefore slow down solvolysis reactions, but it may facilitate hydrogen abstraction from the α-position.[173] In contrast to the above effect, because of the presence of the lone electron pairs on the oxygen atom, alkoxy groups can release electron density on demand to stabilize adjacent cations, *e.g.* (**28**), or radicals, *e.g.* (**29**), by resonance. This effect can only operate at the α-position or positions conjugated to the α-position.

(**28**)

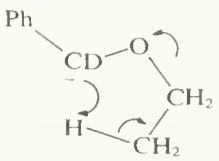
(**29**)

The influence of the inductive withdrawal of electron density by the alkoxy group can be illustrated by reference to the rates of solvolysis of alkoxyalkyl sulphonates shown in Table 8. The rates of reaction of both 2- and 3-alkoxy derivatives are slightly lower than the rate for the standard compound, the effect being more marked when the alkoxy group is closer to the developing carbenium ion.

The polarization of the C—O bond in ethers caused by the different electronegativity of carbon and oxygen is not sufficiently marked to make the bond generally susceptible to cleavage by nucleophilic attack at the α-carbon. An alternative way to reach the same conclusion is to consider the stability of the products of such a reaction. It is apparent that the RO^- anion is not a good leaving group because there is no effective delocalization of the charge and therefore the only circumstances where an RO^- anion will be expelled are when the ether is attacked by powerfully nucleophilic and strongly basic reagents or when the charge on the RO^- is delocalized. It is therefore not surprising that simple dialkyl ethers are stable to alkaline hydrolysis.

Cleavage of ethers by alkyl-sodium or -lithium reagents occurs by β-elimination because an alkene and an alkoxide are formed[174] (equation 109). This cleavage reaction is useful in the determination of polyether structure (see Section 4.3.9). Deuterium labelling studies suggest that the first step in the cleavage of benzyl ethyl ether by propylsodium is removal of a benzylic hydrogen followed by an intramolecular elimination reaction,[175] as in equation (110). In contrast to dialkyl ethers, methyl aryl ethers are cleaved by nucleophiles such as LiI, presumably because of more effective stabilization of the phenoxide ion.[176]

$$C_6H_{13}CH(OMe)Me \xrightarrow{PrLi} C_6H_{13}CH{=}CH_2 + LiOMe \qquad (109)$$



$$\xrightarrow{\qquad} PhCHDO^- + CH_2{=}CH_2 \qquad (110)$$

Facile β-elimination of the alkoxy group can occur when an ether group is in the β-position relative to an electron-withdrawing group (equation 111). The explanation for this facile cleavage is presumably that the electron-withdrawing group can stabilize a negatively charged transition state and therefore promote an *E*1cb-like elimination in which the nature of the leaving group is less important. From the preparative standpoint the reaction is potentially useful in special cases for blocking hydroxy groups with an ether function which can be removed under alkaline conditions,[177] or for generating useful intermediates[178] (equation 112). Other ether groups which can be cleaved by β-elimination reactions but which have not been widely used include β-haloether groups,[179] *e.g.* equation (113).

$$ROCH_2CH_2CN \longrightarrow RO + CH_2{=}CHCN + H^+ \qquad (111)$$

$$MeOCH_2CH_2COCH_2OMe \xrightarrow{KOH} CH_2{=}CHCOCH_2OMe \qquad (112)$$

$$CH_2{=}CHCH_2CH(OEt)CH_2Br \xrightarrow{Zn} CH_2{=}CHCH_2CH{=}CH_2 \qquad (113)$$

When electron density is donated from an ether to an acid the oxygen atom develops oxonium ion character to a greater or lesser extent, depending on the strength and nature of the acid. Consequently the complexed ether becomes more susceptible to nucleophilic attack at the α-carbon atom or attack by base at a β-hydrogen, leading to cleavage of the original C—O bond. Thus the essential requirements for reagents to cleave ethers are an acid to complex with the ether oxygen and provide electrophilic assistance to the C—O bond breaking and a nucleophile or base that is effective under the acidic conditions. Even with strong acids the rate of hydrolysis of simple ethers is low.[180] Concentrated hydriodic

acid, which is a strongly acidic solution containing the powerful nucleophile I^-, is probably the most effective reagent for cleavage of ethers in aqueous medium. This reagent is used in the classical analytical method for determination of methoxy groups,[181] which are converted to volatile iodomethane. It can be used in preparative reactions in certain cases, for example in synthesis of inositols from their naturally occurring methyl ethers[182] (equation 114).

$$C_6H_6(OH)_5OMe \xrightarrow{HI} C_6H_6(OH)_6 + MeI \qquad (114)$$

Mechanistic aspects of the cleavage of ethers with mineral acids, including reaction under anhydrous conditions, have been reviewed.[183] The evidence supports the operation of an A_2 mechanism for the cleavage with hydrogen halides of primary aliphatic ethers with a shift towards the A_1 mechanism with branching at the α-position. A consequence of the operation of the A_2 mechanism is that with unsymmetrical ethers the halide of the less hindered alkyl group is obtained (equation 115).[184] For cleavage of primary ethers with sulphuric acid a change from the A_2 to the A_1 mechanism on increasing the acid concentration has been observed.[22] The acid-catalysed cleavage of alkyl t-butyl ethers with carboxylic acids[185] provides a route to esters, as in equation (116).

$$Bu^tOBu^n + HI \longrightarrow Bu^tOH + Bu^nI \qquad (115)$$

$$Bu^tOMe + RCO_2H \xrightarrow{H^+} RCO_2Me + Me_2C{=}CH_2 + H_2O \qquad (116)$$

Ethers form complexes with Lewis acids as well as with proton acids and there are a number of reagents for cleavage of ethers, often at fairly low temperatures, which depend on this type of acid catalyst. Most of these reagents have a halide ion as the nucleophile and usually the products are an alkoxy derivative of the Lewis acid and a haloalkane, but in some cases an alkene is the second product, particularly with secondary or tertiary ethers. Examples of reagents in this category are thionyl chloride–tin(IV) chloride,[186] acetyl chloride–zinc chloride,[187] phosphoryl chloride–DMF,[188] pyridine iodoborane,[189] iodine–sodium borohydride,[190] dichloromethoxymethane–zinc chloride,[191] triphenylphosphonium bromide,[192] acetic anhydride–iron(III) chloride,[193] bis(trimethylsilyl)mercury,[194] and acetyl methanesulphonate.[195] In the last case, esters are obtained. With most of these reagents the cleavage of constitutionally unsymmetrical aliphatic ethers gives the primary alcohol together with the halide or alkene derived from the secondary or tertiary group, *e.g.* the cleavage with boron trichloride[196] shown in equation (117) (*cf.* equation 115). These results are consistent with the rate-limiting step being heterolysis of the complexed ether to give a carbenium ion. In contrast, in cleavage of sugar methyl ethers the secondary alcohol is obtained.[197] In this case the secondary sugar carbenium ion would be destabilized by the inductive effect of many oxygen substituents.

$$Bu^tOBu^n \xrightarrow{BCl_3} Bu^tCl + Bu^nOH \qquad (117)$$

The ability of the ether oxygen to facilitate the generation of a radical or carbenium ion at the α-position is believed to be the crucial factor in directing the reaction of oxidizing agents to this position. Two general types of mechanism for oxidation of ethers can be envisaged involving abstraction of hydrogen radicals, as in the mechanism proposed for autoxidation[198] (equation 118), or abstraction of hydride ion as proposed for oxidation by bromine[199] (equation 119). In both cases the intermediate can only be effectively resonance stabilized if the hydrogen is removed from the α-position. Because both alkyl and aryl groups can stabilize adjacent radicals or cations, substitution in the α-position should increase the rate of oxidation where loss of hydrogen is the rate-limiting step.

$$R^{\cdot} + H{-}CR_2OR \longrightarrow RH + R_2\dot{C}OR \longrightarrow \text{Products} \qquad (118)$$

$$Br{-}Br \quad H{-}CR_2OR \longrightarrow R_2\overset{+}{C}OR \longrightarrow \text{Products} \qquad (119)$$

Generally, ethers are more resistant to oxidation than aldehydes or acetals, which are the first products of oxidation of primary ethers, and therefore further oxidation to acids or esters is common. In some cases the acetals or aldehydes may be obtained.[200] Because esters or acetals can be readily hydrolysed, oxidations provide a method for cleavage of ethers. Reagents which have been used to oxidize ethers include bromine,[199] chromic oxide–acetic acid,[201] trichloroisocyanuric acid,[202] mercuric acetate,[199] carbenium ions,[203] and electrochemical oxidation.[200] In oxidation with chromic oxide, methyl ether groups are selectively oxidized (equation 120).

$$Me(CH_2)_{15}OMe \xrightarrow{CrO_3,\ AcOH} Me(CH_2)_{15}OCHO \qquad (120)$$

Ethers tend to autoxidize readily in the presence of air or oxygen at normal temperatures to give peroxides.[204] This autoxidation presents a potential hazard to users of ether solvents because the peroxides, which concentrate in the residue on evaporation, can detonate. Therefore before evaporating ether solutions to dryness the solution should be tested and, if necessary, any peroxide removed.[205] Autoxidation commences by production of radicals and so any radical source is an effective catalyst for autoxidation. As well as a range of organic initiators, salts of manganese, iron, cobalt, copper, and lead greatly accelerate autoxidation by catalysing decomposition of peroxides into radicals.[206]

Aliphatic ethers are generally quite resistant to reductive cleavage, but arylmethyl ethers are exceptional and can be readily cleaved by catalytic hydrogenolysis,[207] dissolving metal reduction,[208] or electrochemical reduction.[209]

4.3.6.1 The Wittig rearrangement

Certain ethers undergo base-promoted rearrangement to give an isomeric alcohol, as in equation (121). The rearrangement was discovered and explored by Wittig[210] and co-workers and is called the Wittig rearrangement. The scope and mechanism of the

$$CH_2{=}CHCH_2OCH_2CH{=}CH_2 \xrightarrow[\text{ii, } H_2O]{\text{i, PhLi}} CH_2{=}CHCH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH{=}CH_2 \qquad (121)$$

rearrangement has been reviewed.[211] Wittig suggested that a carbanionic intermediate is involved because kinetic studies show the rearrangement to be first order in ether and base, and the ethers which rearrange most readily are those which have relatively acidic α-hydrogens such as benzyl, allyl, or phenacyl ethers. Further studies of relative rates of rearrangement of various alkali metal salts of phenyl benzyhydryl ether suggest that the cation is coordinated with the oxygen atom rather than the carbanion, giving an ylide intermediate which undergoes rearrangement *via* a [1,2]-shift of the unmodified alkyl group, as in equation (122).

$$PhCH_2OR \xrightarrow{PhLi} \underset{\displaystyle Li^+}{PhCHOR} \rightleftharpoons \underset{\displaystyle Li}{PhCH{-}\overset{+}{O}{-}R} \longrightarrow \overset{\displaystyle R}{\underset{|}{Ph{-}CH}}{-}OLi \qquad (122)$$

Studies of migratory aptitudes of different groups, which show increasing tendency to migrate in the following sequence, benzyl or allyl > alkyl > aryl, suggested a mechanism involving nucleophilic attack of the carbanion on to the α-carbon of the migrating group (S_Ni mechanism), but other evidence is not consistent with this mechanism.[211] If the rearrangement is considered as a sigmatropic shift,[212] this [1,2]-shift in an anion, which involves four electrons, would be symmetry allowed with inversion of configuration at the migrating group, but symmetry forbidden with retention of configuration. The

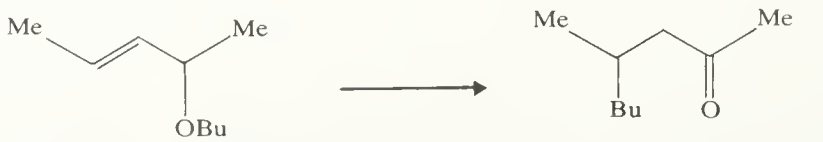
stereochemistry of rearrangement of chiral benzyl 2-butyl ether and benzyl 2-phenyl-2-butyl ether brought about by butyl-lithium in THF at −60 °C was explored[213] under conditions where substrate and product are configurationally stable. The 2-butyl groups migrate with 60% retention of configuration and the 2-phenyl-2-butyl groups migrate with 90% retention of configuration. These stereochemical results suggest that the mechanism is not a one-step pericyclic reaction but suggest a two-step cleavage then recombination scheme.

The observed migratory aptitudes of alkyl groups, which are in the order methyl > ethyl > isopropyl > t-butyl and adamantyl > 1-norbornyl, follow the order of radical stability[214] rather than carbanion stability. However, the observation[213] of CIDNP effects during the Wittig rearrangement is now believed to be due to competing elimination; other evidence for radical intermediates in side reactions has been obtained and a 'concerted radical' mechanism proposed[215] for the Wittig rearrangement. Rapid recombination of radicals in a solvent cage can account for the observed retention of configuration.

Anions of benzyl alkyl ethers and allyl alkyl ethers can also undergo rearrangements involving [1,4]-shifts of the alkyl group which is also a six-electron process that is symmetry allowed in a doubly suprafacial manner. Thus rearrangement of benzyl 2-butyl ether gives *o*-(2-butyl)benzaldehyde in addition to the normal Wittig rearrangement product[213] (equation 123) and a number of allyl butyl ethers undergo rearrangement to give moderate yields of the isomeric carbonyl compounds,[216] as in equations (124) and (125). The cleavage of benzyl ethyl ether with strong base can be formulated as involving a [1,4]-shift of hydrogen (see Section 4.3.6).

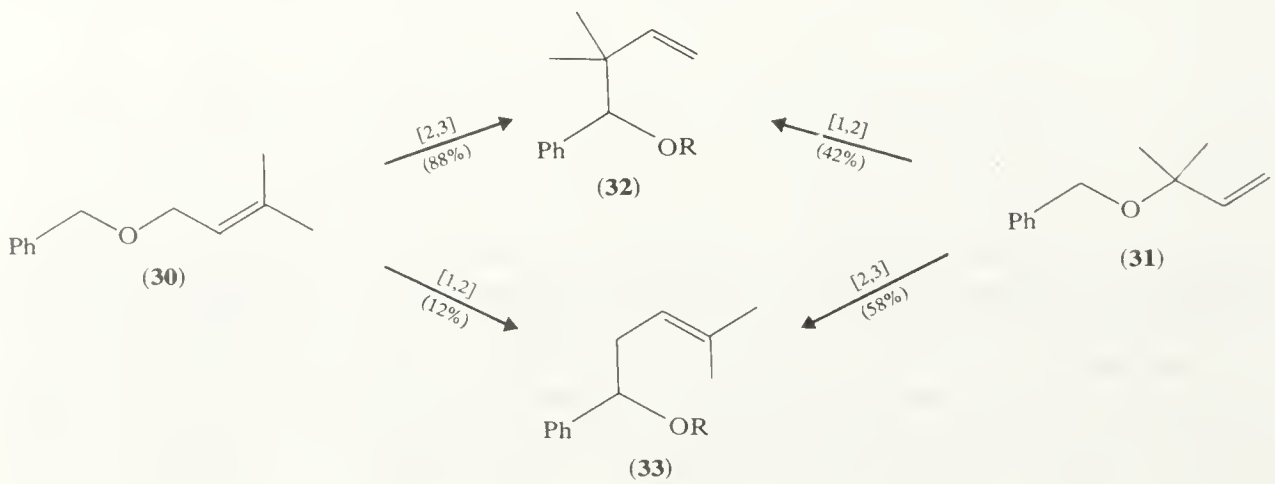
(123)

(124)



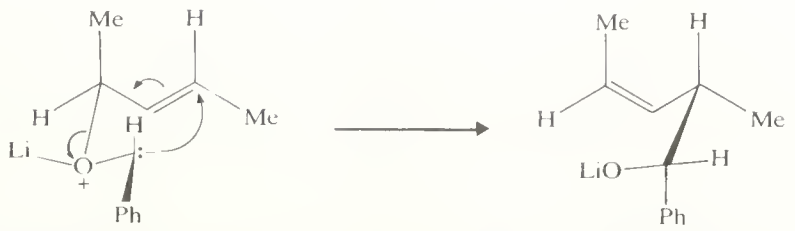
(125)

A further variation in the reaction may occur when an allyl group migrates. Thus rearrangement of the isomeric ethers (**30**) and (**31**) gives[217] the same two products (**32**) and (**33**). The minor product in each case is the Wittig rearrangement product arising *via* a [1,2]-shift and the major product is derived by migration of the substituted allyl group with accompanying allylic inversion, classified as a [2,3]-shift.



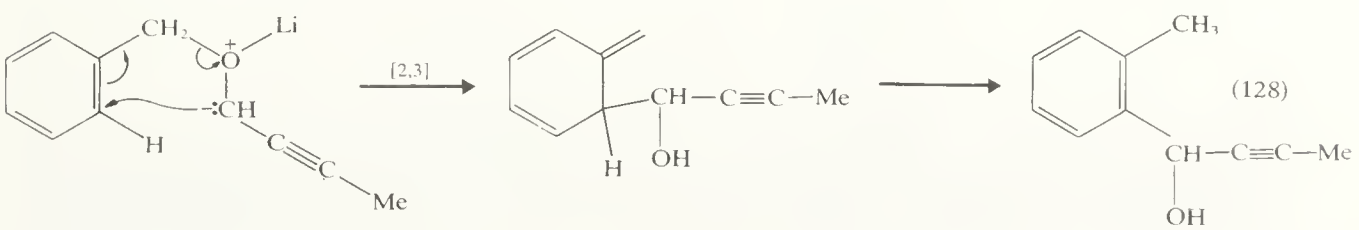
A [2,3]-sigmatropic shift in an anion, which involves six electrons, is a symmetry allowed pericyclic process when doubly suprafacial.[212] The observation[218] of marked stereoselectivity in the rearrangement of the chiral benzyl 1-methylcrotyl ether with (*E*,*S*) configuration (**34**) to two isomeric products with (*E*,*R*) (**35**) and (*Z*,*S*) (**36**) configurations can be rationalized as suprafacial migration in two rotamers of the substrate (equations 126 and 127).

(34) (35) (126)

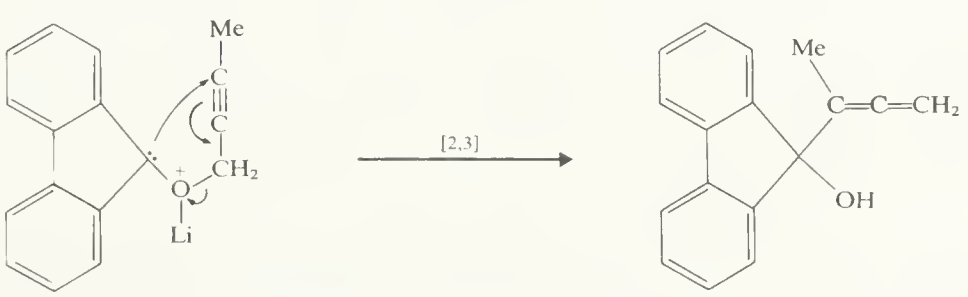


(34) (36) (127)

Two types of [2,3]-shift are observed with propargyl ethers. Benzyl 2-butynyl ether metallates on the butynyl group and undergoes a [2,3]-shift then tautomerization reminiscent of the Sommelet rearrangement (equation 128), whereas 2-butynyl fluorenyl ether metallates on the fluorene group and undergoes rearrangement with accompanying alkynyl to allenyl change (equation 129).[219]



(128)



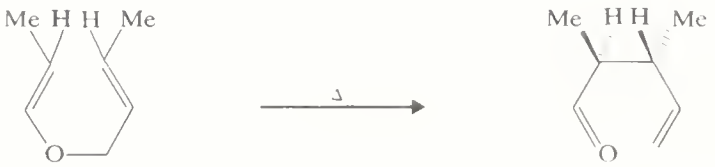
(129)

Silyl and germanyl ethers undergo the Wittig rearrangement and in the case of the silyl ether the reaction is reversible and proceeds with inversion of configuration in both cases.[220]

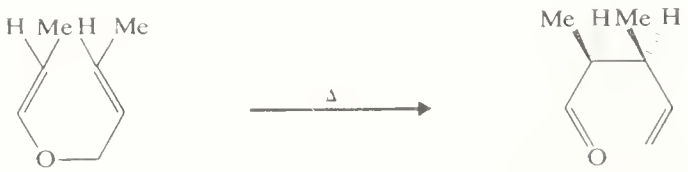
4.3.6.2 The Claisen rearrangement

The thermal rearrangement of allyl vinyl ethers to γ,δ-unsaturated carbonyl compounds, *e.g.* equation (130), is called the Claisen rearrangement. The mechanism is believed[221] to be a concerted reorganization of the bonding electrons and is now classified as a [3,3]-sigmatropic reaction which is symmetry allowed in a doubly suprafacial

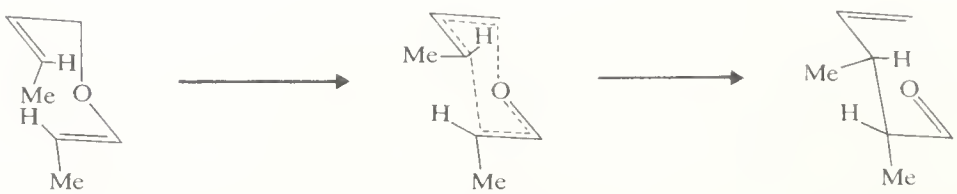
mode.[212] The reaction, like other pericyclic reactions, is highly stereoselective, as shown in equations (130) and (131), and this stereoselectivity is indicative[222] of a doubly suprafacial migration in a chair-like transition state, as shown in equation (132). Because the



(130)

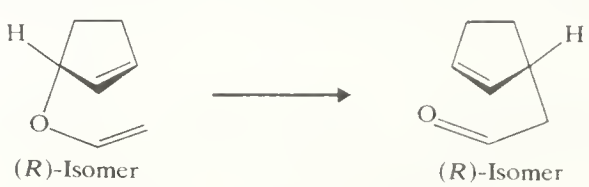


(131)



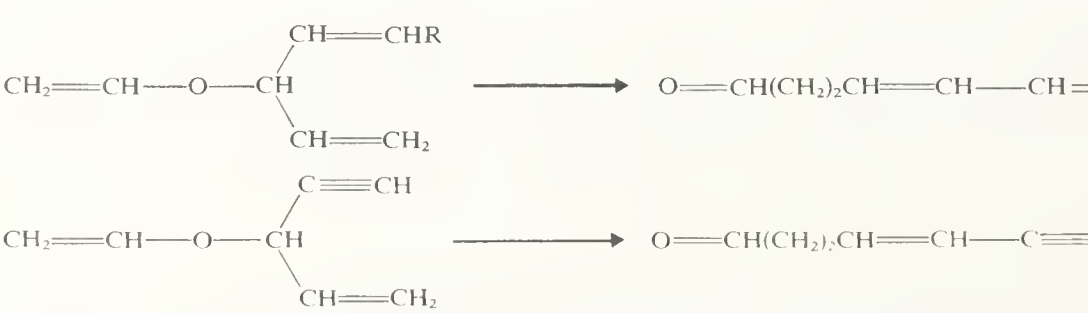
(132)

substrates are achiral in these examples, in the absence of any chiral influence the two possible enantiomeric products will be formed in equal amounts in each case, although equations (130) and (131) depict the formation of only one. Another facet of the stereoselectivity of these rearrangements is the asymmetric induction observed[223] with chiral substrates, as shown in equation (133).



(133)

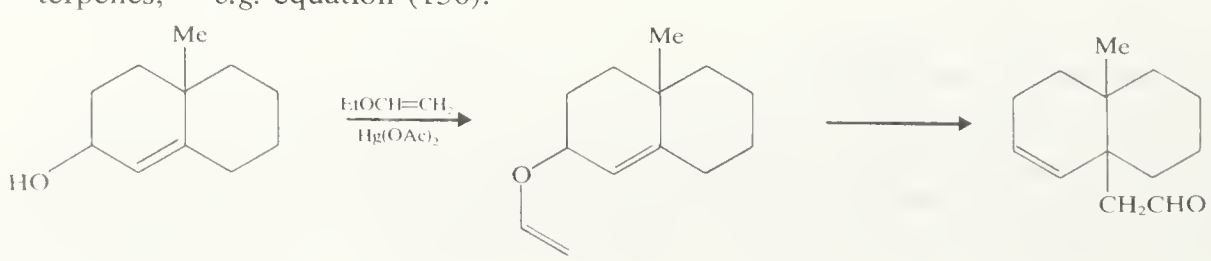
When alternative allyl systems are available the preferred rearrangement involves the less substituted allyl system[224] (equation 134) and, given a choice between rearrangement involving an allyl or a propargyl group, the former is preferred,[225] as in equation (135). If



(134)

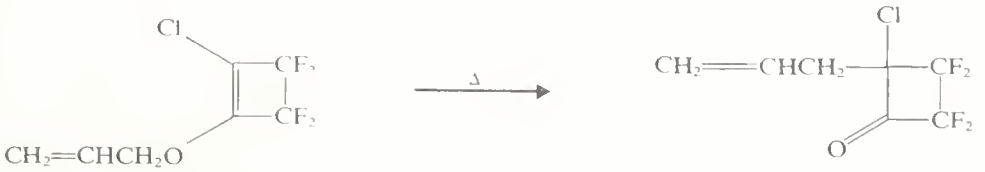
(135)

the allyl double bond is in a ring the reaction usually occurs readily and this constitutes a useful method for introduction of side chains in structures related to steroids and terpenes,[226] *e.g.* equation (136).



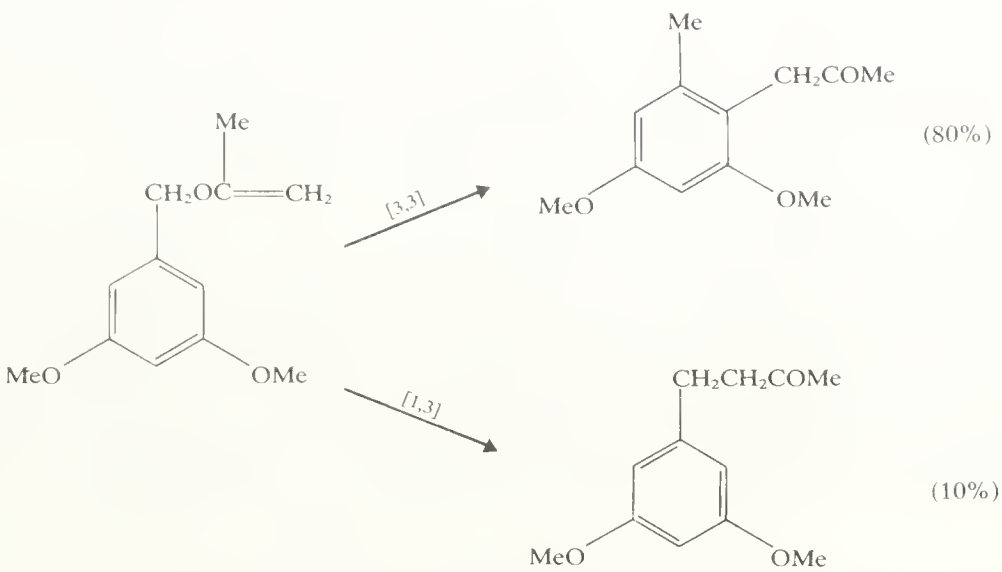
(136)

The rearrangement has also been reported to occur when the vinyl group is part of a ring[227] (equation 137) and also with propargyl vinyl ethers[228] (equation 138) and benzyl vinyl ethers[229] (equation 139). In the last case, some product resulting from a [1,3]-shift was also obtained.



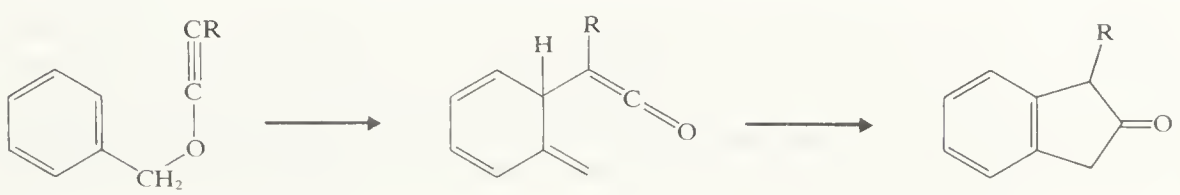
(137)

(138)

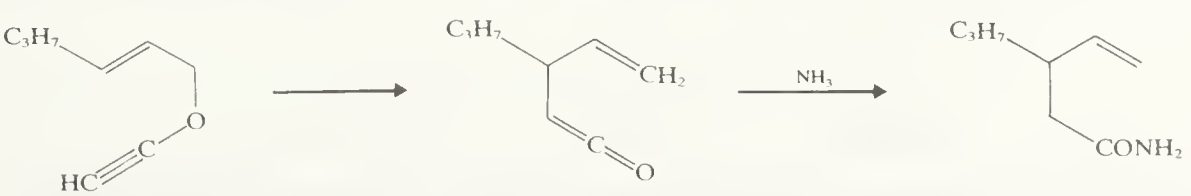


(139)

In Claisen rearrangements of benzyl alkynyl ethers (equation 140) and allyl ethynyl ethers (equation 141) the intermediate ketens undergo further reaction.[230] The wide



(140)



(141)

scope[231] and marked stereoselectivity of the Claisen rearrangement makes it a valuable method for synthesis of unsaturated aldehydes and ketones which is limited only by availability of the unsaturated ether. The *in situ* rearrangement of transient vinyl ethers produced by transvinylation or transacetalation, then elimination, extends the scope of the method considerably and has been applied to several elegant syntheses of terpenes.[232]

4.3.6.3 Photochemical reactions

Saturated ethers only absorb light of wavelength less than 200 nm and, probably because of technical difficulties of working at these short wavelengths, photoreactions of

pure ethers were little studied prior to this decade. Photosensitized reactions had been studied more extensively.[233]

The major product in the direct photolysis of diethyl ether in the gas phase is propane, with butane, ethane, and ethanol also formed in appreciable amounts. The yield of ethanol relative to hydrocarbons increases markedly with increasing pressure. Alcohols are the major products from direct photolysis of ethers in the liquid phase; carbonyl compounds and enol ethers are also obtained.[234]

To explain the products from diethyl ether it has been proposed[235] that the primary processes shown in equations (142)–(146) occur to the extents shown. In the gas phase at low pressure the vibrationally excited alkoxyl radical formed in equation (142) fragments as in equation (147) and the methyl radicals from this reaction and the ethyl radicals from equation (142) combine to give hydrocarbons. At higher pressures and in the liquid phase the vibrational energy of the ethoxyl radical is lost by collision with other molecules, thus preventing the reaction in equation (147), and the ethoxyl radical abstracts hydrogen from ether (equation 148) to give ethanol. Similar reactions occur with other primary and secondary ethers. Direct photolysis of liquid di-t-butyl ether also gives mainly the alcohol but in this case it arises principally by the molecular process shown in equation (149).

$$MeCH_2O^{\cdot} + \dot{C}H_2Me \quad (70\%) \qquad (142)$$

$$MeCH_2OH + CH_2{=}CH_2 \quad (8.5\%) \qquad (143)$$

$$MeCH_2OCH_2Me \xrightarrow{h\nu} MeCHO + MeMe \quad (10\%) \qquad (144)$$

$$MeCH_2OCH{=}CH_2 + H_2 \quad (11\%) \qquad (145)$$

$$Me^{\cdot} + \dot{C}H_2OCH_2Me \quad (0.5\%) \qquad (146)$$

$$MeCH_2O^{\cdot} \longrightarrow Me^{\cdot} + CH_2O \qquad (147)$$

$$MeCH_2O^{\cdot} + MeCH_2OCH_2Me \longrightarrow MeCH_2OH + Me\dot{C}HOCH_2Me \qquad (148)$$

$$Bu^tOBu^t \xrightarrow{h\nu} Bu^tOH + \begin{matrix} Me \\ \diagdown \\ C{=}{=}CH_2 \\ \diagup \\ Me \end{matrix} \qquad (149)$$

The major product from the direct photolysis at 254 nm of oxygenated ether is ethyl acetate.[236] Oxygen-saturated diethyl ether exhibits a charge-transfer absorption band, and absorption of energy is believed to be associated with transfer of charge from ether to an oxygen molecule to give the ether radical cation and oxygen radical anion (equation 150). Loss of a proton from this radical cation gives the 1-ethoxyethyl radical which reacts with oxygen to give products (equation 151).

$$Et_2\ddot{O} + O_2 \xrightarrow{h\nu} Et_2\dot{O}^{+} \; \dot{O}_2^{-} \qquad (150)$$

$$Et\overset{+\cdot}{O}CH_2Me \xrightarrow{-H^{+}} EtO\dot{C}HMe \xrightarrow{O_2} \text{Products} \qquad (151)$$

In the mercury-sensitized photolysis of aliphatic ethers,[237] the major organic product is the dehydro dimer which is believed to arise by dimerization of the initially-formed 1-alkoxyalkyl radical (equation 152).

$$2MeOCH_2Me \xrightarrow{Hg,\ h\nu} MeCH(OMe)\dot{C}H(OMe)Me \qquad (152)$$

The photochemical reactions of ethers with a variety of other compounds generally give α-substituted products which are believed to arise by reaction with the 1-alkoxyalkyl radical, *e.g.* equations (153)–(156). The marked regioselectivity of these photoinduced radical substitutions can be rationalized because of the ability of oxygen to stabilize the adjacent unpaired electron in 1-alkoxyalkyl radicals.

$$MeOCH_2Me + ClCN \xrightarrow{h\nu} MeOCH(CN)Me \quad (153)^{238}$$

$$MeCH_2OCH_2Me + Cl_2 \xrightarrow{h\nu} MeCH_2OCHClMe \quad (154)^{239}$$

$$MeCH_2OCH_2Me + Bu^tO_2COMe \xrightarrow{h\nu} MeCH_2OCHMeOCOMe \quad (155)^{240}$$

$$MeCH_2OCH_2Me + Bu^tOCl \xrightarrow{h\nu} MeCH_2OCHClMe \quad (156)^{241}$$

4.3.7 REACTIONS OF α-HALOETHERS

The ability of alkoxyl groups to stabilize an adjacent cation (see Section 4.3.6) promotes facile heterolysis of the carbon–halogen bond in α-haloethers and consequently these compounds are extremely reactive under conditions that favour both S_N1 or S_N2 mechanisms. Thus, for example, it has been estimated that hydrolysis of chloromethyl methyl ether is 10^{13} times faster than hydrolysis of 1-chloropropane.[242] α,α-Dihaloalkyl alkyl ethers are less reactive.[243]

Bis(chloromethyl) ether is highly carcinogenic and other compounds in this class are potentially hazardous.[244]

The reaction mechanism for solvolysis of chloromethyl methyl ether has been studied in detail and the evidence indicates[245] that the mechanism is of the S_N1 type despite the fact that the entropy of activation is lower than that usually observed for unimolecular processes. The difference can be attributed to development of double bond character, with consequent restriction of rotation, in the transition state for solvolysis of the haloether, because of resonance (**36**) between carbenium and oxonium forms.

$$MeO\ddot{}—\overset{+}{C}H_2 \longleftrightarrow Me\overset{+}{O}{=}CH_2$$

(**36**)

A wide variety of nucleophilic reagents react with α-haloethers to give substituted derivatives.[246] With strongly basic reagents, elimination may occur but, because the α-carbon is relatively unhindered, displacement is the favoured course. From the point of view of organic synthesis the reaction with carbon reagents is of most interest. The reaction of α-haloethers with organometallic reagents to give branched ethers is widely applicable, *e.g.* equations (157a) and (157b). The example shown in equation (157a) illustrates a key step in the Boord olefin synthesis.[247]

$$MeCHBrCBrMeOEt \xrightarrow{Pr^iMgX} MeCHBrCPr^iMeOEt \quad (157a)$$

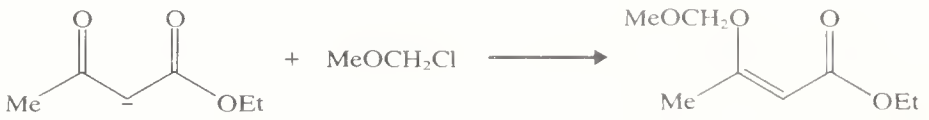
$$MeOCH_2Cl + Bu^nLi \longrightarrow MeOCH_2Bu^n \quad (157b)$$

Simple alkoxyalkylation of enolate anions derived from dialkyl malonates or β-diketones occurs readily to give ether products (equation 158) in which the ether group is in the β-position and consequently prone to undergo elimination, especially in the presence of acid. The product of such an elimination contains an activated double bond which readily undergoes nucleophilic addition so that, in some cases, the reaction of chloromethyl ethers with β-dicarbonyl compounds gives bis-adducts of methane (see equation 159).

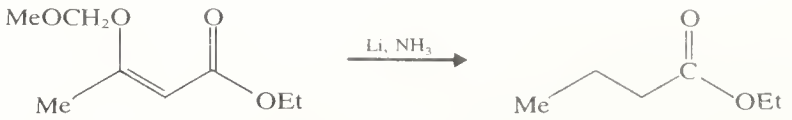
$$MeCHClOEt + Na^+\ \bar{C}H(CO_2Et)_2 \longrightarrow MeCH(OEt)CH(CO_2Et)_2 \quad (158)$$

$$2\bar{C}H(COMe)_2 + MeOCH_2Cl \longrightarrow (MeCO)_2CHCH_2CH(COMe)_2 \quad (159)$$

The sodium salt of ethyl acetoacetate reacts with chloromethyl methyl ether to give only the *O*-alkylated product[248] (equation 160). Enol acetals of this type undergo reductive cleavage (equation 161) so that the two steps provide a mild method for reduction of the ketone group of β-ketoesters to a methylene group, which has been applied in the total synthesis of some bicyclic sesquiterpenes.[249]

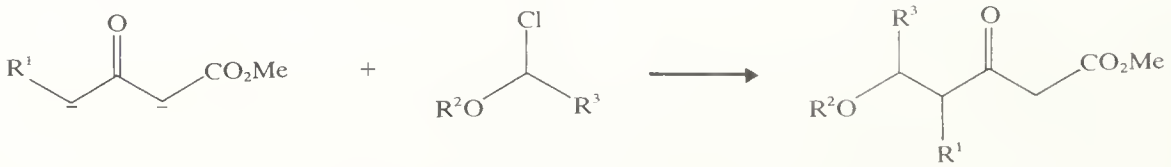


(160)



(161)

The dianions of β-ketoesters react with α-chloroethers to give δ-alkoxy-β-ketoesters (equation 162) which are useful alternatives to esters of 3-oxo-4-enoic acids as intermediates in annelation reactions.[250]



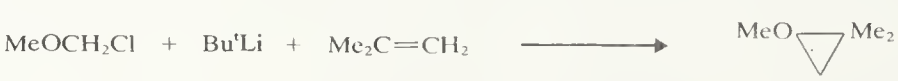
(162)

The reactivity of α-haloethers is enhanced in the presence of Lewis acids so that reaction occurs with weakly nucleophilic species such as alkenes (equation 163) and aromatic rings.[246] With Lewis acids which complex halide ions, alkoxycarbenium ions can be generated from α-haloethers. These ions are ambident electrophiles which can cause alkylation as well as alkoxyalkylation[251] (equation 164).

(163)

(164)

Attempts to form alkoxycarbenes from α-haloethers by α-elimination are complicated by substitution reactions. Thus reaction of chloromethyl alkyl ethers with n-butyl-lithium in the presence of alkenes gives mainly ethers by nucleophilic substitution, *e.g.* equation (157b), but using the more bulky t-butyl-lithium the major product is a methoxycyclopropane arising from addition of the carbenoid reagent to the alkene (equation 165).[252] This is not, however, a very satisfactory method for formation of alkoxycarbenoids because of side reactions induced by the base and better yields are obtained if methyllithium and lithium iodide are added to dichloromethyl alkyl ethers as in equation (166). The utility of this method is illustrated in equation (167), which is the first step in a prostaglandin synthesis.[253]



(165)

(166)

(167)

The conversion of aldehydes or ketones into vinyl ethers *via* the Wittig reaction using ylides derived from α-haloethers has been extensively studied[254] and successfully applied to 20-keto steroids.[255] The corresponding Horner–Wittig reaction using phosphine oxides provides[256] a useful alternative route to vinyl ethers and thence, by hydrolysis, to aldehydes and ketones (see Scheme 3). With aldehydes and constitutionally unsymmetrical ketones the intermediate phosphine oxide adduct is a mixture of diastereoisomers which can be separated and converted into pure (*Z*) and (*E*) diastereoisomers of vinyl ethers.

i, Ph_3P; ii, HO^-, H_2O; iii, Pr^i_2NLi, R_2CO; iv, NaH, THF; v, H_3O^+.

SCHEME 3

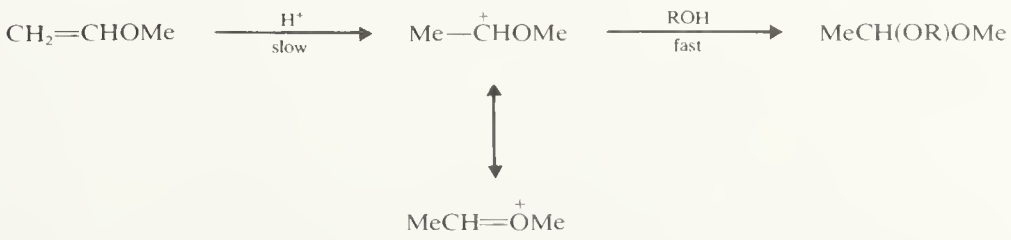
4.3.8 REACTIONS OF UNSATURATED ETHERS

The double bond in unsaturated ethers is, like that in alkenes, subject to electrophilic attack, but in vinyl ethers the presence of the oxygen atom adjacent to the double bond has a marked effect on the rate and regioselectivity of the reaction. Vinyl ethers are hydrolysed readily in acid medium to aldehydes or ketones (equation 168) and react with alcohols under acid catalysis to give acetals (equation 169). The latter reaction is reversible so that by controlling the conditions, acetals can be obtained from vinyl ethers or vinyl ethers from acetals, but also transacetalations and transvinylations can be achieved. The formation of vinyl ethers by this method and their subsequent rearrangement is the basis of several important methods for synthesis of polyenes (see Section 4.3.6.2). The relative thermodynamic stabilities of various vinyl ethers have been obtained.[257]

$$CH_2{=}CROMe \xrightarrow{H_3O^+} MeCOR \qquad (168)$$

$$CH_2{=}CR^1OMe \xrightarrow{R^2OH,\ H^+} MeCR^1(OR^2)OMe \qquad (169)$$

The rate-limiting step in the acid-catalysed solvolysis of enol ethers is the transfer of a proton to the β-position of the double bond to give a resonance-stabilized alkoxycarbenium ion which is rapidly attacked by solvent,[258] as in equation (170).

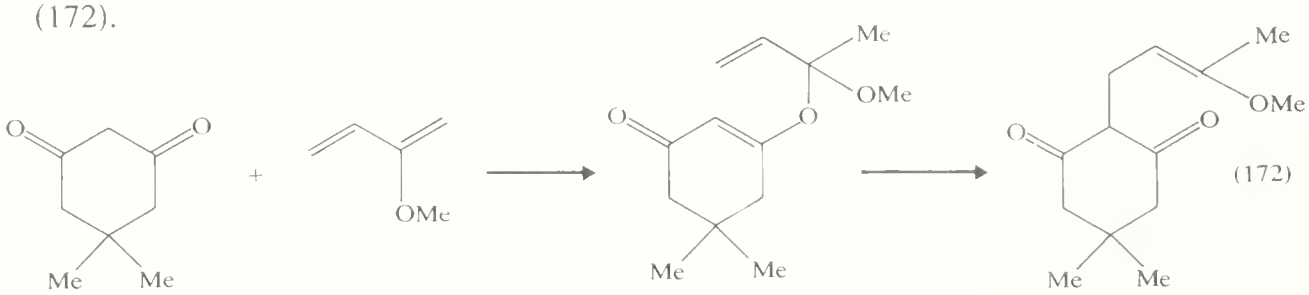


(170)

Because the carbenium ion can only be resonance-stabilized when it is in the α-position with respect to the ether group, the electrophile always adds at the β-position. Hydroboration then oxidation of vinyl ethers gives β-alkoxyalcohols (equation 171) and thus provides a method for hydration with the opposite regioselectivity.[259]

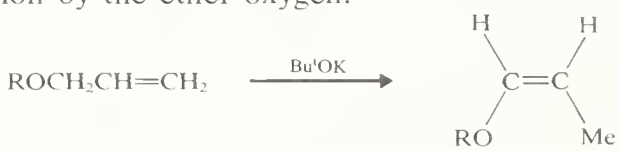
$$CH_2{=}CHOR \xrightarrow[\text{ii, } H_2O_2,\ NaOH]{\text{i, } B_2H_6} HOCH_2CH_2OR \qquad (171)$$

The apparent 1,4-addition of β-dicarbonyl compounds to 2-methoxybuta-1,3-diene gives vinyl ethers which can be used in subsequent annelation reactions.[260] The reaction involves the addition of the enol form of the β-diketone to the activated 1,2-double bond followed by *in situ* Claisen rearrangements (see Section 4.3.6.2), as shown in equation (172).



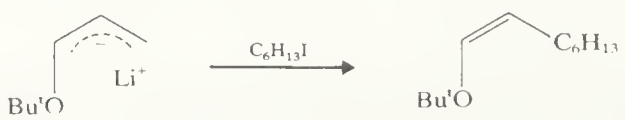
(172)

Allyl ethers are no more susceptible to electrophilic attack than alkenes and are therefore relatively resistant to acid hydrolysis. However, on treatment with potassium t-butoxide they are converted into *cis*-propenyl ethers (equation 173) which are readily hydrolysed.[261] The observed *cis* stereospecificity has been explained in terms of coordination of the potassium ion by the ether oxygen.

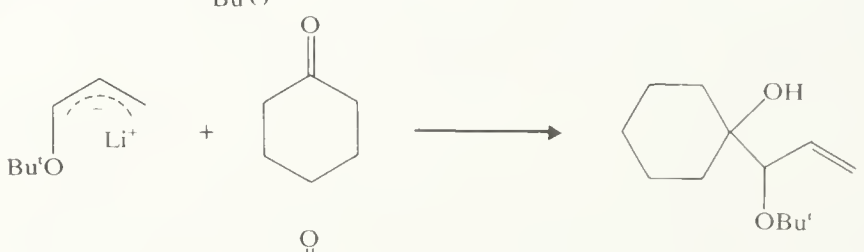


(173)

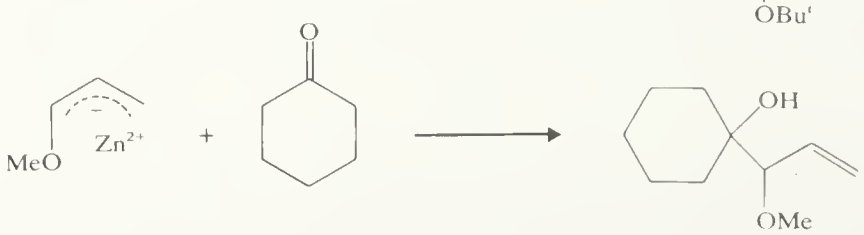
Anions of allyl ethers may undergo Wittig rearrangement (see Section 4.3.6.1) but, at low temperature, alkyl allyl or vinyl ethers may be rapidly metallated with s-butyl-lithium to give the equivalent homoenolate anions. The anions react with electrophiles to give α- or γ-substituted products (equations 174–177). The regioselectivity is influenced by the nature of the alkyl group, the counter ion, and the electrophile.[262] Thus alkylation of the lithium derivative of t-butyl allyl ether with 1-iodohexane gives mainly the γ-substituted product (equation 174), whereas with cyclohexanone the α-substituted product results (equation 175). In a comparative study of alkylation with cyclohexanone of metallated methyl allyl ether, α-alkylation is observed with the zinc counter ion (equation 176) and γ-alkylation of the lithio derivative occurs to give an enol ether which is hydrolysed on acidic work-up (equation 177).



(174)



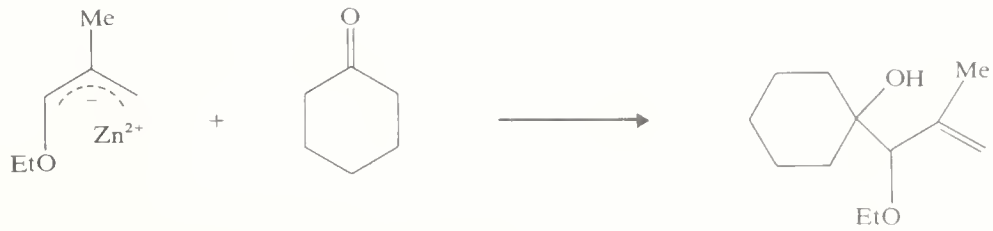
(175)



(176)

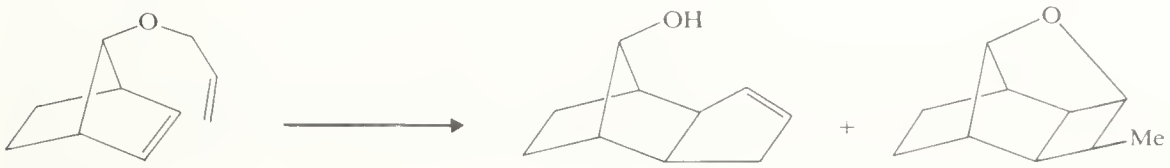
(177)

Methyl-substituted allyl ethers are alkylated at the α-position (equation 178), showing that, under the conditions of this experiment, the alkoxy substituent enhances the acidity of the adjacent proton, though under other conditions the opposite is observed.[263]



(178)

Another interesting example of an allyl ether anion which does not undergo Wittig rearrangement is shown in equation (179). In this case intramolecular cycloaddition is observed and chelation of the lithium cation to the ether oxygen is postulated as a controlling factor.[264]



(179)

4.3.9 POLYETHERS

Extensive commercial use has been made of flexible polymeric materials in which the ether linkage is part of the polymer backbone. Some of the stimulus behind this development came from the realization that the nature of the ether linkage, particularly the low torsion barrier compared with that in alkanes (see Section 4.3.3) and the chemical stability of the C—O bond in ethers (see Section 4.3.6), might confer suitable properties for application of polyethers as high-performance rubbers.[265]

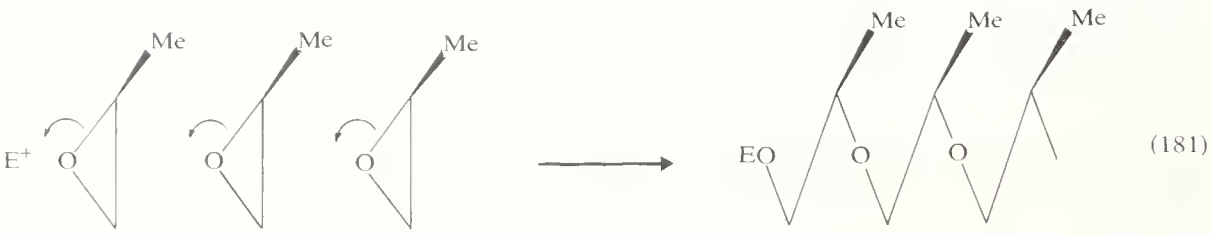
A variety of polyether chains can be generated which differ in the regular spacing between the oxygen atoms. A regular 1,3-arrangement of oxygen atoms occurs in polyacetal chains which are outside the scope of this section, a 1,4-arrangement occurs in poly(alkylene oxide) polymers, a 1,5-arrangement is present in polyoxetan polymers, and poly(tetrahydrofuran) polymers have a 1,6-disposition of oxygen atoms. Polymers containing aryl ether alternating units have been made but will not be considered in this section. Different availability of the monomers has meant that most work has been done on poly(alkylene oxide) polymers, and least on polyoxetans.

Because of the practical importance of stereoselection in polymerization, considerable efforts have been devoted to the stereochemical aspects of polymers. A system of terminology has been developed to describe intramolecular spatial relationships in polymers in which the stereoregularity of a polymer is described in terms of its tacticity,[266] but for discussion of stereochemistry of alkylene oxide monomers and their incorporation into growing chains the terminology which is commonly used in organic chemistry is appropriate. Various catalysts have been used for polymerization of epoxides and the properties of the polymer often depend on the type of catalyst used because it controls the molecular weight and also the regularity of the polymerization. With constitutionally unsymmetrical monomers, aspects of regio- and stereo-selectivity are important in controlling the constitution and configuration of the polymer.

Polymerization of epoxides can be classified in terms of the initiating or propagating species as anionic, cationic, or coordination. The coordination mechanism combines features of the other two and involves coordination of the monomer by a Lewis acid and generation of oxonium ion character in the epoxide and then nucleophilic attack by an

alkoxide ion linked to the catalytic site. Generally the coordination catalysts promote greater stereoselectivity. In each case the epoxide-opening reaction involves attack of the incoming oxygen atom on the epoxide ring with inversion of configuration.[267] A consequence of this mode of opening with terminal epoxides is that attack at the primary position gives retention of configuration at C-2, as shown in equation (180), whereas attack at the non-terminal position involves inversion of configuration at this position, as in equation (181).

(180)



(181)

Therefore, for example, a carbon atom with (*R*) chirality in the polymer may in principle arise by incorporation of the (*R*)-monomer with retention, or from incorporation of the (*S*)-monomer with inversion of configuration. To establish which route is followed, optically active monomer has been used.[268]

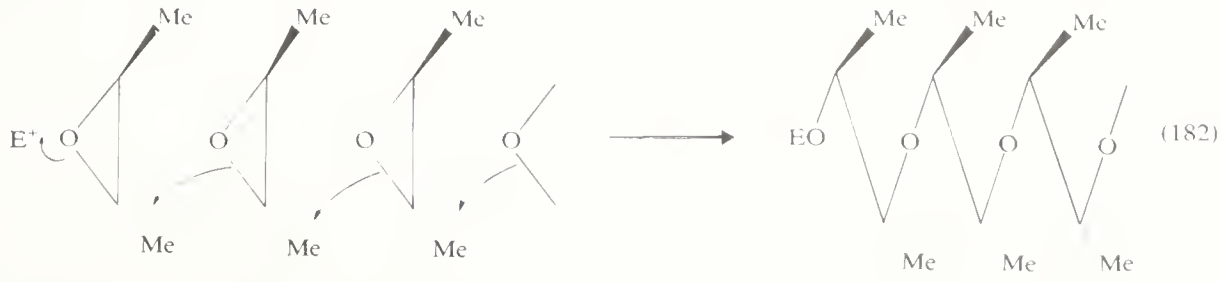
Polymerization of propene oxide with coordination catalysts gives high molecular weight polymers which can be separated easily into crystalline and amorphous fractions. Whilst the polymers obtained from the racemic monomer are necessarily optically inactive, those obtained from chiral monomer are optically active, with the crystalline fraction having the higher specific rotation in each case. By degradation of these polyethers, using β-elimination with pentylsodium or oxidation with ozone followed by reduction, and analysis of the dimeric diols obtained, it was established that crystalline poly(propene oxide) is largely a regular polymer containing primary to secondary ether links resulting from head-to-tail polymerization, and the amorphous polymers contain significant amounts of diprimary and disecondary ether links. Furthermore, from comparison of the specific rotation data with this information about connectivity in the polymer chains, there appears to be a correspondence between configurational and constitutional inversion during polymerization.[269]

The conclusion reached from these studies is that isotactic polymer arises from stereoselective incorporation of monomer in a regioselective polymerization, whereas amorphous polymer can arise when the incorporation of monomer is non-selective or when the polymerization is not regioselective.

An interesting contrast with results from coordination catalysts is observed in the polymerization of chiral propene oxide with potassium hydroxide, which gives an optically active, isotactic polymer.[270] In this experiment the stereoselective approach of one enantiomeric form of the monomer to the growing polymer is ensured by the prior resolution, and regioselective addition is then sufficient to produce a stereoregular polymer. With racemic monomer an isotactic polymer is not obtained using potassium hydroxide catalyst and this must be because there is now no significant stereoselection in the approach of the enantiomeric monomers to the growing polymer.

The cationic polymerization of but-2-ene oxide has been studied[271] and the stereochemistry of incorporation established by degradation reactions involving β-elimination. In this case, polymerization of the (2*S*,3*S*)-monomer with a triisobutylaluminium–water catalyst at dry ice temperature gives a 97% yield of crystalline

polymer with negligible optical activity. This polymer is degraded to *erythro*- or (2*R*,3*S*)-butane-2,3-diol, showing that the polymer is erythrodi-isotactic and must arise by inversion of configuration at one centre during polymerization (equation 182). Furthermore,



(182)

when racemic monomer is used a similar crystalline polymer is also obtained, suggesting that a growing chain derived from (*S*,*S*)-monomer reacts stereoselectively with another (*S*,*S*)-monomer rather than the enantiomeric (*R*,*R*)-monomer. An explanation for this selectivity in terms of 'chain end' stereoselection was proposed.[271] Polymerization of (2*R*,3*S*)-monomer gives an amorphous polymer composed of both (2*R*,3*R*)- and (2*S*,3*S*)-diol units which arise by inversion of configuration at one chiral centre of the monomer.

Another type of polyether can be obtained by polymerization of vinyl ethers. In this case the polymer comprises a carbon chain with pendant ether groups. As with other monomers, suitable conditions have been found to produce isotactic crystalline polymers of this type.[272]

The conformational consequences of introducing oxygen atoms into polymers chains have been discussed (see Section 4.3.3) and excellent agreement has been obtained between predicted and observed[273] conformations. For poly(tetrahydrofuran), poly(hexamethylene oxide), and higher homologues the preferred conformation is a planar zig-zag chain. For polyoxetan a folded conformation of the chain is predicted and observed in the stable crystalline form, whereas in the hydrated form a planar zig-zag chain is adopted. The presence of the 1,4-dioxa grouping, with its preference for the *gauche* conformation, in poly(ethylene oxide) means that these chains are inclined to fold and this folding can bring several oxygen atoms simultaneously into appropriate positions for chelating cations.[274] The attachment of alkyl groups to the poly(ethylene oxide) chains may interfere with this folding because the chains in crystalline poly(propene oxide) are close to planar zig-zag, but crystalline poly(t-butylethylene oxide) adopts a helical conformation. Because of the tendency for poly(ethylene oxide) chains to fold and present an array of oxygen atoms to a potential acceptor, liquid oligomers of poly(ethylene oxide) are effective agents for solvating cations although they are not as effective as the cyclic analogues or crown ethers[274] (see Section 4.4.5.2).

Interesting compounds of a new type, which are remarkably powerful complex ligands for alkali metals and alkaline earth cations, have been reported.[275] These are benzene rings with many polyether arms and they are claimed to be more effective than crown ethers and comparable to cryptands in their complexing ability.

References

1. 'IUPAC Nomenclature of Organic Chemistry', Butterworths, London, 1969.
2. J. A. Riddick and W. B. Bunger, in 'Techniques of Chemistry, Vol. II, Organic Solvents', 3rd edn., ed. A. Weissberger, Wiley-Interscience, New York, 1970.
3. E. R. Larsen, *Fluorine Chem. Rev.*, 1969, **3**, 1.
4. R. C. Terrell, L. Speers, A. J. Szur, T. Ucciardi, and J. F. Vitcha, *J. Medicin. Chem.*, 1972, **15**, 604.
5. S. L. Fishbein, *Sci. Total Environ.*, 1974, **2**, 305.
6. K. Biemann, in 'Techniques of Chemistry, Vol. IV, Elucidation of Organic Structures by Physical and Chemical Methods', 2nd edn., ed. K. W. Bentley and G. W. Kirby, Wiley-Interscience, New York, 1972, part 1, p. 377.
7. M. J. S. Dewar and S. D. Worley, *J. Chem. Phys.*, 1969, **50**, 654.
8. E. L. Hirst, *J. Chem. Soc.*, 1926, 350.

9. H. Björndal, C. G. Hellerquist, B. Lindberg, and S. Svensson, *Angew. Chem. Internat. Edn.*, 1970, **9,** 610; J. Lönngren and S. Svensson, *Adv. Carbohydrate Chem. Biochem.*, 1974, **29,** 41.
10. J. Dale, *Tetrahedron*, 1974, **30,** 1683.
11. F. Bernardi, N. D. Epiotis, R. L. Yates, and H. B. Schlegel, *J. Amer. Chem. Soc.*, 1976, **98,** 2385.
12. E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, 'Conformational Analysis', Interscience, New York, 1965, p. 373.
13. J. P. Lowe, *Progr. Phys. Org. Chem.*, 1968, **6,** 1.
14. W. L. Jorgensen and L. Salem, 'The Organic Chemist's Book of Orbitals', Academic, New York, 1973, p. 167.
15. N. L. Allinger, *Adv. Phys. Org. Chem.*, 1976, **13,** 1.
16. R. S. Mulliken, *J. Amer. Chem. Soc.*, 1952, **74,** 811.
17. T.-L. Ho, *Chem. Rev.*, 1975, **75,** 1.
18. S. Searles, Jr. and M. Tamres, in 'The Chemistry of the Ether Linkage', ed. S. Patai, Interscience, London, 1967, chapter 6.
19. B. J. Cocksey, J. H. D. Eland, and C. J. Danby, *J. Chem. Soc. (B)*, 1971, 790.
20. B. E. Mills, R. L. Martin, and D. A. Shirley, *J. Amer. Chem. Soc.*, 1976, **98,** 2380.
21. A. Hantzsch, *Z. phys. Chem.*, 1908, **65,** 41.
22. D. Jaques and J. A. Leisten, *J. Chem. Soc.*, 1961, 4963.
23. W. Hofman, L. Stefaniak, and T. Urbanski, *J. Chem. Soc.*, 1962, 2343.
24. F. Klages, H. Meuresch, and W. Steppich, *Annalen*, 1955, **592,** 81.
25. Y. Marcus and A. S. Kertes, 'Ion Exchange and Solvent Extraction of Metal Complexes', Wiley-Interscience, New York, 1969, chapter 9.
26. G. A. Olah, A. M. White, and D. H. O'Brien, *Chem. Rev.*, 1970, **70,** 561.
27. L. P. Hammett, *J. Amer. Chem. Soc.*, 1928, **50,** 2666.
28. W. Gerrard and E. D. Macklen, *Chem. Rev.*, 1959, **59,** 1105.
29. J. F. Bunnett and F. P. Olsen, *Canad. J. Chem.*, 1966, **44,** 1899.
30. P. Bonvicini, A. Levi, V. Lucchini, G. Modena, and G. Scorrano, *J. Amer. Chem. Soc.*, 1973, **95,** 5960; E. M. Arnett and G. Scorrano, *Adv. Phys. Org. Chem.*, 1976, **13,** 83.
31. R. W. Taft and J. F. Wolf, unpublished observation cited in Ref. 30.
32. J. Long and B. Munson, *J. Amer. Chem. Soc.*, 1973, **95,** 2427.
33. G. C. Pimental and A. L. McClellan, *Ann. Rev. Phys. Chem.*, 1971, **22,** 347.
34. R. D. Green, 'Hydrogen Bonding by C—H Groups', Macmillan, London, 1974.
35. F. L. Slejko and R. S. Drago, *J. Amer. Chem. Soc.*, 1973, **95,** 6935.
36. 'Ions and Ion Pairs in Organic Reactions', ed. M. Szwarc, Wiley-Interscience, New York, 1972.
37. P. A. Scherr, R. J. Hogan, and J. P. Oliver, *J. Amer. Chem. Soc.*, 1974, **96,** 6055.
38. J. M. Timko, R. C. Helgeson, M. Newcomb, G. W. Gokel, and D. J. Cram, *J. Amer. Chem. Soc.*, 1974, **96,** 709.
39. W. I. Sullivan, F. W. Swamer, W. J. Humphlett, and C. R. Hauser, *J. Org. Chem.*, 1961, **26,** 2306.
40. E. J. Panek, B. L. Neff, H. Chu, and M. G. Panek, *J. Amer. Chem. Soc.*, 1975, **97,** 3996.
41. E. Grovenstein, Jr. and R. E. Williamson, *J. Amer. Chem. Soc.*, 1975, **97,** 646.
42. D. Bryce-Smith and G. F. Cox, *J. Chem. Soc.*, 1958, 1050; 1961, 1175.
43. E. C. Ashby, J. Laemmle, and H. N. Neumann, *Accounts Chem. Res.*, 1974, **7,** 272.
44. H. W. H. J. Bodewitz, C. Blomberg, and F. Bickelhaupt, *Tetrahedron*, 1975, **31,** 1053.
45. J. D. Morrison and H. S. Mosher, 'Asymmetric Organic Reactions', Prentice-Hall, New Jersey, 1971, p. 414.
46. T. D. Inch, G. J. Lewis, G. L. Sainsbury, and D. J. Sellars, *Tetrahedron Letters*, 1969, 3657.
47. S. H. Bauer, G. R. Finlay, and A. W. Laubengayer, *J. Amer. Chem. Soc.*, 1945, **67,** 339.
48. H. C. Brown and R. M. Adams, *J. Amer. Chem. Soc.*, 1942, **64,** 2557.
49. E. Bonitz, *Chem. Ber.*, 1955, **88,** 742.
50. J. W. Akitt, in 'Annual Reports on N.M.R. Spectroscopy', ed. E. F. Mooney, Academic, London, 1972, vol. 5A, p. 466.
51. H. Meerwein, G. Hinz, P. Hoffman, E. Kronig, and E. Pfeif, *J. prakt. Chem.*, 1939, **154,** 83.
52. H. Perst, in 'Carbonium Ions', ed. G. A. Olah and P. von R. Schleyer, Wiley-Interscience, New York, 1976, vol. V, p. 1972.
53. M. G. Ahmed, R. W. Alder, G. H. James, M. L. Sinnott, and M. C. Whiting, *Chem. Comm.*, 1968, 1533.
54. H. Meerwein, *Org. Synth.*, 1966, **46,** 120.
55. F. Klages and H. Meuresch, *Chem. Ber.*, 1952, **85,** 863.
56. F. Klages and H. Meuresch, *Chem. Ber.*, 1953, **86,** 1322.
57. H. Meerwein, *Org. Synth.*, 1966, **46,** 113.
58. H. Teichmann and G. Hilgetag, *Angew. Chem. Internat. Edn.*, 1967, **6,** 1013.
59. S. Kabuss, *Angew. Chem. Internat. Edn.*, 1966, **5,** 675; H. Meerwein, *Angew. Chem.*, 1955, **67,** 374.
60. J. W. Blunt, M. P. Hartshorn, and D. N. Kirk, *Chem. and Ind. (London)*, 1963, 1955.
61. F. Klages, E. Mühlbauer, and G. Lukaszyk, *Chem. Ber.*, 1961, **94,** 1464.
62. R. L. Burwell, Jr., *Chem. Rev.*, 1954, **54,** 637.
63. S. Winstein, E. Allred, R. Heck, and R. Glick, *Tetrahedron*, 1958, **3,** 1.
64. S. Winstein and R. E. Buckles, *J. Amer. Chem. Soc.*, 1942, **64,** 2780.
65. B. Capon, *Quart. Rev.*, 1964, **18,** 45.

66. E. Allred and S. Winstein, *J. Amer. Chem. Soc.*, 1967, **89,** 3881.
67. A. Kirrmann and L. Wartski, *Bull. Soc. chim. France*, 1965, 3077.
68. H. Meerwein, P. Borner, O. Fuchs, H. J. Sasse, and J. Spille, *Chem. Ber.*, 1956, **89,** 2060.
69. W. Kirmse, 'Carbene Chemistry', Academic, New York, 2nd edn., 1971, p. 430.
70. H. Meerwein, H. Rathjen, and H. Werner, *Chem. Ber.*, 1942, **75,** 1610.
71. H. M. Frey and M. A. Voisey, *Trans. Faraday Soc.*, 1968, **64,** 954.
72. R. Huisgen, *Angew. Chem.*, 1955, **67,** 439.
73. V. Franzen and L. Fikentscher, *Annalen*, 1958, **617,** 1.
74. J. Warkentin, E. Singleton, and J. F. Edgar, *Canad. J. Chem.*, 1965, **43,** 3456.
75. G. B. R. de Graaff and G. van de Kolk, *Rec. Trav. chim.*, 1958, **77,** 224.
76. H. Iwamura and Y. Imahashi, *Tetrahedron Letters*, 1975, 1401.
77. W. Kirmse and M. Kapps, *Chem. Ber.*, 1968, **101,** 994.
78. D. Seyferth and V. A. Mai, *J. Amer. Chem. Soc.*, 1970, **92,** 7412.
79. H. H. Sisler, H. H. Batey, B. Pfahler, and R. Mattair, *J. Amer. Chem. Soc.*, 1948, **70,** 3821.
80. R. S. Mulliken and W. B. Person, 'Molecular Complexes: A Lecture and Reprint Volume', Wiley-Interscience, New York, 1969.
81. R. Foster, 'Organic Charge Transfer Complexes' Academic, New York, 1969.
82. *e.g.* P. A. D. deMaine, *J. Chem. Phys.*, 1957, **26,** 1036, 1189.
83. J. Prochorow and A. Tramer, *J. Chem. Phys.*, 1966, **44,** 4545.
84. S. M. Nelson, in 'MTP International Review of Science, Inorganic Chemistry Series Two', Butterworths, London, 1974, vol. 5, p. 171.
85. A. K. Bose, P. R. Srinivasan, and G. Trainor, *J. Amer. Chem. Soc.*, 1974, **96,** 3670.
86. E. J. Corey and K. Bock, *Tetrahedron Letters*, 1976, 3269.
87. E. S. Amis and J. F. Hinton, 'Solvent Effects on Chemical Phenomena', Academic, New York, 1973, vol. 1, p. 389.
88. L. I. Katzin, *J. Inorg. Nuclear Chem.*, 1957, **4,** 187.
89. H. Meerwein, in 'Methoden der Organischen Chemie (Houben-Weyl)', ed. E. Müller, 1965, vol. 6, part 3, p. 1.
90. H. Feuer and J. Hooz, in 'The Chemistry of the Ether Linkage', ed. S. Patai, Interscience, London, 1967, chapter 10.
91. C. A. Buehler and D. E. Pearson, 'Survey of Organic Syntheses' Wiley-Interscience, New York, 1970, chapter 6.
92. I. T. Harrison and S. Harrison, 'Compendium of Organic Synthetic Methods', Wiley-Interscience, New York, 1971, chapter 9; S. R. Sandler and W. Karo, 'Organic Functional Group Preparations', Academic, New York, 1968, chapter 5.
93. W. Williamson, *J. Chem. Soc.*, 1852, **4,** 106, 229.
94. U. E. Diner, F. Sweet, and R. K. Brown, *Canad. J. Chem.*, 1966, **44,** 1591.
95. S. Hakomori, *J. Biochem. (Japan)*, 1964, **55,** 205.
96. W. N. Haworth, *J. Chem. Soc.*, 1915, **107,** 8.
97. T. Purdie and J. C. Irvine, *J. Chem. Soc.*, 1903, **83,** 1021.
98. R. Kuhn and H. Trischmann, *Chem. Ber.*, 1963, **96,** 284.
99. A. McKillop and M. E. Ford, *Tetrahedron*, 1974, **30,** 2467.
100. K. Mislow, *J. Amer. Chem. Soc.*, 1951, **73,** 4043.
101. H. O. Kalinowski, D. Seebach, and G. Crass, *Angew. Chem. Internat. Edn.*, 1975, **14,** 762.
102. P. Veeravagu, R. T. Arnold, and E. W. Eigenmann, *J. Amer. Chem. Soc.*, 1964, **86,** 3072.
103. C. H. Snyder and A. R. Soto, *J. Org. Chem.*, 1964, **29,** 742.
104. J. F. Bunnett, M. M. Robison, and F. C. Pennington, *J. Amer. Chem. Soc.*, 1950, **72,** 2378.
105. J. B. Senderens, *Compt. rend.*, 1926, **182,** 612.
106. J. F. Norris and G. W. Rigby, *J. Amer. Chem. Soc.*, 1932, **54,** 2088.
107. D. Y. Curtin and S. Lescowitz, *J. Amer. Chem. Soc.*, 1951, **73,** 2630.
108. I. M. Heilbron, E. R. H. Jones, J. T. McCombie, and B. C. L. Weedon, *J. Chem. Soc.*, 1945, 88.
109. H. A. Smith and R. J. Smith, *J. Amer. Chem. Soc.*, 1948, **70,** 2400.
110. R. W. Herbert, E. L. Hirst, E. G. V. Percival, R. J. W. Reynolds, and F. Smith, *J. Chem. Soc.*, 1933, 1270.
111. H. Meerwein, H. Disselnkötter, F. Rappen, H. von Rintelen, and H. van de Vloed, *Annalen*, 1957, **604,** 151.
112. J. A. Kerr, B. V. O'Grady, and A. F. Trotman-Dickenson, *J. Chem. Soc.* (*A*), 1967, 897.
113. M. C. Caserio, J. D. Roberts, M. Neeman, and W. S. Johnson, *J. Amer. Chem. Soc.*, 1958, **80,** 2584; M. Neeman, M. C. Caserio, J. D. Roberts, and W. S. Johnson, *Tetrahedron*, 1959, **6,** 36.
114. J. O. Deferrari, E. G. Gros, and I. O. Mastronardi, *Carbohydrate Res.*, 1967, **4,** 432.
115. M. S. Newman and P. F. Beal, *J. Amer. Chem. Soc.*, 1950, **72,** 5161.
116. P. Yates, *J. Amer. Chem. Soc.*, 1952, **74,** 5376.
117. M. Takebayashi, T. Ibata, H. Kohara, and B. H. Kim, *Bull. Chem. Soc. Japan*, 1967, **40,** 2392.
118. D. Bethell, A. R. Newall, G. Stevens, and D. Whittaker, *J. Chem. Soc.* (*B*), 1969, 749.
119. R. A. Mitsch, and J. E. Robertson, *J. Heterocyclic Chem.*, 1965, **2,** 152.
120. T. W. Campbell, W. Burney, and T. L. Jacobs, *J. Amer. Chem. Soc.*, 1950, **72,** 2735.
121. S. O. Lawesson and N. C. Yang, *J. Amer. Chem. Soc.*, 1959, **81,** 4230.
122. *e.g.* see Y. Ito, T. Konoike, and T. Saegusa, *J. Amer. Chem. Soc.*, 1975, **97,** 649.

123. A. E. Pierce, 'Silylation of Organic Compounds', Pierce Chemical Co., Rochford, Illinois, 1968.
124. G. Stork and P. F. Hudrlik, *J. Amer. Chem. Soc.*, 1968, **90,** 4462.
125. K. K. Ogilvie and D. J. Iwacha, *Tetrahedron Letters*, 1973, 317.
126. J. F. Klebe, H. Finkbeiner and D. M. White, *J. Amer. Chem. Soc.*, 1966, **88,** 3390.
127. R. D. Morin and A. E. Bearse, *Ind. and Eng. Chem.*, 1951, **43,** 1596.
128. H. C. Brown and M.-H. Rei, *J. Amer. Chem. Soc.*, 1969, **91,** 5646.
129. R. L. Adelman, *J. Amer. Chem. Soc.*, 1953, **75,** 2678.
130. W. H. Watanabe and L. E. Conlon, *J. Amer. Chem. Soc.*, 1957, **79,** 2828.
131. G. L. Grady and S. K. Chokshi, *Synthesis*, 1972, 483.
132. G. Sosnovsky, 'Free Radical Reactions in Preparative Organic Chemistry', Macmillan, New York, 1964, pp. 121–125.
133. S. N. Massie and H. S. Bloch (to Universal Oil Prod. Co.) *U.S. Pat.* 3 821 315.
134. J. A. Marshall, *Accounts Chem. Res.*, 1969, **2,** 33.
135. B. A. Feit and A. Zilkha, *J. Org. Chem.*, 1963, **28,** 406.
136. R. D. Chambers, and R. H. Mobbs, *Adv. Fluorine Chem.*, 1965, **4,** 50.
137. W. P. Utermohlen, Jr., *J. Amer. Chem. Soc.*, 1945, **67,** 1505.
138. U. E. Wiersum and T. Nieuwenhuis, *Tetrahedron Letters*, 1973, 2581.
139. P. W. Townsend (to Air Reduction Company), *U.S. Pat.* 2 870 218 (1959).
140. W. L. Howard and J. H. Brown, Jr., *J. Org. Chem.*, 1961, **26,** 1026.
141. M. Verzele, M. Acke, and M. Anteunis, *J. Chem. Soc.*, 1963, 5598.
142. I. Wender, R. Levine, and M. Orchin, *J. Amer. Chem. Soc.*, 1950, **72,** 4375.
143. L. M. Zakharkin and I. M. Khorlina, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 1959, 2255 (*Chem. Abs.*, 1960, **54,** 10 837).
144. E. Frainnet and C. Esclamadon, *Compt. rend.*, 1962, **254,** 1814.
145. B. Fleming and H. I. Bolker, *Canad. J. Chem.*, 1974, **52,** 888.
146. G. Zweifel, A. Horng, and J. E. Plamondon, *J. Amer. Chem. Soc.*, 1974, **96,** 316.
147. B. E. Leggetter and R. K. Brown, *Canad. J. Chem.*, 1965, **43,** 1030.
148. C. Blomberg and A. D. Vreugdenhil, *Rec. Trav. chim.*, 1962, **81,** 238.
149. C. Fengears and J.-P. Gally, *Compt. rend.* (*C*), 1968, **266,** 1175.
150. H. Ishikawa, S. Ikeda, and T. Mukaiyama, *Chem. Letters*, 1975, 1051 (*Chem. Abs.*, 1975, **83,** 206 434).
151. G. R. Pettit and D. M. Piatak, *J. Org. Chem.*, 1962, **27,** 2127.
152. J. Tsurugi, R. Nakao, and T. Fukumoto, *J. Amer. Chem. Soc.*, 1969, **91,** 4587; *J. Org. Chem.*, 1973, **38,** 795; 1975, **40,** 3885.
153. J. H. P. Utley, in 'Techniques of Chemistry, Vol. V., part 1, Technique of Electroorganic Synthesis', ed. N. L. Weinberg, Wiley-Interscience, New York, 1974, chapter 6.
154. W. J. Koehl, *J. Amer. Chem. Soc.*, 1964, **86,** 4686.
155. F. N. Stepanov, V. F. Baklan, and S. S. Guts, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1965, 95 (*Chem. Abs.*, 1966, **65,** 627).
156. N. L. Weinberg, in 'Techniques of Chemistry, Vol. V, part 1, Technique of Electroorganic Synthesis', ed. N. L. Weinberg, Wiley-Interscience, New York, 1974, chapter 4.
157. T. Inoue and S. Tsutsumi, *Bull. Chem. Soc. Japan*, 1965, **38,** 661.
158. B. Belleau and Y. K. Au-Young, *Canad. J. Chem.*, 1969, **47,** 2117.
159. T. Shono and Y. Matsumura, *J. Org. Chem.*, 1970, **35,** 4157.
160. A. J. Baggaley and R. Brettle, *J. Chem. Soc.* (*C*), 1968, 2055.
161. H. Schäfer and E. Steckhan, *Angew. Chem. Internat. Edn.*, 1969, **8,** 518.
162. K. Sasaki, H. Urata, K. Uneyama, and S. Nagaura, *Electrochim. Acta*, 1967, **12,** 137.
163. R. F. Garwood, N.-ud-Din, and B. C. L. Weedon, *J.C.S. Perkin I*, 1975, 2471.
164. G. G. S. Dutton, *Adv. Carbohydrate Chem. Biochem.*, 1973, **28,** 11.
165. J. F. W. McOmie, 'Proctective Groups in Organic Chemistry', Plenum, New York, 1973.
166. A. M. Michelson and A. Todd, *J. Chem. Soc.*, 1956, 3459.
167. J. F. Klebe, *Adv. Org. Chem.*, 1972, **8,** 162.
168. E. W. Yankee, C. H. Lin, and J. Fried, *J.C.S. Chem. Comm.*, 1972, 112
169. R. K. Lustgarten and H. G. Richey, Jr., *J. Amer. Chem. Soc.*, 1974, **96,** 6393.
170. J. M. Simpson and H. G. Richey, Jr., *Tetrahedron Letters*, 1973, 2545.
171. W. Kirmse and H.-R. Murawski, *J.C.S. Chem. Comm.*, 1977, 122; W. Kirmse and M. Zeppenfeld, *J.C.S. Chem. Comm.*, 1977, 124.
172. M. T. Reetz, *Angew. Chem. Internat. Edn.*, 1972, **11,** 129, 131.
173. E. S. Huyser, 'Free-Radical Chain Reactions' Wiley-Interscience, New York, 1970, p. 80.
174. R. L. Letsinger, A. W. Schnizer, and E. Bobko, *J. Amer. Chem. Soc.*, 1951, **73,** 5708.
175. R. L. Letsinger and D. F. Pollart, *J. Amer. Chem. Soc.*, 1956, **78,** 6079.
176. I. T. Harrison, *Chem. Comm.*, 1969, 616.
177. H. A. Bruson, *Org. Reactions*, 1949, **5,** 79.
178. E. Wenkert and D. A. Berges, *J. Amer. Chem. Soc.*, 1967, **89,** 2507.
179. O. Grummitt, E. P. Budewitz, and C. C. Chudd, *Org. Synth. Coll. Vol. 4*, 1963, 748.
180. A. Skrabal and Z. Skrabal, *Z. phys. Chem.*, 1938, **A181,** 449.
181. S. Zeisel, *Monatsh.*, 1885, **6,** 989.
182. H. G. Fletcher, Jr., *Adv. Carbohydrate Chem.*, 1948, **3,** 45.

183. E. Staude and F. Patat, in 'The Chemistry of the Ether Linkage', ed. S. Patai, Interscience, London, 1967, chapter 2.
184. W. Lippert, *Annalen*, 1893, **276,** 148.
185. V. A. Derevitskaya, E. M. Klimov, and N. K. Kochetkov, *Tetrahedron Letters*, 1970, 4269.
186. J. L. Goldfarb and L. M. Smorgonski, *Ber.*, 1936, **69,** 1036.
187. F. G. Mann and F. H. C. Stewart, *J. Chem. Soc.*, 1954, 2819.
188. T. I. Lonshchakova, B. I. Buzykin, and V. S. Tsivunin, *Zhur. org. Khim.*, 1974, **10,** 2459 (*Chem. Abs.*, 1975, **82,** 57 625).
189. G. E. Ryschkewitsch and W. W. Lochmaier, *J. Amer. Chem. Soc.*, 1968, **90,** 6260.
190. L. H. Long and G. F. Freeguard, *Nature*, 1965, **207,** 403.
191. A. Rieche and H. Gross, *Chem. Ber.*, 1959, **92,** 83.
192. H. J. Bestmann, L. Mott, and J. Lienert, *Annalen*, 1967, **709,** 105.
193. B. Ganem and V. R. Small, Jr., *J. Org. Chem.*, 1974, **39,** 3728.
194. C. Eaborn, R. A. Jackson and R. W. Walsingham, *J. Chem. Soc.* (*C*), 1967, 2188.
195. M. H. Karger and Y. Mazur, *J. Amer. Chem. Soc.*, 1968, **90,** 3878.
196. W. Gerrard and M. F. Lappert, *Chem. Rev.*, 1958, **58,** 1081.
197. T. G. Bonner, E. J. Bourne, and S. McNally, *J. Chem. Soc.*, 1960, 2929.
198. G. O. Schenck, H.-D. Becker, K.-H. Schulte-Elte, and C. H. Krauch, *Chem. Ber.*, 1963, **96,** 509.
199. R. M. Barter and J. S. Littler, *J. Chem. Soc.*, 1967, 205.
200. T. Shono and Y. Matsumura, *J. Amer. Chem. Soc.*, 1969, **91,** 2803.
201. I. T. Harrison and S. Harrison, *Chem. Comm.*, 1966, 752.
202. E. C. Juenge and D. A. Beal, *Tetrahedron Letters*, 1968, 5819.
203. N. Deno, G. Saines and M. Spangler, *J. Amer. Chem. Soc.*, 1962, **84,** 3295.
204. N. V. Steere, in 'The Chemistry of the Ether Linkage', ed. S. Patai, Interscience, London, 1967, chapter 16.
205. A. I. Vogel, 'Practical Organic Chemistry', Longmans, London, 3rd edn. 1956, p. 163.
206. G. Sosnovsky and D. J. Rawlinson, in 'Organic Peroxides', ed. D. Swern, Wiley-Interscience, New York, 1970, vol. 1, chapter 9.
207. M. Freifelder, 'Practical Catalytic Hydrogenation', Wiley-Interscience, New York, 1971, chapter 14.
208. D. R. Moore, *J. Org. Chem.*, 1961, **26,** 3596.
209. E. Santiago and J. Simonet, *Electrochim. Acta*, 1975, **20,** 853.
210. G. Wittig and L. Löhmann, *Annalen*, 1942, **550,** 260.
211. G. Wittig, *Bull. Soc. chim. France*, 1971, 1921.
212. R. B. Woodward and R. Hoffmann, *Angew. Chem. Internat. Edn.*, 1969, **8,** 781.
213. U. Schöllkopf, *Angew. Chem. Internat. Edn.*, 1970, **9,** 763.
214. H. Schäfer, U. Schöllkopf, and D. Walter, *Tetrahedron Letters*, 1968, 2809.
215. J. F. Garst and C. D. Smith, *J. Amer. Chem. Soc.*, 1976, **98,** 1526.
216. H. Felkin and A. Tambute, *Tetrahedron Letters*, 1969, 821.
217. J. E. Baldwin, J. De Bernardis, and J. E. Patrick, *Tetrahedron Letters*, 1970, 353.
218. J. E. Baldwin and J. E. Patrick, *J. Amer. Chem. Soc.*, 1971, **93,** 3556.
219. U. Schöllkopf, K. Fellenberger, and M. Rizk, *Annalen*, 1970, **734,** 106.
220. A. Wright and R. West, *J. Amer. Chem. Soc.*, 1974, **96,** 3222.
221. A. Jefferson and F. Scheinmann, *Quart. Rev.*, 1968, **22,** 391.
222. P. Vittorelli, T. Winkler, H.-J. Hansen, and H. Schmid, *Helv. Chim. Acta*, 1968, **51,** 1457.
223. R. K. Hill and A. G. Edwards, *Tetrahedron Letters*, 1964, 3239.
224. P. Cresson and L. Lacour, *Compt. rend.*, 1966, **262,** 1157.
225. S. Bancel and P. Cresson, *Compt. rend.*, 1970, **270,** 2161.
226. W. G. Dauben and T. J. Dietsche, *J. Org. Chem.*, 1972, **37,** 1212.
227. C. G. Krespan, *Tetrahedron*, 1967, **23,** 4243.
228. D. K. Black and S. R. Landor, *J. Chem. Soc.*, 1965, 6784.
229. W. J. Le Noble, P. J. Crean, and B. Gabrielsen, *J. Amer. Chem. Soc.*, 1964, **86,** 1649.
230. J. A. Katzenellenbogen and T. Utawanit, *Tetrahedron Letters*, 1975, 3275.
231. S. J. Rhoads and N. B. Raulins, *Org. Reactions*, 1975, **22,** 1.
232. D. J. Faulkner and M. R. Petersen, *J. Amer. Chem. Soc.*, 1973, **95,** 553; A. F. Thomas, *ibid.*, 1969, **91,** 3281.
233. D. Elad, in 'The Chemistry of the Ether Linkage', ed. S. Patai, Interscience, London, 1967, chapter 8.
234. H.-P. Schuchmann, C. von Sonntag, and G. Schomburg, *Tetrahedron*, 1972, **28,** 4333.
235. C. von Sonntag and H.-P. Schuchmann, *Adv. Photochem.*, 1977, **10,** 59.
236. C. von Sonntag, K. Neuwald, H.-P. Schuchmann, F. Weeke, and E. Janssen, *J.C.S. Perkin II*, 1975, 171; K. Maeda, A. Nakane and H. Tsubomura, *Bull. Chem. Soc. Japan*, 1975, **48,** 2448.
237. R. Payette, M. Bertrand, and Y. Rousseau, *Canad. J. Chem.*, 1968, **46,** 2693.
238. E. Müller and H. Huber, *Chem. Ber.*, 1963, **96,** 2319.
239. G. E. Hall and F. M. Ubertini, *J. Org. Chem.*, 1950, **15,** 715.
240. G. Sosnovsky, *J. Org. Chem.*, 1963, **28,** 2934.
241. C. Walling and M. J. Mintz, *J. Amer. Chem. Soc.*, 1967, **89,** 1515.
242. P. Ballinger, P. B. D. de la Mare, G. Kohnstam, and B. M. Prestt, *J. Chem. Soc.*, 1955, 3641.
243. J. Hine and R. J. Rosscup, *J. Amer. Chem. Soc.*, 1960, **82,** 6115.

244. B. L. Van Duuren, A. Sivak, B. M. Goldschmidt, C. Katz, and S. Melchionne, *J. Nat. Cancer Inst.*, 1969, **43,** 481.
245. T. C. Jones and E. R. Thornton, *J. Amer. Chem. Soc.*, 1967, **89,** 4863.
246. L. Summers, *Chem. Rev.*, 1955, **55,** 301.
247. F. J. Soday and C. E. Boord, *J. Amer. Chem. Soc.*, 1933, **55,** 3293.
248. J. L. Simonsen and R. Storey, *J. Chem. Soc.*, 1909, **95,** 2106.
249. R. M. Coates and J. E. Shaw, *J. Org. Chem.*, 1970, **35,** 2597, 2601.
250. P.-E. Sum and L. Weiler, *J.C.S. Chem. Comm.*, 1977, 91.
251. G. A. Olah and J. J. Svoboda, *Synthesis*, 1973, 52.
252. U. Schöllkopf and W. Pitteroff, *Chem. Ber.*, 1964, **97,** 636.
253. E. J. Corey, Z. Arnold, and J. Hutton, *Tetrahedron Letters*, 1970, 307.
254. G. Wittig, W. Böll, and K.-H. Krück, *Chem. Ber.*, 1962, **95,** 2514.
255. G. R. Pettit, B. Green, G. L. Dunn, and P. Sunder-Plassmann, *J. Org. Chem.*, 1970, **35,** 1385.
256. C. Earnshaw, C. J. Wallis, and S. Warren, *J.C.S. Chem. Comm.*, 1977, 314.
257. E. Taskinen and K. Jokila, *Acta Chem. Scand.*, 1975, **29B,** 249.
258. A. Kankaanpera and M. Mattsen, *Acta Chem. Scand.*, 1975, **29A,** 419.
259. H. C. Brown, 'Hydroboration', Benjamin, New York, 1962, p. 112.
260. L. J. Dolby, C. A. Ellinger, S. Esfandiari, and K. S. Marshall, *J. Org. Chem.*, 1968, **33,** 4508.
261. T. J. Prosser, *J. Amer. Chem. Soc.*, 1961, **83,** 1701.
262. D. A. Evans, G. C. Andrews, and B. Buckwalter, *J. Amer. Chem. Soc.*, 1974, **96,** 5561.
263. D. H. Hunter, Y. Lin, A. L. McIntyre, D. J. Shearing, and M. Zvagulis, *J. Amer. Chem. Soc.*, 1973, **95,** 8327.
264. G. W. Klumpp and R. F. Schmitz, *Tetrahedron Letters*, 1974, 2911.
265. C. C. Price, *Accounts Chem. Res.*, 1974, **7,** 294.
266. G. Natta, *J. Polymer Sci.*, 1955, **16,** 143.
267. E. J. Vandenberg, *J. Polymer Sci.* (*B*), 1964, **2,** 1085.
268. T. Tsuruta, *J. Polymer Sci.* (*D*), 1972, **6,** 179.
269. C. C. Price, R. Spector, and A. L. Tumolo, *J. Polymer Sci.* (*A1*), 1967, **5,** 407.
270. C. C. Price and M. Osgan, *J. Amer. Chem. Soc.*, 1956, **78,** 4787.
271. E. J. Vandenberg, *J. Polymer Sci.*, 1960, **47,** 489.
272. J. Lal, J. E. McGrath, and G. S. Trick, *J. Polymer Sci.* (*A1*), 1967, **5,** 795.
273. H. Tadokoro, Y. Takahashi, Y. Chatani, and H. Kakida, *Macromol. Chem.*, 1967, **109,** 96.
274. J. Smid, *Angew. Chem. Internat. Edn.*, 1972, **11,** 112.
275. F. Vogtle and E. Weber, *Angew. Chem. Internat. Edn.*, 1974, **13,** 814.

4.4

Cyclic Ethers

A. H. HAINES
University of East Anglia

4.4.1 NOMENCLATURE 853
4.4.2 BONDING AND MOLECULAR GEOMETRY IN CYCLIC ETHERS 854
4.4.3 BASICITY AND SOLVENT PROPERTIES 857
4.4.4 CYCLIC ETHERS CONTAINING ONE OXYGEN ATOM IN THE RING 860
4.4.4.1 Synthesis of oxirans 860
4.4.4.2 Reactions of oxirans 866
4.4.4.3 Synthesis of oxetans 870
4.4.4.4 Reactions of oxetans 873
4.4.4.5 Tetrahydrofurans, tetrahydropyrans, and higher members of the series 875
4.4.5 CYCLIC ETHERS CONTAINING MORE THAN ONE OXYGEN ATOM IN THE RING (EXCLUDING CYCLIC ACETALS) 881
4.4.5.1 1,4-Dioxan and 1,4-dioxepan 881
4.4.5.2 Macrocyclic polyethers 883

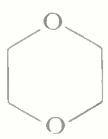
4.4.1 NOMENCLATURE

Monocyclic ethers of three- to ten-membered rings are named, preferably, by the Hantzsch–Widman system,[1] whereby a prefix, denoting the number of oxygen atoms, is combined with a suffix denoting ring size and the state of saturation of the ring. Thus the saturated cyclic ethers containing only one oxygen atom in the ring, and having three-, four-, five-, six-, seven-, eight-, nine-, and ten-membered rings, are named oxiran, oxetan, oxolan, oxan, oxepan, oxocan, oxonan, and oxecan, respectively.* However, it is not usual for the five- and six-membered ring compounds to be named in this way; they are regarded as derivatives of the parent unsaturated systems, which bear the trivial names furan and pyran, and therefore are termed tetrahydrofuran and tetrahydropyran, respectively. Additive nomenclature is sometimes used for oxirans when systematic naming might obscure the relation to the parent compound, *e.g.* styrene oxide instead of 2-phenyloxiran, but its use is generally discouraged. Substitutive nomenclature, involving the use of the prefix 'epoxy', is useful to preserve the name of a specific complex structure, *e.g.* of a steroid. Cyclic ethers derived from compounds containing hydroxy groups, *e.g.* carbohydrates, may be named by subtractive nomenclature, the loss of water being denoted by the prefix 'anhydro', with locants indicating the positions of the two hydroxy groups involved.

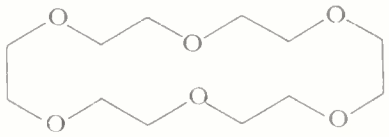
Monocyclic ethers containing more than one oxygen atom in the ring are described by a prefix dioxa-, trioxa-, tetraoxa-, *etc.*, placed before the appropriate descriptor of ring size and state of saturation, the positions of the oxygen atoms being indicated by numbers; in

* U.K. Chemical Society rules; IUPAC rules add a terminal 'e' to all these names, giving oxirane, *etc.*

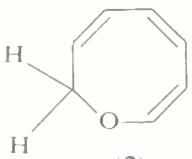
these cases, five- and six-membered ring compounds follow the Hantzsch–Widman system. Therefore (**1**) is 1,4-dioxan. For monocyclic ethers with ring sizes greater than ten, a replacement name is formed from the cycloalkane of the corresponding ring size. Thus (**2**) is 1,4,7,10,13,16-hexaoxacyclo-octadecane.



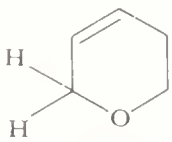
(1)



(2)



(3)



(4)

Unsaturated monocyclic ethers are readily named using the Hantzsch–Widman system, which designates a characteristic stem name for the corresponding ring containing the maximum number of non-cumulative double bonds, but in certain cases a locant is required to indicate the position of the saturated atom. For example, (**3**) is 2*H*-oxocin. The five- and six-membered ring cases are again treated less systematically, and are named from furan and pyran, respectively. Thus (**4**) is 5,6-dihydro-2*H*-pyran.

4.4.2 BONDING AND MOLECULAR GEOMETRY IN CYCLIC ETHERS

A well recognised property of the ether linkage is its unreactivity, which leads to the extensive use of ethers as solvents for many organic reactions. In tetrahydrofuran and tetrahydropyran, angle strain is relatively small in their minimum energy conformations, and these compounds have properties which are, largely, typical of their acyclic counterparts. However, in oxiran and oxetan, considerable angle strain is present in addition to torsional strain resulting from eclipsing interactions, leading to the greatly enhanced reactivity that is generally observed for these compounds in ring-opening reactions. Measurements of the heats of formation[2] and heats of combustion[3] of the simpler cyclic ethers indicate the considerable strain present in the three- and four-membered rings (see Table 1), but they also reveal that, even in tetrahydropyran, a slight ring strain is present. This has been suggested[2] to be angular in origin, and results from the fact that a carbon–oxygen bond is shorter than a carbon–carbon bond.

TABLE 1

Strain Energies in Cyclic Ethers

Cyclic ether	*Strain energies* (kJ mol^{-1})	
$(CH_2)_2O$	117.2[a]	114.1[b]
$(CH_2)_3O$	—	106.7[b]
$(CH_2)_4O$	28.0[a]	23.6[b]
$(CH_2)_5O$	9.2[a]	4.9[b]

[a] See Ref. 2. [b] See Ref. 3.

Replacement of a CH_2 group in a cycloalkane by an O atom introduces a dipole moment into the molecule. Values obtained[4] for the dipole moments of oxiran in benzene solution are around 1.8–1.9 D, whilst those of oxetan, tetrahydrofuran, and tetrahydropyran in the same solvent are reported[5] as 1.92, 1.75, and 1.55 D, respectively. In comparison, diethyl ether has a dipole moment of 1.26 D in benzene. Although there is some evidence based on donor ability for an abnormally high electron density on the oxygen atom of oxetan (see Section 4.4.3), this is not reflected in its dipole moment, which falls within the range expected on the basis of a normal C—O bond moment.

As the C—O bond is generally found to be shorter than the C—C bond, replacement of

a CH_2 group in a cycloalkane by an O atom might be expected to cause small but significant changes in ring geometry. However, the C—C bond length in oxiran[4] at 147 pm is less than that of a normal C—C bond (154 pm), and this fact, coupled with a C—O bond length of 144 pm, means that oxiran possesses internal bond angles of 61° 24′ for COC, close to those in cyclopropane (60°). On the other hand, electron diffraction spectroscopy has shown that in oxetan both the C—C and C—O bond lengths, at 155.3 ± 0.3 and 145.7 ± 0.2 pm respectively[5], are close to normal values and the molecule is not quite square-shaped. The largest internal angle, $94.2 \pm 2.5°$, is that at the oxygen atom, and the smallest, $86.8 \pm 2.5°$, is at the carbon atom opposite to it.

Electron diffraction studies of tetrahydrofuran[6] and 1,4-dioxan[7] show that the bond lengths do not differ significantly from those normally found for C—H, C—O, and C—C bonds. Similar experimental data on tetrahydropyran do not appear to be available. For tetrahydrofuran, the extreme values of the ranges of the bond angles CCO and CCC, computed for a pseudorotating molecule, lie within 6° of the extreme values of the similarly calculated CCC bond-angle range in cyclopentane,[8] and for 1,4-dioxan the sizes of the bond angles CCO ($109.2 \pm 0.5°$) and COC ($112.45 \pm 0.5°$) are close to that of the CCC angle ($111.55 \pm 0.15°$) in cyclohexane. X-Ray crystallographic measurements on pyranoid derivatives of carbohydrates indicate the C—O and C—C bond lengths are generally close to 142 and 154 pm, respectively, and that endocyclic COC angles are usually larger than the tetrahedral value, leading, as with cyclohexane, to considerable flattening of the ring.[9]

Three-membered rings must be planar, but cyclobutane is puckered[10] and undergoes conformational inversion with an energy barrier of approximately 5.9 kJ mol^{-1}. Through puckering, strain is relieved that would occur in a planar form as a result of C—H bond-eclipsing interactions. In contrast, spectroscopic measurements on oxetan indicate that it is an essentially planar molecule; although an inversion barrier of approximately 0.17 kJ mol^{-1} separates the puckered forms, the zero-point energy of the puckering vibration is sufficient to surmount this small barrier, and the four-membered ring may be considered to be vibrating about the planar form. This difference between the two four-membered ring compounds may be a result of there being only half as many hydrogen-eclipsing interactions in oxetan as in cyclobutane.

Infrared[11] and electron diffraction[6] measurements on tetrahydrofuran in the gas phase show the ring is puckered and that it exhibits pseudorotational behaviour (somewhat impeded) similar to cyclopentane, but it appears that the amplitude of puckering is smalter than in cyclopentane.[8] This finding has been rationalized in terms of the larger force-constant for COC valency angle deformation and the smaller barrier to internal rotation around the C—O bonds in tetrahydrofuran.

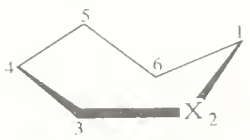
N.m.r. spectroscopic measurements[12] suggest that tetrahydropyran adopts a chair conformation in solution, and X-ray studies[13] on pyranoid carbohydrates provide ample support for the relative stability of this ring conformer in the solid state. The free energies of activation, $\Delta G^{\neq}_{c-tb}$, for the chair to twist-boat interconversion in cyclohexane and tetrahydropyran measured in carbon disulphide have been recorded[14] as 43.1 and 41.4 kJ mol^{-1}, respectively.* Although deductions from such small differences may be hazardous in view of the likely experimental errors, the lower value of $\Delta G^{\neq}_{c-tb}$ for the heterocycle may be understood in terms of internal rotation barriers in analogous acyclic compounds.[14] The barrier to the conformational interconversion of cyclohexane is predominantly the result of torsional strain in the half-chair transition state (**5**), in which there is

* The values for free energy of activation reported in table 1 and table 2 of Ref. 14 are for the chair to twist-boat interconversion, and it is useful to distinguish them by the symbol $\Delta G^{\neq}_{c-tb}$ in order to avoid confusion with the free energy of activation for the chair–chair inversion, described by $\Delta G^{\neq}_{c-c}$. Values of $\Delta G^{\neq}_{c-tb}$ in Ref. 14 were calculated by the following equation:

$$\Delta G^{\neq}_{c-tb} = 19{\cdot}16\ T_c[9.67 + \log_{10}(T_c/\delta\omega)]\ \text{J mol}^{-1}$$

which is equation (3) given in that paper but corrected for a misprint. In table 1 of Ref. 14, equation (3) is incorrectly referred to as equation (4) (R. K. Harris, personal communication).

eclipsing across the C-2—C-3 bond, and the torsional angles across the C-1—C-2 and C-3—C-4 bonds are small. In contrast, torsional angles about the C-5—C-6 bond are close to 60°. Replacement of the 5-CH_2 group by an O atom has only a small effect on the enthalpy of formation of the half-chair form, but a considerable effect occurs when the 2-CH_2 group (or to a lesser extent the 1-CH_2 group) is replaced by an O atom. Thus the barrier to ring inversion in tetrahydropyran may be significantly decreased compared with that in cyclohexane, especially if the transition state is (**6**). On similar considerations, the estimated barrier for 1,4-dioxan is lower by approximately 3.8 kJ mol^{-1} than that for cyclohexane and it is interesting that variable-temperature ^1H n.m.r. spectroscopy affords[15] a free energy of activation for the chair to twist-boat interconversion of 39.3 kJ mol^{-1}. In 1,3,5-trioxan, ring inversion is very fast indeed.[16]



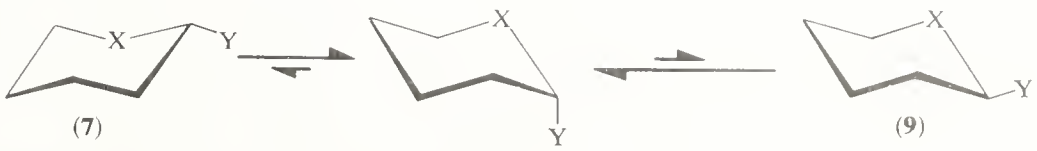
(**5**) X = CH_2
(**6**) X = O

Consideration of the preferred conformations of cycloalkanes, of the reduction in steric interactions which may occur on replacing a CH_2 group in cycloalkanes by an O atom, and of the conformational preferences about C—C and C—O bonds in the O—CH_2—CH_2—O unit,[17] has led to predictions concerning the most probable conformations of some cyclic polyethers. X-Ray crystallography confirmed that 1,5,9,13-tetraoxacyclohexadecane crystallized in the expected square-ring conformation, with the skeleton based on the diamond lattice, and with ether oxygens in the middles of all four sides. In the case of 1,4,7,10,13,16-hexaoxacyclo-octadecane, the similarity of the i.r. spectrum of its potassium bromide complex to that of crystalline polyethylene glycol, which is known to have helically arranged monomer units O—CH_2—CH_2—O with antiperiplanar (*ap*), synclinal (*sc*), and antiperiplanar (*ap*) conformations about the O—C, C—C, and C—O bonds respectively, led to the suggestion that, with a central ion present, the cyclic polyether adopts the conformation with virtual D_{3d} symmetry. This is the only diamond lattice conformation able to accommodate six identical *ap*, *sc*, *ap* units. X-Ray crystallography confirmed strikingly that this conformation was present in the crystals of the potassium, rubidium, and caesium cationic complexes, all torsion angles about C—C bonds being close to 65° and those about C—O bonds being close to 180°. However, this ring geometry is not invariant with respect to the metal ion, nor is it adopted in the absence of the latter. In the case of the sodium complex, the central ion is too small to fill the central cavity and the cyclic polyether adopts an alternative conformation in which one of the oxygen atoms is drawn out of the mean plane of the other five to give a pentagonal-pyramidal coordination about the sodium ion. The uncomplexed cyclic polyether adopts a conformation of the diamond lattice type, but one in which there are three kinds of O—CH_2—CH_2—O units, *ap*, *sc*, *ap* (as in the D_{3d} conformation), *ap*, *ap*, *ap*, and *sc*, *sc*, *ap*.* If the uncomplexed cyclic polyether adopted the conformation present in the potassium complex, all six dipoles would point together, presumably an unfavourable situation.

One of the most fruitful concepts that has come from a study of carbohydrates is that of the anomeric effect.[19] From the beginning of conformational analysis it was apparent that the basic tenet, that a bulky substituent on a six-membered ring is energetically more favoured in the equatorial orientation, did not apply to electronegative substituents at the anomeric centre of a carbohydrate, that is at C-1 of a glycopyranose ring. The term 'anomeric effect' was initially introduced to describe the special driving force that appeared to exist for the 1-acetoxy group to achieve an axial orientation in acetylated

* The conformations adopted by 1,4,7,10,13,16-hexaoxacyclo-octadecane in its uncomplexed and complexed forms may best be appreciated by means of the published[18] stereoscopic diagrams.

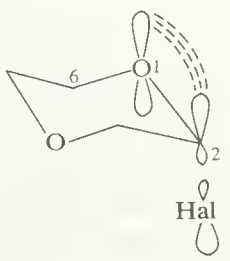
pento- and hexo-pyranoses. However, the more general nature of the effect was soon recognized and, for six-membered rings containing a heteroatom, the situation may be summarized as shown in equation (1), where X is generally O or S, and Y is an electronegative substituent, *e.g.* halogen, RCOO, or RO. The preferred axial orientation for Y may be achieved either by conformational inversion, (**7**)⇌(**8**), or by configurational inversion, (**8**)⇌(**9**).



(**7**) (**8**) (**9**) (1)

The anomeric effect has been studied in 2-halotetrahydropyrans[20,21] and in their 4-methyl derivatives[21] by determination of the conformational equilibrium (**7**)⇌(**8**) using ^{1}H n.m.r. spectroscopy. The sole detectable conformation of 2-chloro- and 2-bromo-tetrahydropyran was that one containing the axial halogen, and values for the magnitude of the anomeric effect for the chloro and bromo substituents were ⩾11.3 and ⩾13.4 kJ mol^{-1}, respectively.

X-Ray studies[22] of *trans*-2,3- and *trans*-2,5-dihalo-1,4-dioxans show that they adopt chair conformations in the crystalline state and that the halogen atoms occupy axial positions, in accordance with the expected influence of the anomeric effect. Accurate determination of bond lengths in these and in related compounds has led to one of the several[19] explanations proposed for the origin of the anomeric effect.* The C-2—O bonds in the above compounds are found to be consistently shorter than C-6—O bonds, the latter having similar lengths to C—O bonds in simple aliphatic ethers. A description of bonding has been suggested in which non-bonding electrons on ring oxygens are delocalized by quantum mechanical mixing of the oxygen *p*-orbital with the antibonding orbital of the C-2—halogen bond (see **10**). This would lead to strengthening (and thus shortening) of the C-2—O bond and weakening (and thus lengthening) of the C-2—halogen bond. Indeed, in many such compounds the C—halogen bond is longer than the corresponding bond in simpler aliphatic halides.



(**10**)

The existence of a reverse anomeric effect has been noted; the equatorial orientation for an electropositive substituent at a position α to a heteroatom in a six-membered ring appears to be energetically favoured.

4.4.3 BASICITY AND SOLVENT PROPERTIES

The chemistry of the ether linkage is governed largely by the behaviour of the lone-pair electrons on oxygen. Although the conventional picture of these lone-pairs is one with them localized in two sp^3-hybrid orbitals, it is often advantageous to take account of their energetic non-equivalence.[23] In any event, the lone-pair electrons form a basic site for the addition of protons and Lewis acids, and for the formation of oxonium salts. Therefore an

* For a fuller discussion of the anomeric effect, the reader should consult Ref. 9, pp. 72–87.

understanding of the chemistry of cyclic ethers must depend, to a great extent, on a knowledge of how the nucleophilicity of the ether oxygen atom varies with ring size. This variation results, presumably, from changes in hybridization of the orbitals at the oxygen atom, from changes in steric hindrance towards electrophilic attack at oxygen, and from changes in interactions of electrons in the lone-pair orbitals with those in orbitals on adjacent atoms.

A property reflecting the tendency of an ether to undergo electrophilic attack is its basicity.[24] Although the concept of basicity is commonly recognized, it is not possible to define it in an absolute sense, and therefore an immutable basicity scale for this or any other series of compounds cannot be constructed. The relative basicities of ethers, as measured by their interactions with electrophilic species, may depend, amongst other things, on the type of bonding between the entities, the medium in which measurement is made, and even on the temperature of measurement. Thus the relative orders of basicity towards protonic and non-protonic acids may not necessarily be the same. Other types of measurement, based on dipole moments or ionization potentials, may involve the lone molecule and give an indication of basicity by measuring electron density or electronic energies associated with the basic site, but because of the completely different nature of the experiment, it is not improbable that a different order of basicity will be indicated from that obtained by other means. Nevertheless, many of the measurements in solution do provide a similar pattern for the variation of basicity with ring size.

The literature on the basicity of the ethers, and of their complexing abilities, is vast and has been discussed in some detail.[24,25] The few examples cited here are chosen because, in the main, they concerned studies made on a representative number of the cyclic ethers $(CH_2)_nO$ from $n = 2$ to 7, with a particular method of measurement.

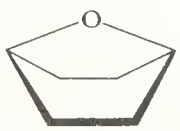
The relative basicity of some ethers towards aqueous sulphuric acid have been measured by a solvent extraction–g.l.c. procedure.[24] The pK_a values of their oxonium ions indicated that cyclic ethers, in general, are markedly more basic than simple acyclic ones, and that basicity decreases in the order: oxepan (−2.02), tetrahydrofuran (−2.08), tetrahydropyran (−2.79), 1,4-dioxan (−3.22), diethyl ether (−3.59). The greater basicity of tetrahydrofuran over tetrahydropyran towards hydrogen chloride has been observed using Henry's law constants as criteria, and this order has been rationalized in terms of the relief, on protonation, of non-bonded repulsions between lone-pair electrons on oxygen and electrons in the adjacent C—H bonds.

Tetrahydrofuran was found to be a stronger complexing agent than tetrahydropyran towards boron trifluoride[24,26] and stannic chloride.[27] Substitution of a methyl group for a hydrogen atom at C-2 in tetrahydrofuran decreases the degree of interaction,[27,28] indicating steric factors are important in interactions of this ether with these bulky electrophiles. The strength of complexing of dinitrogen tetraoxide with cyclic ethers has been determined by cryoscopic methods; interestingly, the alkyl groups in 2-methyl- and 2,5-dimethyl-tetrahydrofuran appeared to offer little steric hindrance to complexing.[25]

The electron-donor abilities of oxetan, tetrahydrofuran, tetrahydropyran, and 2-methyloxiran towards iodine in hexane have been measured by u.v. spectroscopy[24] and found to decrease in the order given. The same order was observed[24] in a study of their hydrogen-bonding with methan[^{2}H]ol using i.r. spectroscopy, and by measurement of their heats of mixing with chloroform. Further confirmation of these relative donor abilities (with oxiran instead of 2-methyloxiran) comes from n.m.r. spectroscopic studies[29] using the change in chemical shift of the ^{1}H signal of chloroform induced by these ethers as a measure of the extent of bonding. I.r. spectroscopic studies[30] on hydrogen bonding between cyclic ethers and phenol afforded association constants which were also consistent with the order above, and which emphasized the low and high donor abilities, respectively, of three- and four-membered ring ethers. An interesting rationalization of the position of oxetan in the order is based on the premise that a strong hydrogen bond to the ether will occur if the lone pair engaged in bonding has a large atomic dipole moment at the donor atom. That supposition is best fulfilled by an *sp*-hybrid orbital. If the further assumptions are made that in oxiran the lone-pair electrons occupy *s*- and *p*-orbitals,

whereas in tetrahydrofuran they occupy sp^3-hybrid orbitals, it is apparent that oxetan may reasonably be expected to possess one orbital occupied by non-bonding electrons, which has approximately *sp*-character, thus endowing the ether with the highest donor-ability.

In contrast to the above results, the ionization potentials of cyclic ethers, obtained by photoelectron spectroscopy, have been taken to indicate that the basicity of the lone-pair electrons in these compounds increases with ring size.[31] However, in view of the fact that such measurements reflect electronic energies rather than electron densities, it is questionable, perhaps, whether these or related measurements can afford a meaningful measure of basicity. Alternatively, the results may indicate the important influence of solvent. An illustration of solvent effects is provided[32] by basicity measurements on 7-oxabicyclo-[2,2,1]heptane (**11**). In aqueous sulphuric acid the ether is less basic than tetrahydrofuran and has about the same basicity as tetrahydropyran, an unexpected result as the COC bond angle is comparable with that in oxetan. However, the hydrocarbon cage which surrounds part of the protonated oxygen atom in the oxonium ion may well prevent solvent stabilization of the species. Significantly, hydrogen-bonding measurements, and iodine complexation studies in heptane, indicated that ether (**11**) is a better donor than tetrahydrofuran; in these cases, solvent stabilization of the complexed species would be expected to be less important.



(**11**)

There is ample evidence[25,33] that metal cations are very efficiently solvated by ethers and that the constitution of certain organometallic derivatives is strongly influenced by the donor ability of the ether solvent in which they are frequently prepared. A consideration of the 'Principle of Hard and Soft Acids and Bases'[34] suggests that oxygen-containing bases, usually classified as hard, should readily coordinate with hard acids, those hard acids of particular interest to the present discussion being cations of the alkali and alkaline-earth metals. The extensive hydration of such ions in aqueous solution is, of course, in direct accord with the Principle and it is to be expected, therefore, that ethers should readily occupy the coordination sphere of those metal ions, and that there will be a variation in coordinating ability with ether structure. The complexing action of ethers towards alkali metal ions finds full expression in the macrocyclic polyethers, which are discussed in Section 4.4.5.2, but the discussion here is confined to simpler cyclic ethers.

The dissolution of sodium and potassium in certain ethers to afford blue solutions containing solvated cations and solvated electrons appears to be controlled by the ability of the solvent to stabilize the cation.[35] Simple acyclic ethers, tetrahydropyran, 1,4-dioxan, and oxetan were not effective in this reaction, but tetrahydrofuran was moderately effective. Significantly, 2-methoxymethyltetrahydrofuran, which contains an extra coordination site leading to the possibility of ion chelation, was a particularly good solvent for this reaction, as was 2,5,8,11-tetramethyl-1,4,7,10-tetraoxacyclododecane. Tetrahydrofuran shows a similar superior ability over diethyl ether for solvating sodium ions in the reaction[36] between sodium and naphthalene to afford sodium dihydronaphthylide ($Na^+ C_{10}H_8^{\bullet -}$).

Some of the most pertinent data on the relative solvating abilities of cyclic ethers towards alkali metal ions has arisen from a study[37] of contact and solvent-separated ion pairs. From u.v. spectroscopic measurements on 9-fluoroenyl-lithium in many ether solvents it was concluded that the proportion of solvent-separated ion pairs — and thus presumably the degree of cation solvation — was closely related to the basicity of the oxygen atom as measured by hydrogen bonding, calorimetry, and iodine complexation studies. Oxepan, however, was found to be less effective than tetrahydrofuran in promoting ion separation, which contrasts with its reported greater basicity, based on pK_a

measurements, than tetrahydrofuran.[24] The solvating power of 2-methoxymethyltetrahydrofuran was found to be vastly superior to that of tetrahydrofuran, illustrating again the importance of chelation in ether–ion interactions. However, two oxygen atoms in the same ring are not similarly effective: 1,4-dioxan was less effective than tetrahydrofuran in inducing ion separation. Steric effects are important in these interactions; 2-methyl- and 2,5-dimethyl-tetrahydrofuran showed poorer solvating properties than tetrahydrofuran itself.

In organometallic chemistry the advantages of replacing diethyl ether by tetrahydrofuran for many reactions have long been recognised. For example, vinyl Grignard reagents may be prepared readily in tetrahydrofuran, but in diethyl ether the preparation is usually unsuccessful or unsatisfactory.[38] Also, various reactions of simple alkyl-lithium compounds occur more rapidly in tetrahydrofuran than in diethyl ether, and, indeed, reactions may take a different course in the two solvents. Increased nucleophilic character of the carbanion when lithium is coordinated with a strong donor and an accompanying decrease in the degree of aggregation[33] of the organometallic compound seem to be the reasons for these variations in reactivity with solvent.

Although the structure of Grignard reagents in solution has been a matter of much controversy,[39] it appears that reagents prepared from alkyl bromides or iodides in diethyl ether at concentrations of 0.5–1M, or from alkyl chlorides in diethyl ether at all concentrations, are dimeric. However, in tetrahydrofuran, over a wide range of concentrations, Grignard reagents from alkyl bromides and iodides are monomeric, and ethyl magnesium chloride appears to be monomeric even at concentrations of 2M. These differences are presumably a result of the more basic tetrahydrofuran being able to displace halogen from the coordination positions about the metal better than the weakly basic diethyl ether, with which halogen can compete with some success.

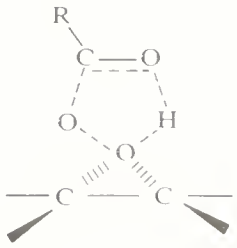
4.4.4 CYCLIC ETHERS CONTAINING ONE OXYGEN ATOM IN THE RING

A chapter on cyclic ethers by Gritter[40] lists earlier reviews on the chemistry of various members of this series of compounds. More recently, oxiran synthesis,[41] oxiran reactions,[42] and carbohydrate oxirans[43] have been discussed, and a monograph on heterocyclic compounds containing oxygen and sulphur has appeared.[44] This section comprises a brief, general survey of the synthesis and reactions of monocyclic ethers, with emphasis on some recent developments.

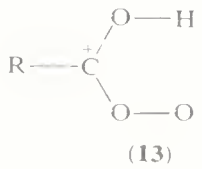
4.4.4.1 Synthesis of oxirans

Perhaps the most widely used laboratory method of oxiran synthesis is the peroxy acid oxidation of alkenes. The high stereoselectivity of the addition reaction indicates a mechanism involving a cyclic transition state such as (**12**) which is also in accord with the finding that peroxy acids exist as monomeric, intramolecularly hydrogen-bonded species in solution. Basic solvents lower the rate of oxiran formation*, but in solvents with negligible donor properties the rates of reaction are related to their dielectric constants, a dependence which would be expected for a reaction in which the transition state is more polar than the reactants. Alternative mechanisms have been suggested, involving 1,3-dipolar addition to the alkene of a dipolar tautomer of the peroxy acid such as (**13**), but no conclusive evidence is forthcoming.

* The term 'epoxidation' is commonly used to describe the process of oxiran formation but in view of the fact that oxiran, and not epoxide, is the class name for the three-membered ring heterocycle, the continued use of the term epoxidation is not to be encouraged. If a word is required to describe the synthetic step, logically, it would be oxiranation.

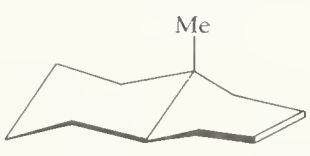


(12)

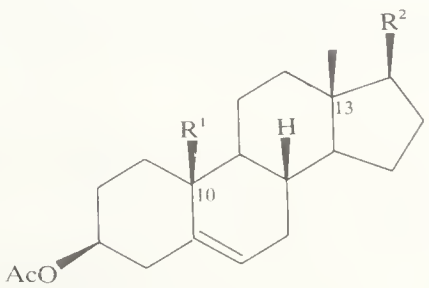


(13)

The factors which control the stereochemistry of oxiran synthesis are summarized in an excellent review by Berti.[41] In compounds devoid of polar groups, steric factors are very important in controlling the direction of addition of peroxy acids to alkenes. This is perhaps most clearly illustrated in molecules possessing at least partial conformational rigidity, for example in some polycyclic alkenes, where the most sterically favoured direction for reagent approach can often be defined. Thus on reaction with *p*-nitroperbenzoic acid, the cycloalkene (**14**) affords,[45] exclusively, the oxiran resulting from attack *trans* to the methyl group. However, factors more subtle than simple steric hindrance to the reagent may influence the preferred direction of addition. Steric hindrance arising from the axial methyl groups at C-10 and C-13 in the carbon skeleton of cholestane is often invoked to rationalize the predominance of α-attack that occurs in reactions on some of its derivatives. Thus treatment of cholesteryl acetate (**15**) with peroxy acids gives[46] α- and β-5,6-oxides in the ratio of approximately 7:3. However, oxiranation of the related 19-nor-androstene derivative (**16**), which lacks one of the axial methyl groups present in (**15**), shows an even greater stereoselectivity for α-attack.[47] A rationalization[41] of these results has been based on the supposition that α-attack on the $^5\Delta$-compounds is favoured with or without the C-10 methyl group present and that since *syn* diaxial-type interactions between the C-10 methyl group and H-8 are higher in the α- than in the β-oxide derivative of (**15**), the presence of the axial methyl group at C-10 diminishes the preference for the formation of the α-oxide.

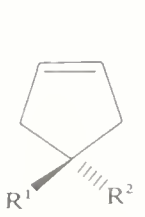


(14)

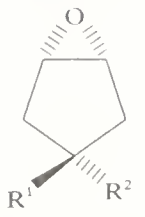


(**15**) $R^1 = Me$, $R^2 = C_8H_{17}$
(**16**) $R^1 = H$, $R^2 = OAc$

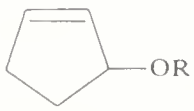
Control exercised by an alkyl group in oxiran formation from a monocyclic alkene is illustrated by reaction of 4-methylcyclopentene (**17**) with peroxylauric acid in cyclopentane or acetonitrile, which yields[48] a mixture of *trans*- and *cis*-oxides, (**18**) and (**19**), respectively, in the ratio of approximately 3:1. The apparent lack of solvent effect suggests that the directing influence is steric and not polar in origin. With 4-cyanocyclopentene (**20**), oxiran formation in cyclopentane led to *trans* attack to the extent of 95%, notwithstanding the smaller size of the cyano group, but reaction in acetonitrile gave 76% *trans* attack. These results strongly suggest that the directive influence of the cyano group is largely polar in origin. On oxidation of 4-cyano-4-methyl- and 4-cyano-4-isopropylcyclopentene, (**21**) and (**22**), respectively, in cyclopentane the directive influence of the cyano group was dominant, and only by reaction of (**22**) in acetonitrile did the directive influence of the 4-alkyl group outweigh that of the cyano group, leading to 74% attack *trans* to the alkyl substituent.



(**17**) $R^1 = Me$, $R^2 = H$
(**20**) $R^1 = CN$, $R^2 = H$
(**21**) $R^1 = CN$, $R^2 = Me$
(**22**) $R^1 = CN$, $R^2 = CHMe_2$



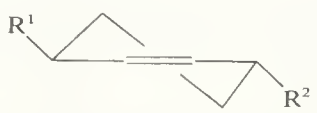
(**18**) $R^1 = Me$, $R^2 = H$
(**19**) $R^1 = H$, $R^2 = Me$



(**23**) R = H
(**24**) R = Me

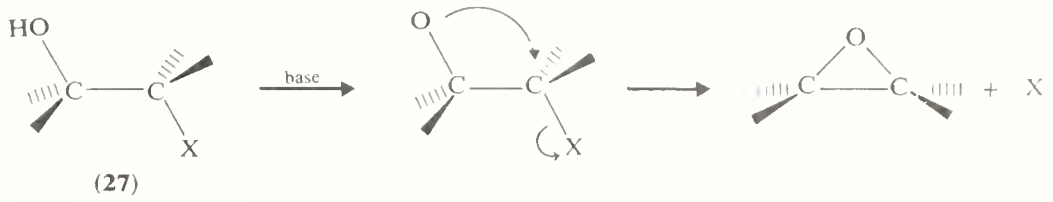
Directive effects of another kind may be caused by association of the reagent with a substituent, *e.g.* an hydroxy group, through some form of bonding. An illustration is the oxidation of cyclopent-2-en-1-ol (**23**), which with a peroxy acid in cyclopentane or acetonitrile afforded 90% and 79% respectively of the *cis*-oxide.[48] However, in diethyl ether or methanol, larger amounts of the *trans*-oxide were produced, probably because the hydroxy group of (**23**) tends to be hydrogen bonded to the solvent instead of to the peroxy acid. In the case of 3-methoxycyclopentene (**24**), the chelation mechanism cannot operate and, in cyclopentane, 92% of the *trans*-oxide is produced on treatment with peroxy acid.

An understanding of the course of oxiran formation from alkyl-substituted cyclohexenes is aided by the assumption that the product ratios may be rationalized in terms of steric properties and of the conformational population of the ground state.[49] For example, 3-t-butylcyclohexene (**25**), which affords[50] *trans*- and *cis*-oxides in the ratio of about 9 : 1, would be expected to adopt a half-chair conformation with the alkyl group occupying a pseudoequatorial position, leading to partial shielding of the double bond towards attack *cis* to the alkyl substituent. With *trans*-3-isopropyl-6-methylcyclohexene (**26**), favoured attack *cis* to the methyl group[51] is readily understood from a consideration of the relative steric hindrance provided by the two alkyl groups. However, reactions on similar substrates are not so easily rationalized, *e.g.* that on 1,6-dimethylcyclohexene which undergoes attack predominantly *cis* to the allylic methyl group, and other factors such as torsional strain in the transition state must be invoked to provide a reasonable explanation of observed stereoselectivities.[52]



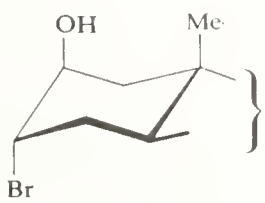
(**25**) $R^1 = CMe_3$, $R^2 = H$
(**26**) $R^1 = CHMe_2$, $R^2 = Me$

The second important method for oxiran synthesis involves a 1,3-elimination reaction on an alcohol possessing a leaving group in the α-position, and may be summarized by the sequence shown in equation (2). The group X in (**27**) is often halogen, but can also be alkyl- or aryl-sulphonyloxy (RSO_2O), trialkylammonium (R_3N^+), dialkylsulphonium (R_2S^+), diazonium (N_2^+), or any other group able to depart readily with the electron pair of the C—X bond. The stereoelectronic requirement for such a reaction is that the four centres involved shall be able to attain an *anti*-coplanar arrangement. The ease with which a molecule attains such a disposition of groups is reflected in the case of oxiran formation. Thus, under standard basic conditions, 3α-bromo-5α-cholestan-2β-ol (**28**) and 2α-bromo-5α-cholestan-3β-ol (**29**) require reaction times of less than 30 seconds and of 24 hours, respectively, for 70% conversion to 2β,3β-epoxy-5α-cholestane.[53] If the groups OH and X of (**27**) are *cis* disposed on a five- or six-membered ring, treatment with base will usually bring about an alternative reaction, *e.g.* dehydrohalogenation when X is halogen, or ester hydrolysis where X is a sulphonyloxy group.

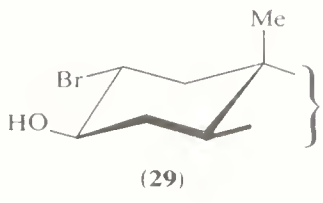


(2)

(27)

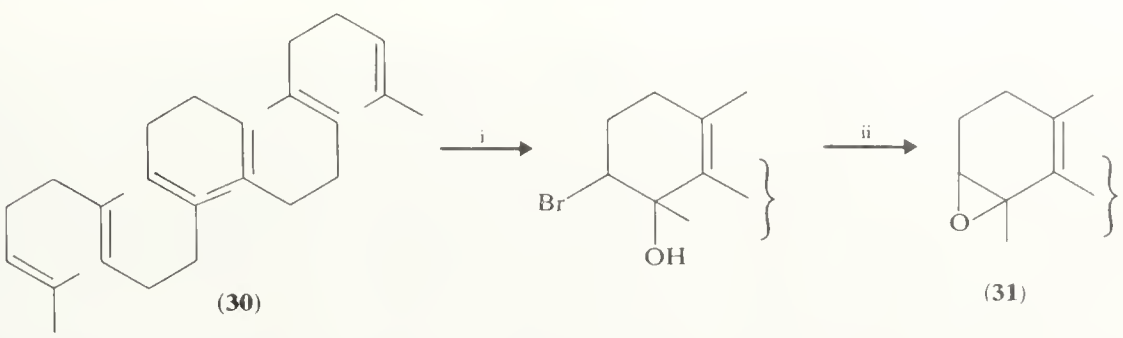


(28)



(29)

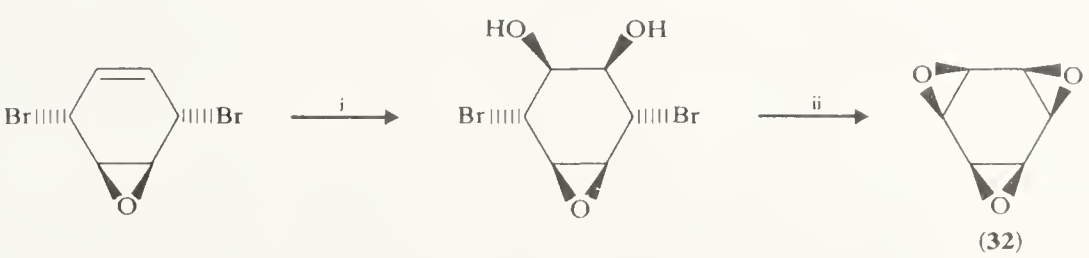
The arrangement of functional groups in the oxiran precursor (**27**) of equation (2) may be derived in a variety of ways. A particularly good route to bromohydrins (**27**; X = Br) involves reaction of *N*-bromosuccinimide on alkenes in an aqueous organic medium, and a particularly elegant application of this reagent was in the synthesis[54] — in racemic form — of the important biosynthetic intermediate squalene 2,3-oxide (**31**) by a remarkably selective reaction on squalene (**30**) as shown in Scheme 1.



(30) (31)

i, *N*-bromosuccinimide; ii, ethanolic base.

SCHEME 1



(32)

i, $KMnO_4$; ii, KOH, MeOH.

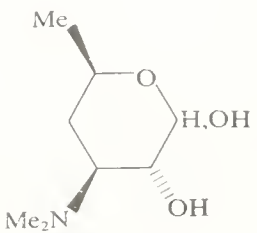
SCHEME 2

The halohydrin route to epoxides has been used in the synthesis[55] (Scheme 2) of *syn*-benzene trioxide (**32**), a compound of surprisingly high melting point (242 °C) and stability. Cycloreversion of (**32**) to *cis,cis,cis*-1,4,7-trioxacyclononatriene occurs only on heating at 200 °C.

The synthesis of oxirans using sulphonyloxy derivatives (equation 2; X = RSO_2O) finds particular application with polyhydroxy compounds, for example the carbohydrates,[43] as monosulphonylation of vicinal diols is a practical possibility, especially with the use of hindered sulphonyl chlorides. Interesting variations of this method, which avoid the actual isolation of monoester intermediates, involve the reaction of the disodium salt of a vicinal diol with one molar equivalent of toluene-*p*-sulphonyl chloride, and treatment of vicinal

disulphonate esters with base; in the latter case one of the ester groups must preferentially undergo S—O bond cleavage.

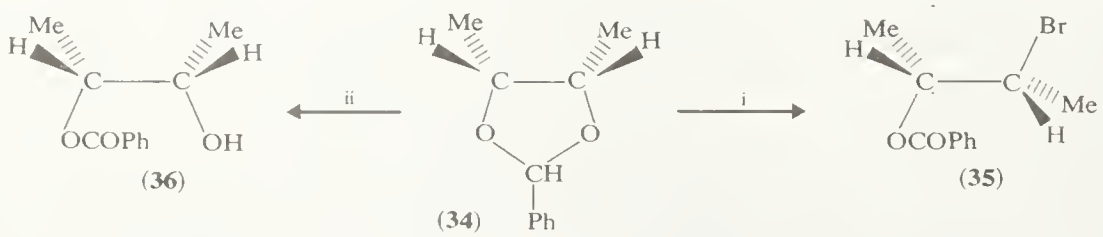
Vicinal amino alcohols are convenient synthetic precursors of oxirans as the amino group may be transformed into a leaving group. Thus treatment with an alkyl halide brings about quaternization at nitrogen and pyrolysis of the quaternary ammonium hydroxide obtained by anion exchange of the halide ion for hydroxide ion can lead to oxiran formation if steric constraints do not prevent achievement of an anticoplanar transition-state. The steric requirements for oxiran formation can provide a method for the determination of relative configurations at contiguous carbon atoms bearing amino and hydroxy groups, when the carbon atoms are part of a ring. Thus the fact that desosamine (**33**) could be converted to a 2,3-anhydro sugar by an essentially similar procedure to that described above for amino alcohols established[56] a *trans* orientation of the substituents at C-2 and C-3.



(**33**)

In contrast to the other methods for oxiran formation involving 1,3-elimination, nitrous acid deamination of an α-amino alcohol, which may be considered to involve the species (**27**) of equation (2) with $X = N_2^+$, is generally only successful when the groups are disposed in an antiperiplanar arrangement in the conformational ground state. The product-forming steps in deamination reactions occur at rates that are normally greater than or comparable with the rates of conformational inversion,[57] and the reaction will follow alternative pathways if conformational change is necessary to attain the required transition state for oxiran formation.

A versatile method for the synthesis of an oxiran from a vicinal diol is based on the reaction of the benzylidene acetal of the latter with *N*-bromosuccinimide. For example, reaction (Scheme 3) of the benzylidene acetal of *erythro*-butane-2,3-diol (**34**) with *N*-bromosuccinimide in carbon tetrachloride yields the bromohydrin ester (**35**), which affords *cis*-2,3-epoxybutane on treatment with base.[58] Reaction of the same acetal with *N*-bromosuccinimide in water yields the monobenzoate (**36**) of the starting diol, which can be converted by sequential *p*-toluenesulphonylation and base treatment into *trans*-2,3-epoxybutane. As *cis*-1,2-diols on cyclic systems readily form benzylidene acetals, the reaction in carbon tetrachloride leading to epoxides should complement nicely the more usual methods of oxiran formation from vicinal diols of cyclic compounds which usually require a *trans* disposition of the hydroxy groups. A simple synthesis of oxirans from cyclic *trans*-vicinal diols involves heating the latter with *N*,*N*-dimethylformamide dimethyl acetal;[59] *trans*-cyclohexane-1,2-diol yielded cyclohexene oxide in 88% yield and 5α,6β-dihydroxycholestane gave 5α,6α-epoxycholestane in 80% yield. The reaction appears to proceed through a cyclic acetal obtained from the reactants by a simple acetal exchange



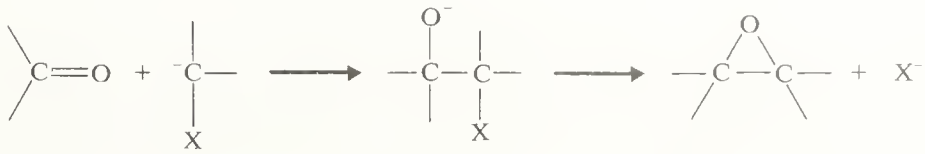
(**36**) (**34**) (**35**)

i, *N*-bromosuccinimide, CCl_4; ii, *N*-bromosuccinimide, H_2O.

SCHEME 3

reaction; in the case of *cis*-cyclohexane-1,2-diol the cyclic acetal does not undergo decomposition to the oxiran.

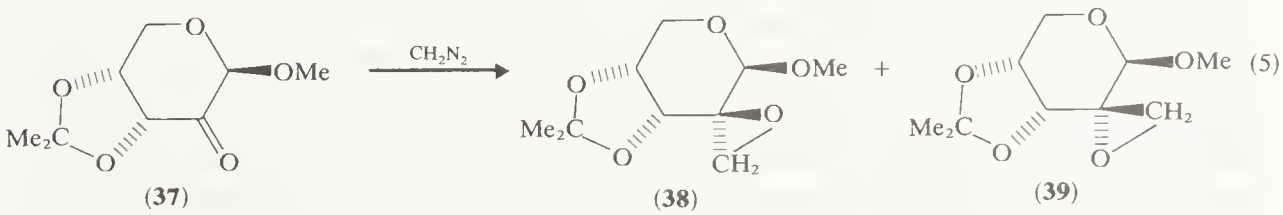
The last methods of oxiran synthesis to be considered here are those in which the fragment (**27**) — or its ionized equivalent — of equation (2) is created by formation of a C — C bond, as shown in equation (3). The most generally useful of these procedures is Darzen's reaction,[4] which entails reaction of a carbonyl-containing substance with a carbanion derived from a halogenomethylene compound (equation 3; X = halogen). The requirement of carbanion formation places some limits on the types of halogen-containing component that may be used, but α-halo carbonyl compounds are suitable. A typical reaction is that shown in equation (4) between benzaldehyde and ethyl chloroacetate to form ethyl 2,3-epoxy-3-phenylpropionate, a representative of a class of compounds often termed 'glycidic esters'. The product of such a reaction may exist in *cis* and *trans* forms and, for a given carbonyl component, the ratio of isomers produced can depend on the base, the halogen derivative used, and on the solvent. The factors influencing the *cis*/*trans* ratio have been fully discussed by Berti.[41]



(3)

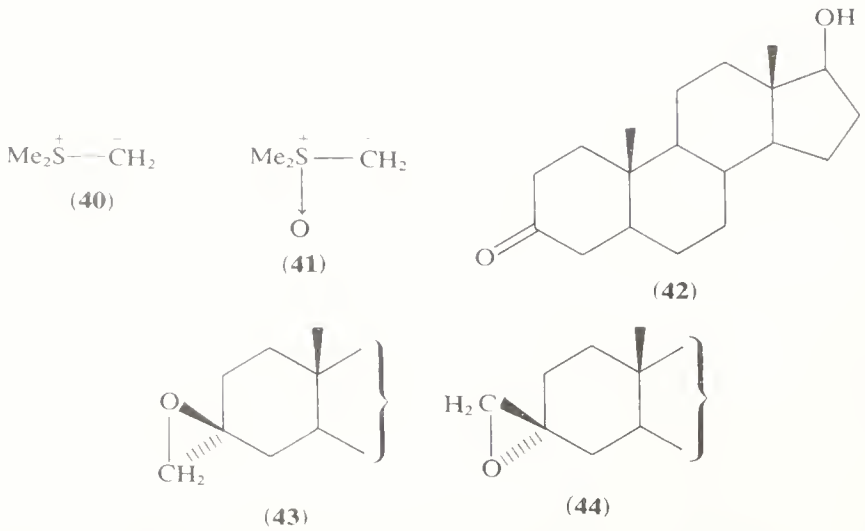
(4)

The role of the carbanion in equation (3) can be assumed by diazoalkanes, $RCHN_2$, which in two of their canonical forms bear a formal negative charge on the carbon atom attached to nitrogen. The intermediate obtained after nucleophilic attack (equation 3; $X = N_2^+$) can react by internal nucleophilic attack of oxygen to give an oxiran. Alternatively, a homologous carbonyl compound can be produced as a result of a 1,2-bond shift. It is interesting that similar alternative bond-making pathways are observed in the nitrous acid deamination of vicinal amino alcohols, a reaction which can be envisaged as proceeding through a similar intermediate. Oxiran formation is favoured by electron-withdrawing substituents α to the carbonyl group, and this may partly explain the high yield (98%) of the mixture of oxirans (**38**) and (**39**) obtained on reaction[60] of the keto-sugar (**37**) with diazomethane (equation 5). The product (**39**) with the *ribo*-configuration predominates, and on hydrolysis yields the branched-chain sugar D-hamamelose.



(37) (38) (39) (5)

An extremely useful synthesis of oxirans has been developed[61] based on the reaction of carbonyl compounds with certain sulphur ylides, those most commonly used being dimethylsulphonium methylide (**40**) and dimethyloxysulphonium methylide (**41**). The mechanism of oxiran formation with these reagents is described by equation (3) with $X = —\overset{+}{S}—$ or $—\overset{+}{S}O—$. The ylides are to some extent complementary in their synthetic uses as they exhibit differing stereoselectivities; (**40**) usually attacks a carbonyl group from its more hindered side, and the opposite is true for (**41**). Reaction of dihydrotestosterone (**42**) with (**40**) afforded[62] a mixture of the oxirans (**43**) and (**44**) in the ratio of 2 : 1, whereas reaction of (**42**) with (**41**) yielded the oxiran (**44**), exclusively.

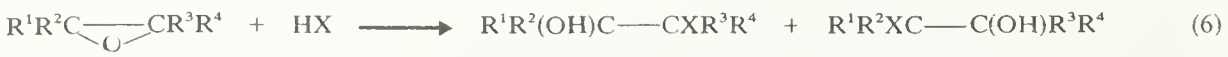


(40) (41) (42) (43) (44)

The last synthetic method to be noted here, catalytic air oxidation, is by far the most important industrial process for the production of oxiran itself, and it may also be used for the preparation of other relatively simple oxirans, *e.g.* propene oxide and trifluorochloroethylene oxide. The production of ethylene oxide is usually carried out over supported silver catalysts at 260–390 °C. Air oxidations may be carried out also in the liquid phase.

4.4.4.2 Reactions of oxirans

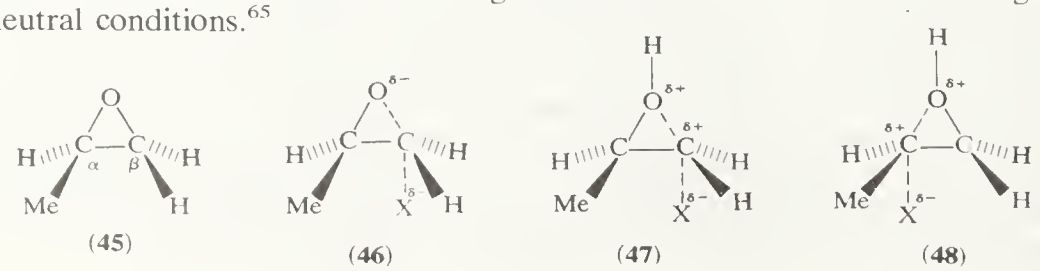
The chemistry of oxirans is almost totally concerned with cleavage of the strained three-membered ring, as indicated in equation (6). The reactions of these compounds are discussed in three extremely thorough reviews,[4,42,63] one of them[42] being particularly concerned with stereoselectivity in oxiran cleavage. Accounts of the chemistry of oxiran derivatives of aldoses[43] and of steroids[64] are also available.



(6)

Ring scission reactions can occur under neutral, acidic, and basic conditions. The ease with which they take place stands in contrast to the relative stability, especially under non-acidic conditions, of the higher homologues tetrahydrofuran and tetrahydropyran, and of acyclic ethers. Steric, polar, and resonance effects can contribute to the regioselectivity that is observed in the ring cleavage reactions of unsymmetrically substituted oxirans. Although it is unwise to make broad generalizations concerning the preferred direction of ring opening, certain patterns of reactivity are discernible, and are explicable in terms of an interplay of the various substituent effects.[63]

In the case of a monoalkyl substituted oxiran such as 2-methyloxiran (**45**) which is shown in the (*R*) enantiomeric form, basic reagents such as sodium methoxide or ammonia yield, predominantly, products of nucleophilic attack at C_β, *i.e.* at the least-substituted carbon. In such a reaction the oxygen atom is unprotonated in the transition state, represented by (**46**), and steric factors are probably of paramount importance. The reaction may be regarded as having, largely, S_N2 character, although bond breaking assumes greater importance in (**46**) than in the usual S_N2 transition state because of the strain inherent in the three-membered ring. A similar situation obtains for ring-opening under neutral conditions.[65]



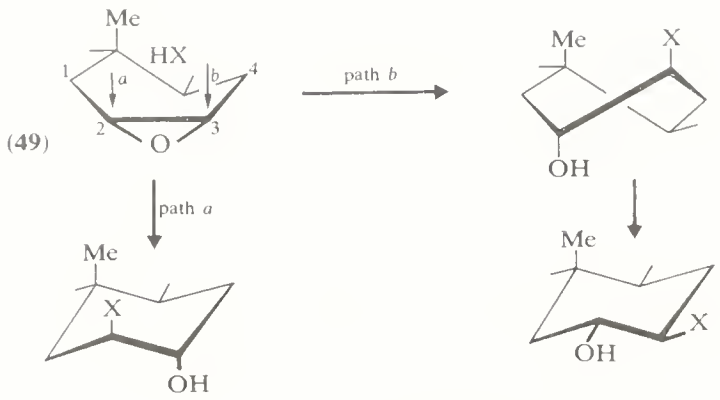
(45) (46) (47) (48)

Under acidic conditions, a greater proportion of attack occurs at C_α in (**45**) than under basic conditions, although it is to be noted that in many cases attack at C_β still predominates. Kinetic investigations[65] and a consideration of product ratios[63] indicate that in acidic media the reaction proceeds largely by nucleophilic attack on the protonated oxiran. In the transition states for attack at C_β and C_α, (**47**) and (**48**) respectively, bond breaking has progressed to a greater extent than in (**46**), resulting in a partial carbenium ion character for the carbon at the reaction centre. An alkyl group is able to stabilize this fractional positive charge in (**48**) but will have little effect in (**47**). Thus the steric disadvantage for attack at C_α is counteracted by the inductive effect of the methyl group lowering the energy of the transition state (**48**) relative to that of (**47**). An increase in nucleophilicity of the nucleophile might be expected to influence the product ratio in favour of β-attack, as bond making should be more important in (**47**) than in (**48**). Reaction of (**45**) with the halogen acids supports this concept, but the same trend in product ratios can be explained, at least in part, in terms of the relative sizes of the halide ions.

Consistent with the above mechanistic concepts are the observations that in an oxiran an electron withdrawing group with no conjugative effect, *e.g.* a trifluoromethyl group, inhibits reaction at that carbon to which it is attached.[63] In the case of a substituent capable of delocalizing a charge on a neighbouring atom by resonance interaction, nucleophilic attack appears to be favoured both under neutral and basic conditions, but even more so under acidic conditions, at the carbon atom to which it is attached. Thus reaction of 2-phenyloxiran with methanol, catalysed by sulphuric acid, yields 2-methoxy-2-phenylethanol as the major product. However, in contradiction to the above generalization, 2-phenyloxiran is preferentially attacked at the primary position by methoxide anion, and it is clear that the steric effects of a bulky substituent on an oxiran ring may dominate reactivity even when conjugation is possible. The bulk of the nucleophile is also a factor influencing regioselectivity in ring cleavages of oxirans.

As expected from mechanistic considerations, ring-opening reactions under basic or neutral conditions cause inversion of configuration at the carbon atom undergoing attack, and this is also true for many acid-catalysed reactions. However, solvent may play an important part in deciding the stereochemical outcome of the reaction. Treatment of (+)-(*R*)-2-phenyloxiran with hydrogen chloride in chloroform yielded[66] 2-phenyl-2-chloroethanol with, predominantly, inversion at C-2, whereas reaction in dry ethers yielded the 2-phenyl-2-chloro derivative mainly with retention of configuration at C-2. A solvated ion-pair intermediate would seem to be involved in the latter case.

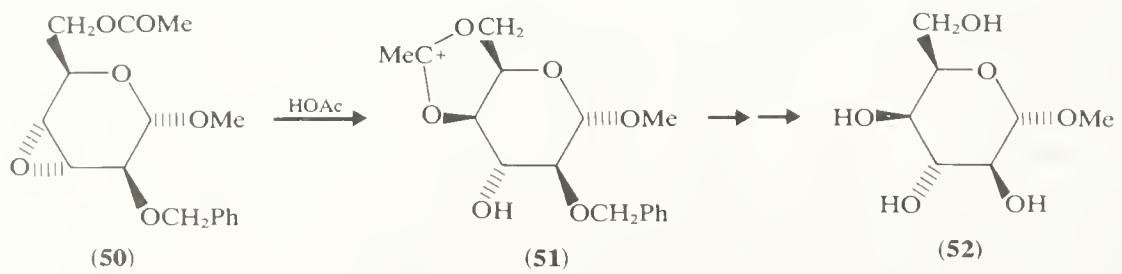
The reactions considered above refer to oxirans derived from acyclic systems where conformational flexibility may permit reactions not available to rigid, cyclic counterparts. Early in the study of conformational analysis it was apparent that oxirans on six-membered rings were subject to special constraints which controlled the direction of their ring-opening reactions.[67] Epoxy-steroids have played a particularly important role in aiding our understanding of this area of stereochemistry. A consideration of the reaction of 2α,3α-epoxy-5-α-cholestane — (**49**) in Scheme 4 — with reagents of the type HX affords an illustration of the important conformational aspects of ring-opening in oxiran derivatives of six-membered ring compounds. Noting that the most favourable transition state for ring-opening will have X, C-2, C-3, and O as nearly as possible in an *anti* coplanar arrangement, nucleophilic attack at C-2 (path *a*) along the axial direction allows the six-membered ring to be transformed smoothly and directly into a chair form, resulting in a diaxial orientation of the OH and X ligands. This reaction pathway is energetically favoured over path *b* in which similar attack at C-3 leads directly to a twist-boat conformation, which may then interconvert into the more favoured chair form, in which the substituents OH and X are attached equatorially. Thus the experimental observation that epoxy-steroids are regioselective in their ring-scission reactions, and that the major products have their new groups diaxially disposed, finds a ready explanation. Deviations from this reaction pattern may arise if ring-cleavage is a two-step rather than a concerted process, and also if the epoxide-containing ring is in a conformation other than a half-chair one.



SCHEME 4

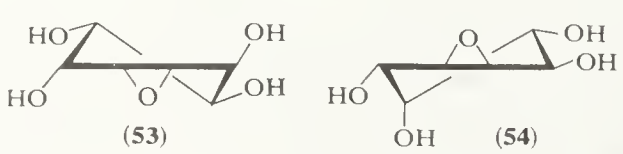
The cleavage of oxirans derived from flexible six-membered ring compounds is a somewhat more complex situation than that of the ring-opening of steroid oxirans. However, the course of these reactions may generally be understood[42] in terms of the requirement for *anti* parallel attack of the nucleophile along an axial direction, and on the relative energies of the transition states for the various ring-opening possibilities.

Oxirans containing suitably disposed substituents may undergo internal nucleophilic attack on the three-membered ring.[42] The formation of the idose derivative (**52**) on hydrolysis of the anhydro-altroside (**50**) with acetic acid and subsequent removal of the protecting group appears to be an example of this (Scheme 5). This interconversion most probably involves participation of the neighbouring acyloxy group at C-6 by internal attack of the carbonyl oxygen on the nearest oxiran carbon atom, to give the acetoxonium ion (**51**).



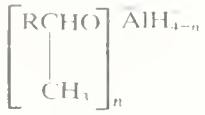
SCHEME 5

If intramolecular attack on the oxiran is by an oxy-anion attached to a carbon adjacent to the three-membered ring, then the phenomenon of oxiran migration can occur. A particularly instructive example involves[68] the inositol oxirans (**53**) and (**54**), which interconvert under suitable alkaline conditions to afford an equilibrium mixture in which the ratio of (**53**):(**54**) is 1 : 9. The predominance of (**54**) at equilibrium is in accordance with conformational considerations; (**53**) has two pseudoaxial hydroxy groups whereas (**54**) has only one axial group.



Reductions of oxirans with lithium aluminium hydride are generally regarded as proceeding by bimolecular attack of the aluminohydride anion, and, mechanistically, they should be similar to other nucleophilic reactions on oxirans. When the hydride is not present in excess, then reducing species such as (**55**) will be formed during the reduction of a monoalkyloxiran, and these will then act as the reducing agents. The steric bulk of the

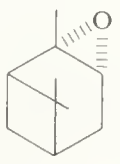
anionic species (**55**) increase as n increases, and differing regioselectivities of the species would be expected; these have, in fact, been noted. Reduction of 3,4-epoxybut-1-ene with 2.1 and 0.26 molar equivalents of lithium aluminium hydride afforded, respectively, 30% and 17% attack at the secondary positions.[69]



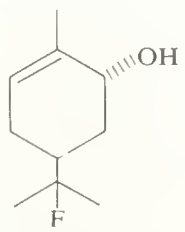
(**55**)

Although, in the reduction of oxirans with lithium aluminium hydride, attack by the complex hydride is usually favoured at the least substituted side of the ring, reductions with lithium aluminium hydride–aluminium chloride reagent can in some instances lead to a reversal of the outcome of the reaction, *i.e.* it appears that attack has occurred at the most substituted carbon atom. However, in the latter case the observed regioselectivity is generally a result of a hydride shift producing a carbonyl intermediate, which is then reduced to the alcohol.[70]

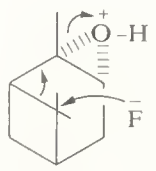
The oxidation of oxirans to α-hydroxyketones may be achieved by heating them with dimethyl sulphoxide in the presence of boron trifluoride etherate.[71] Both $2\alpha,3\alpha$-epoxy- and $2\beta,3\beta$-epoxy-5α-cholestane afforded 5α-cholestane-3β-ol-2-one; the 2,3-dione and $2\beta,3\alpha$-diol were minor by-products.



(**56**)

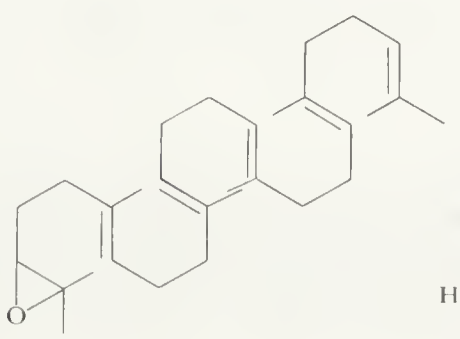


(**57**)

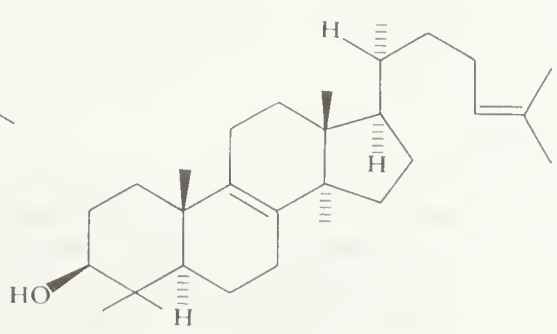


(**58**)

With certain types of oxiran, acid-catalysed ring-scission can follow a different course to that indicated in equation (6). In these instances, alternative reaction pathways are open to the protonated oxiran, and these generally result in intramolecular rearrangement. Thus treatment of α-pinene oxide (**56**) with hydrogen fluoride in diethyl ether gave,[72] as the major product, the fluoro alcohol (**57**), the formation of which can be summarized by the electron shifts shown in (**58**) (a fully concerted reaction is not implied). Formolysis of *cis*-cyclo-octene oxide provides a further interesting example: saponification of the reaction product gave a complex mixture containing *trans*-cyclo-octane-1,2-diol (5–19%), *cis*-cyclo-octane-1,4-diol (23–30%), cyclo-oct-3-en-1-ol (11%), and cyclo-oct-4-en-1-ol (4%), together with minor quantities of other compounds.[73] The formation of these products may be interpreted by a mechanism in which ring opening of the protonated oxiran affords a classical ion preserving some tetrahedral character. This can either undergo nucleophilic attack at the developing carbenium ion centre at C-2 or, owing to the close proximity of opposite sides of the ring in some conformations of medium-ring compounds, undergo hydride transfer from C-4 or C-6 to C-2. The extent to which transannular reactions occur is remarkably solvent dependent and appears to be related to acid strength. Thus in trifluoroacetic acid all of the products arise from transannular



(**59**)

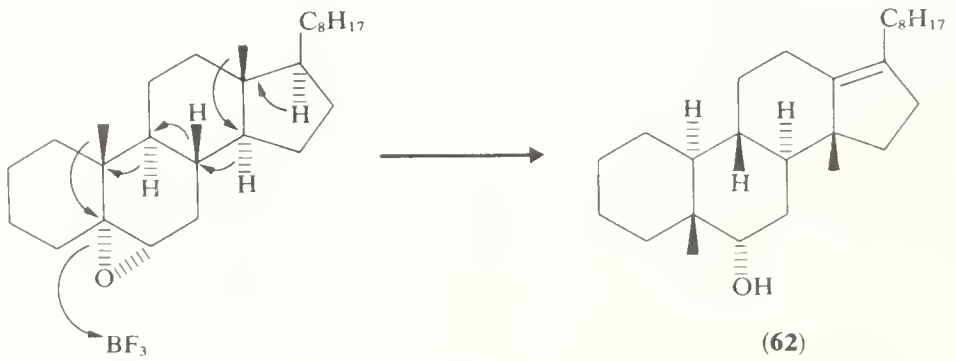


(**60**)

reactions, whereas in acetic acid containing sodium acetate, 76% of the isolated product was the *trans*-1,2-diol.[74]

Perhaps the most important of the oxiran ring-scissions leading to rearrangement is the enzyme-controlled cyclization of squalene 2,3-oxide (**59**), which occupies[54] a key position in the biosynthetic sequence leading to sterols *via* lanosterol (**60**). Although this cyclization is mediated by enzymes, non-enzymic cyclization experiments have confirmed the overall tendency for squalene 2,3-oxide to undergo polycyclization. Significantly, however, the identified products do not possess the lanosterol skeleton but have tricyclic structures, with ring C five-membered, which presumably reflects the utilization of a more stable tertiary carbocation in the non-enzymic process during ring C formation.

Many further examples of rearrangements during ring-cleavage reactions of oxirans arise in steroid chemistry.[64,75] The possible complexity of such processes is illustrated by the treatment of 5α,6α-epoxy-5α-cholestane (**61**) with boron trifluoride etherate, which affords 5β-cholestan-6-one (resulting from stereospecific hydride migration from C-6 to C-5) and the hydroxyalkene (**62**), which is the product of a 'backbone rearrangement' indicated by the electron shifts on structure (**61**) in equation (7).



(61) (62) (7)

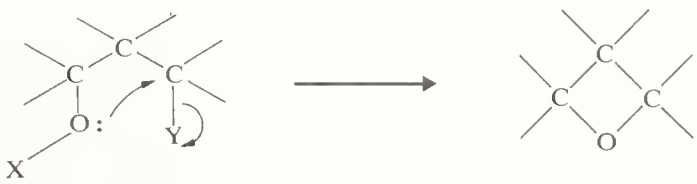
Arene oxides, such as benzene oxide, toluene 3,4-oxide and naphthalene 1,2-oxide, have been suggested as possible intermediates in the metabolism of organic compounds. Of particular interest is the so called NIH shift[76] in which, during enzymatic hydroxylation of an aromatic substrate, intramolecular migration is observed of the group displaced by hydroxyl to an adjacent position on the aromatic ring. For example, hydroxylation of [4-^{2}H]toluene with rabbit liver microsomes afforded 4-hydroxytoluene in which 56% of the material was labelled with deuterium at the carbon adjacent to that one carrying the hydroxy group. The fact that [4-^{2}H]toluene 3,4-oxide undergoes a spontaneous or catalysed NIH shift to an extent comparable with that in enzymic hydroxylation[77] lends credence to the idea that arene oxides are intermediates in this type of enzymic conversion.

Mention should be made of the important industrial uses of oxirans in the form of epoxy resins, the latter being materials containing an average of more than one oxiran ring per molecule, and capable of being converted by reaction at these groups into useful thermosetting resins, usually by the addition of a cross-linking agent, such as a polyamine. Such cross-linked or 'cured' epoxy resins show remarkable adhesion to many different materials, including metals, and have the property of outstanding toughness. As well as their uses as adhesives, they find application in the encapsulation of electrical components, as protective coatings, and in the preparation of laminates.

4.4.4.3 Synthesis of oxetans

The formation of four-membered rings by ring-closure reactions is usually difficult compared with similar reactions leading to three-, five-, and six-membered rings. Qualitatively, this may be understood in terms of two competing factors, ring strain in the cyclic product and a probability factor. The former, which should be related to the enthalpy of activation for cyclization, generally decreases in going from three- to six-membered ring

compounds, whereas the probability that the two ends of the chain in the reactant will be in close enough proximity to react decreases with increasing chain length, and this will be reflected in the entropy of activation for cyclization. Combination of these two factors leads to an unfavourable situation for four-membered ring formation. Nevertheless, a great proportion of oxetan synthesis using non-photochemical means do proceed by base-induced cyclization of 1,3-disubstituted compounds, as indicated by equation (8), in which at least one of the substituents is a free or masked hydroxy group.[5]

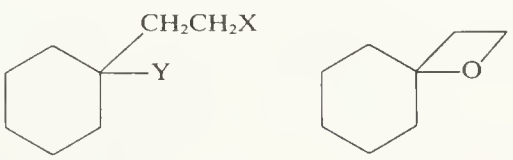


(8)

(**63**)

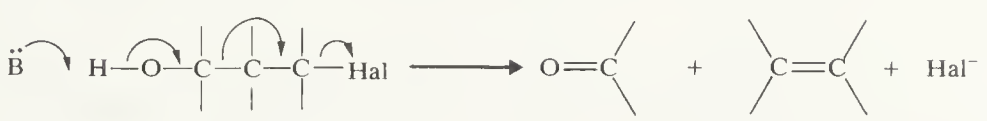
The most commonly used substrates for such cyclizations are 3-halo-1-alcohols (**63**; X = H, Y = Hal) and their acyl esters (**63**; X = RCO, Y = Hal) (see equation 8). The relative difficulty in forming four- and three-membered rings is indicated by measurement of second-order rate constants for reaction of a number of chloroalcohols in alkaline solution; for those 3-halo-1-alcohols undergoing predominantly intramolecular substitution the rate-constants at 80 °C were approximately one-hundredth of those for related 2-chloro-1-alcohols at 20 °C.[78]

Alkyl substitution in (**63**) can affect markedly the yields of oxetan obtained in these ring-closure reactions. Substitution on the hydroxyl-bearing carbon atom generally leads to increased yields, but the opposite trend is observed when substitution is on either of the other two carbon atoms. An increase in steric hindrance towards intramolecular attack by the oxy-anion may explain the deleterious effect of substitution at the halogen-carrying carbon atom, and there appear to be no examples of oxetan formation by ring closure with displacement of halide from a tertiary centre. Because of the opposite effects that alkyl substituents may have on the ease of ring closure, depending on their point of attachment, it is sometimes necessary to choose the oxetan precursor carefully. For example, the synthesis of the spiro compound (**66**) was achieved[79] in 55% yield when 1-(2-chloroethyl)cyclohexan-1-ol (**64**) was treated with base, but 2-(1-chlorocyclohexyl)-ethanol (**65**) gave no oxetan, and underwent dehydrohalogenation instead.



(**64**) X = Cl, Y = OH
(**65**) X = OH, Y = Cl

(**66**)



(9)

Substitution on the central carbon atom of a 1,3-haloalcohol favours 1,4-elimination (Grob fragmentation[80]) on reaction with base (equation 9) rather than oxetan formation. The substituents favour 1,4-elimination over intramolecular substitution in the order Ph ≫ Me > Et, Bu^n > H, and this order appears to parallel the thermodynamic stability of the olefin formed. There is a marked solvent effect on the competition between the alternative reaction pathways, more ionizing media favouring elimination.[81]

There appears to be considerable advantage in respect of yield in using the esters of 1,3-haloalcohols rather than the haloalcohols themselves as precursors of the four-membered ring system. A convenient synthesis of oxetan itself involves treatment of

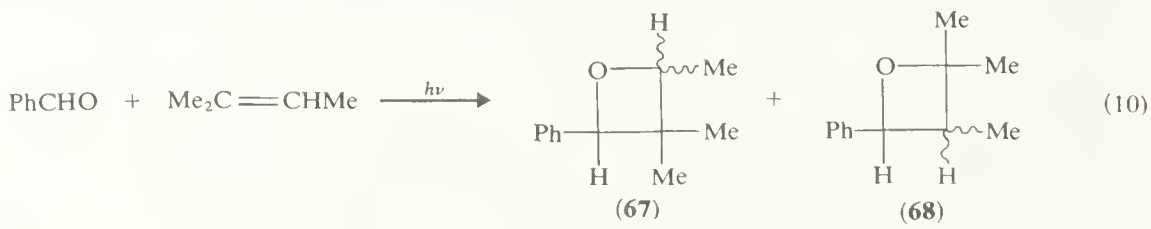
propane-1,3-diol with calcium chloride and acetyl chloride to give 1-chloro-3-acetoxypropane which is then cyclized by treatment with aqueous potassium hydroxide.[82] The reported yield of 43% in the last step should be compared with the 20–25% yield obtained by treating 3-chloropropan-1-ol with base.[83] The reason for higher yields in the ester procedure is difficult to explain, but may be linked with the formation of an orthoester type of intermediate by hydroxide ion attack at the carbonyl group of the ester function.

An oxetan may be conveniently prepared from a 1,3-diol if one of the hydroxy groups is first transformed into a leaving group by sulphonylation to give a diol monosulphonate (equation 8; X = H, Y = OSO_2R). The requirement for efficient ring closure — that of the two terminal carbon atoms the one bearing the hydroxy group should be the most highly substituted — is compatible, fortunately, with the likely stereoselectivity in monosulphonylation reactions on diols. Thus treatment of cholestane-3β,5α-diol with one molar equivalent of toluene-*p*-sulphonyl chloride gave the 3-sulphonate, which on reaction with potassium t-butoxide in t-butyl alcohol gave 3α,5α-oxidocholestane in 55% yield together with 37% of the product of 1,4-elimination.[84]

Related to these oxetan syntheses are the interconversions of oxiran and oxetan ring systems which are observed in some carbohydrate derivatives. As an example, aqueous alkali converts methyl 2,3-anhydro-β-D-ribofuranoside into methyl 3,5-anhydro-β-D-xylofuranoside. The reaction is reversible and the equilibrium favours the oxetan by approximately 20 : 1.[85]

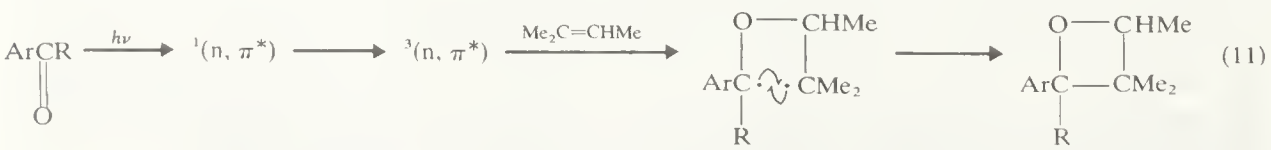
The synthesis of oxetans by acid-catalysed dehydration of 1,3-diols is not a general reaction; rearrangement and cleavage products generally result from their acid treatment. However, the pyrolysis of cyclic carbonates of 1,3-diols at approximately 200 °C in the presence of a basic catalyst is a useful preparative method for oxetans, and it is the best means of synthesizing 3,3-dialkyloxetans.[5]

The other major route to oxetans is the photochemical cycloaddition of aldehydes and ketones to alkenes, often called the Paterno–Büchi reaction.[86,87] It is illustrated in equation (10) for the reaction[88] between benzaldehyde and 2-methylbut-2-ene, which affords the oxetans (**67**) and (**68**) in the ratio of 1.6 : 1 and in 64% combined yield. When benzaldehyde is replaced by acetophenone, the cycloaddition is more stereoselective and the oxetans corresponding to (**67**) form 90% of the oxetan mixture.



(10)

For aromatic aldehydes and ketones the predominant mode of addition in the Paterno–Büchi reaction can often be predicted.[89] Irradiation of the aromatic carbonyl compound leads to its conversion into an n → π^* triplet state [^{3}(n,π^*)] *via* an n → π^* singlet state [^{1}(n,π^*)], and by assuming that the radical-like oxygen of the n → π^* triplet state adds to the olefin to give, preferentially, the most stable biradical intermediate, it can be seen that the oxygen atom in the oxetan will be bonded to that carbon atom of the olefin which is the least substituted (equation 11).



(11)

Benzophenone reacts with both *cis*- and *trans*-but-2-ene to give the same mixture of adducts,[86] which is understandable if rotation about the carbon–carbon bond in the biradical intermediate corresponding to that in equation (11) is rapid relative to ring

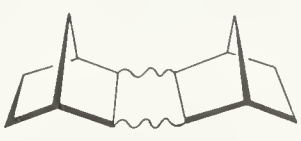
closure; in this respect it is to be noted that addition of triplet carbonyl to a singlet ground-state olefin gives a triplet biradical which must undergo spin inversion before ring closure can occur.

Although the biradical hypothesis is useful for predictive purposes, it is not adequate as a mechanism. For additions involving the $n \rightarrow \pi^*$ triplet state of a carbonyl compound, *cis–trans* isomerization of the starting alkene is often observed,[90] and although carbon–oxygen bond cleavage in the biradical intermediate after rotation about the carbon–carbon bond could explain this result, there are cases where isomerization of alkene occurs without oxetan formation. Also, for the few cases that have been studied, the rate constant for the reaction of excited ketones with ground-state alkene is several orders of magnitude higher than rate constants for the addition of oxy radicals to olefins.[91] Mounting evidence suggests that the reaction course for both alkene isomerization and oxetan formation involves a complex between the excited ketone and the olefin, sometimes termed an *exciplex*, and this intermediate can subsequently lead to the biradical or to a mixture of *cis*- and *trans*-alkenes.[90,92]

An important difference appears to exist between the mechanism of the Paterno–Büchi reaction for aliphatic aldehydes and that for aromatic carbonyl compounds. For example, photochemical reaction of acetaldehyde with *cis*- and *trans*-but-2-ene proceeds with a high degree of stereoselectivity, and there is no detectable isomerization of the starting alkene during the reaction.[93] It has been suggested, therefore, that such reactions proceed through the $n \rightarrow \pi^*$ singlet state of acetaldehyde, which would afford a singlet biradical on interaction with the alkene. Ring closure of singlet biradicals is known to be appreciably faster than the bond rotation which would cause randomization in product. In view of the fact that non-terminal alkenes afford oxetans on photochemical reaction with aldehydes, whereas terminal alkenes give ketones, it has been further suggested that oxetan formation is controlled by ease of formation of an exciplex between an excited aldehyde and alkene; the exciplex may collapse subsequently to give the biradical intermediate. Exciplex formation would be more favoured the more highly alkylated is the alkene.

The formation of side products from the alkene may completely suppress the Paterno–Büchi reaction. These products can result from transfer of triplet energy, E_T, from the triplet excited state of the carbonyl compound to the olefin. This is especially likely when the triplet energy of the donor is greater than that of the olefin. A particularly striking example is in the irradiation of norbornene (**69**) with benzophenone ($E_T = 286.6$ kJ mol^{-1}), acetophenone ($E_T = 307.9$ kJ mol^{-1}), and acetone ($E_T \approx 313.8$ kJ mol^{-1}).[94] With benzophenone the expected oxetan is produced in 80% yield, whereas with acetone only norbornene dimers (**70**) are produced. Acetophenone gives both the oxetan and dimers. Thus energy transfer from the carbonyl component to the olefin places a limit on the Paterno–Büchi reaction, and for a successful oxetan synthesis the triplet energy of the olefin must be substantially larger than that of the carbonyl component. Another side reaction to oxetan formation is hydrogen abstraction from the alkene by the excited ketone.

(**69**)

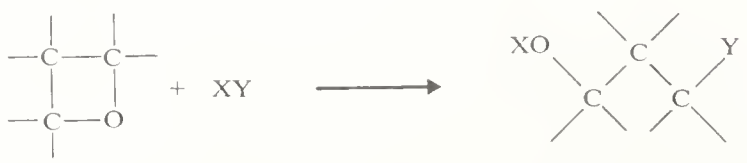


(**70**)

4.4.4.4 Reactions of oxetans

Oxetans undergo ring-opening reactions (equation 12) similar to those of oxirans. However, the smaller degree of strain in the four-membered ring makes the very important difference that nucleophilic substitutions on oxetans without strong acid catalysis generally occur very much more slowly than those on the three-membered

heterocycle. This is illustrated by the rate coefficients of 1.1×10^{-4} and approximately 10^{-7} l mol^{-1} s^{-1} listed by Pritchard and Long[95] for the base-catalysed hydrolysis of oxiran and oxetan, respectively. On the other hand, under acidic catalysis the rates of ring-opening reactions for oxetans may be of comparable magnitude to those for oxirans, and values of 9.86×10^{-3} and 1.57×10^{-3} l mol^{-1} s^{-1} have been reported[95] for the acid-catalysed hydrolysis of the three- and four-membered ring systems, respectively. The markedly greater electron donating ability of the ring-oxygen atom in oxetans compared with oxirans (see Section 4.4.3) apparently compensates adequately for the lower degree of reactivity expected for the former compounds purely on the basis of ring strain, leading to comparable reactivities of the two ring systems when electrophilic attack on ring oxygen precedes ring opening.



(12)

Many acid-catalysed reactions of oxetans lead to 1,3-disubstituted propane derivatives.[5] Treatment of the parent heterocycle or its derivatives with hydrogen halides, alcohols in the presence of acid, and acyl halides gives 3-halo-1-alcohols, 3-alkoxy-1-alcohols, and 3-halo-1-alcohol esters, respectively. It appears that in unsymmetrically substituted oxetans the direction of acid-catalysed ring-opening can depend on the stability of the developing carbenium ion at the α-position to oxygen and on steric hindrance to attack by the nucleophilic species. Thus 2-methyloxetan is converted by aqueous hydrochloric and hydrobromic acids and by hydrogen chloride or hydrogen bromide in benzene into, predominantly, the corresponding 4-halobutan-2-ol by cleavage of the O—CH_2 bond, whereas 2-phenyloxetan yields products only from cleavage between oxygen and the benzylic carbon. In the case of 2-methyloxetan it appears, therefore, that the transition states must have a reasonable degree of S_N2 character, as the observed major products are not those expected from a purely S_N1 process. Comparable results to those with oxetans have been obtained in corresponding reactions with 2-methyloxiran and 2-phenyloxiran.

Interestingly, Friedel–Crafts reaction of both 2-methyl- and 2-phenyl-oxetan with benzene, in the presence of aluminium chloride, gives 3-arylpropan-1-ol derivatives resulting from cleavage between oxygen and the substituted α-methylene group of the oxetan. Friedel–Crafts alkylation with oxetan itself proceeds without isomerization of the entering group.

Polymerization of oxetans may be achieved readily by treatment with strong Lewis acids in non-polar media, with no nucleophilic species present. These polymers have been studied extensively, especially those derived from 3,3-disubstituted oxetans, which are readily obtained from pentaerythritol. Although a mechanism for polymerization involving a chain process initiated by carbenium ions could be envisaged, it would not really be consistent with the observation that when 3,3-disubstituted oxetans are the monomers there appears to be little evidence of the type of rearrangement often found with neopentyl carbenium ions.

As noted previously, nucleophilic ring-opening of oxetans occurs relatively slowly if acid catalysis is absent. Reactions of amines and thiols with oxetans occur much less readily than with oxirans, and a competition reaction between oxiran and oxetan towards sodium thiophenoxide confirms the greater reactivity of the former heterocycle.[96] With organometallic reagents, oxetan affords 3-substituted propan-1-ols.[97] These syntheses proceed more satisfactorily with Grignard reagents derived from primary than from secondary or tertiary alkyl halides; in the latter cases, 1,3-halohydrins are significant by-products.

The reduction of oxetans by lithium aluminium hydride yields alcohols resulting from hydride attack at the least substituted α-carbon atom.

4.4.4.5 Tetrahydrofurans, tetrahydropyrans, and higher members of the series

(i) Synthesis

There are surprisingly few review articles dealing with the chemistry of tetrahydrofurans and tetrahydropyrans, but a report by Gritter[40] gives a useful coverage of these ring systems up to 1967. The chemistry of seven-membered oxygen heterocycles is the subject of a recent monograph,[44] and appropriate volumes of Houben-Weyl[98,99] contain valuable practical information and leading references on the cyclic ethers.

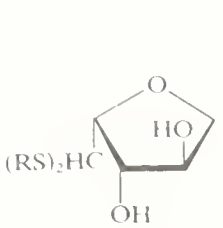
The most important and general methods for synthesis of these five-, six-, and seven-membered heterocycles are still those based on cyclization of diols and haloalcohols. Yields are usually good in the case of tetrahydrofuran and tetrahydropyran, and are sometimes acceptable for oxepan, but these methods have little preparative value for higher members of the series. The cyclodehydration of diols can be conducted in the liquid or gas phase, and in the former case, inorganic or organic acids, acidic salts, and acidic ion-exchange resins have been used as catalysts. Dehydration in the gas phase may be performed over metal oxides, aluminosilicates, *etc.* at elevated temperatures. Acid-catalysed dehydration of hexane-1,6-diol affords low yields (<10%) of oxepan, but gas-phase dehydrations yielding over 30% of the cyclic ether have been reported; in both types of reaction, smaller ring ethers are formed concomitantly.

A very simple synthesis of the five- to seven-membered ring cyclic ethers involves heating the appropriate α,ω-diol with 0.5 molar equivalents of dimethyl sulphoxide.[100] Tetrahydrofuran, tetrahydropyran, and oxepan were obtained in yields of 70, 47, and 24%, respectively. The reasonable yield of oxepan is noteworthy, but the original report suggests that the product may have required further purification. Dehydration of α,δ-diols by a related procedure using larger amounts of dimethyl sulphoxide can be used to synthesize a variety of tetrahydrofurans,[101] but the reaction is not completely general as tertiary alcohols tend to give unsaturated acyclic compounds as well as the required product.

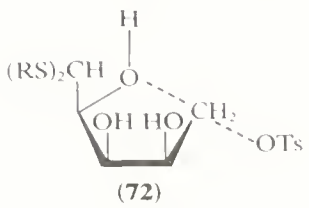
Polyhydroxy compounds, for example the alditols, which may be derived from aldose sugars by reduction, show a marked propensity for forming tetrahydrofuran-type rings on acid-catalysed intramolecular dehydration,[102] but the ease of ring formation can vary between stereoisomers. Erythritol and threitol both yield 1,4-anhydro derivatives, but in the pentitol series, ribitol readily forms a 1,4-anhydride under acidic conditions which do not cause cyclization of arabinitol or xylitol. Mannitol and glucitol (sorbitol) afford mono- and bi-cyclic internal ethers, and in both of these types of derivative, five-membered rings are present. In the acid-catalysed dehydration of a polyol, intermolecular condensation may be a competing process and 2,5-disubstituted 1,4-dioxan has been isolated from erythritol.[103] Such a reaction is analogous to the well-known formation of 1,4-dioxans from the acid-catalysed dehydration of 1,2-diols (Section 4.4.5).

Generally, ring-closure reactions on haloalcohols — or equivalent species — under basic conditions are useful methods for preparing five-, six-, and seven-membered cyclic ethers, although the yield of oxepan is usually low by this method. α,ω-Dibromoalkanes may, on occasion, be used as substrates since, under aqueous conditions, they are hydrolysed to haloalcohols. A further variation consists of treating a diol with one molar equivalent of a sulphonyl halide, whereby a monosulphonate ester is produced, in which the sulphonyloxy function may act as an effective leaving group. An interesting dependence of tendency towards ring closure on stereochemistry is found in the reactions of the dithioacetals of ribose, xylose, lyxose, and arabinose with sulphonyl halides in pyridine.[104] The first three pentoses listed yield 2,5-anhydro compounds, whereas under the same conditions arabinose is reported to yield a sulphonic ester at the primary alcohol group. For each of those pentoses forming a 2,5-anhydride, one of the three substituents attached to the tetrahydrofuran ring is located *trans* to the other two, as indicated in (**71**) for the *xylo* derivative, whereas the *arabino*-anhydride would have all three groups on the same side. Accordingly, steric compression between those three groups destabilizes the transition state,

represented by (**72**), that would lead to cyclization. This concept appears to apply to similar reactions on related substrates derived from higher sugars.



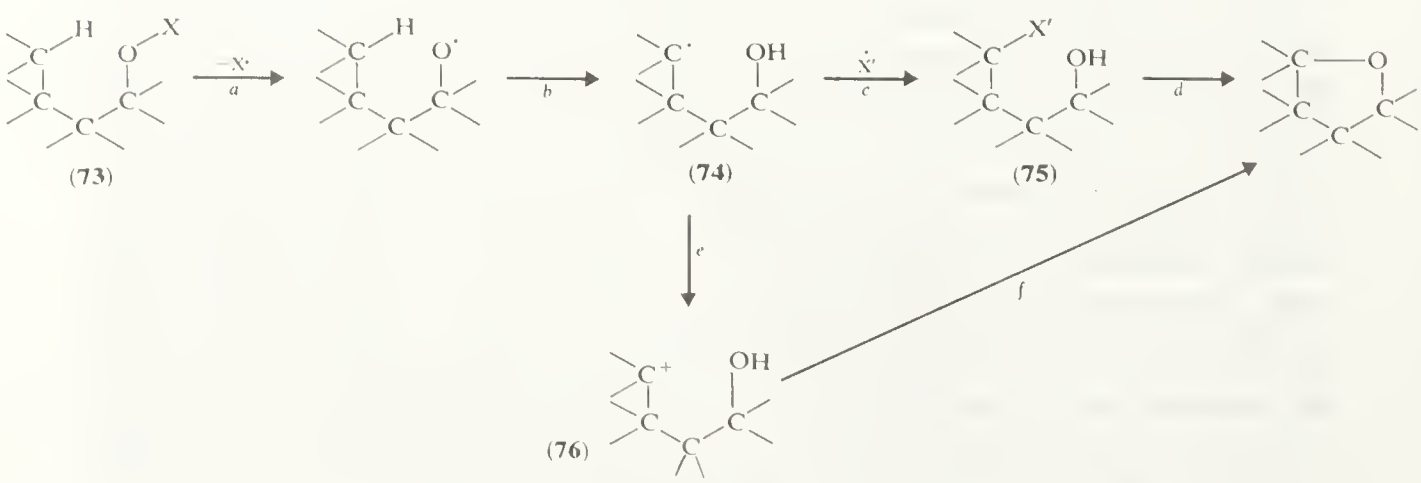
(**71**)



(**72**)

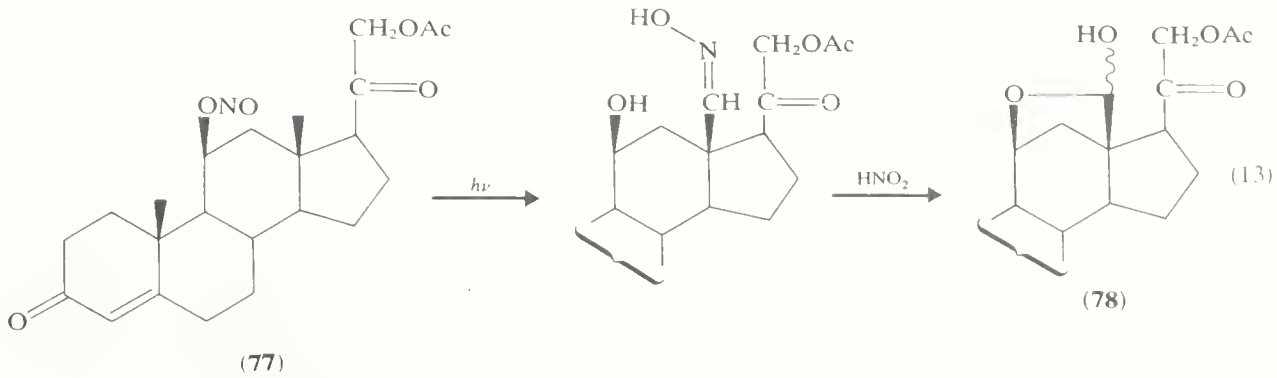
Ring closure of bromomethoxyalkanes with catalysis by ferric chloride is noteworthy.[105] Quantitative yields of tetrahydrofuran and tetrahydropyran were reported by this procedure, and the surprisingly high yield of 70% for oxepan was obtained, which makes this method the one of choice for the preparation of the latter compound. For cyclic ethers of larger ring sizes the more satisfactory synthetic procedure is to achieve ring closure by C—C bond formation in a preformed acyclic ether, using the acyloin or Ziegler cyclization procedures, which are so successful in the synthesis of medium and large ring carbocycles.

Significant developments have taken place in recent years in the synthesis of tetrahydrofuran ring systems from simple and complex alcohols, based on oxidative cyclization reactions.[106,107] Especially noteworthy is the fact that these intramolecular cyclizations, which proceed through radical intermediates, generally occur by reaction at unactivated C—H bonds, and particularly at those which have a certain spatial disposition to the oxygen atom of the hydroxy group. Studies on steroidal substrates have been particularly valuable in ascertaining the factors which control such ring closures. The key steps in these reactions are indicated in Scheme 6. An alcohol derivative (**73**), which may be a nitrite (X = NO), a hypohalite (X = halogen), or a lead alkoxide [X = Pb(OAc)$_3$] undergoes thermolytic or photolytic cleavage of the O—X bond (step *a*). In the alkoxy radical so formed, hydrogen transfer occurs (step *b*) which, because of geometrical requirements of the transition state, takes place from a carbon in the δ-position with respect to oxygen. The carbon radical (**74**) may then react (step *c*) with the free radical $\dot{X}'$, which may or may not be identical to $\dot{X}$, leading to the δ-substituted alcohol (**75**). When X = X′ = NO, nitroso–oximino tautomerism may develop carbonyl functionality at the δ-carbon, and after hydrolysis of the oxime, spontaneous cyclization to an α-hydroxytetrahydrofuran occurs. This reaction sequence was utilized by Barton and Beaton[108] in their elegant synthesis of aldosterone 21-acetate (**78**) by photolysis of corticosterone 11-nitrite 21-acetate (**77**) in toluene solution (equation 13).



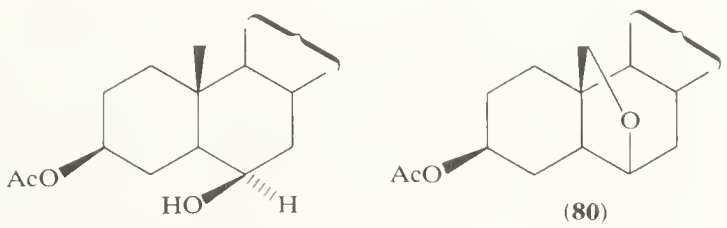
(**73**) (**74**) (**75**) (**76**)

SCHEME 6



(77) (78)

Hypochlorites (**73**; X = Cl) (Scheme 6) may be prepared by reaction of an alcohol with hypochlorous acid or chlorine monoxide and although most experiments have been on tertiary alcohols, the thermal and photochemical decomposition of n-butyl hypochlorite has been reported to yield approximately 16% of 4-chlorobutan-1-ol.[109] Chloroalcohols, which are produced by the rearrangement, may be transformed readily into tetrahydrofurans by treatment with alkali. Hypobromites (**73**; X = Br) are thought to be involved in reactions of alcohols with bromine and silver acetate.[110] Cyclic ether formation with these reagents has been reported in the case of the 6β-alcohol (**79**), which gave cyclic ether (**80**) in 60% yield; apparently step *d* (Scheme 6) occurs spontaneously under the reaction conditions.

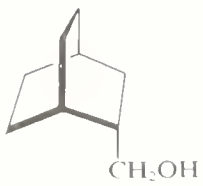


(79) (80)

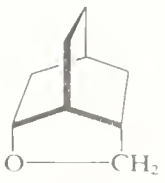
The formation of hypoiodites (**73**; X = I) is usually achieved by treatment of an alcohol with lead tetra-acetate and iodine, with an iodoamide or acyl hypoiodite, or, conveniently, by irradiation of a solution of an alcohol in the presence of iodine and mercuric oxide. Tetrahydrofuran-type ethers can be produced directly in these reactions, but in certain cases further substitution takes place at the α-position, leading to derivatives of hemiacetals.[106]

Probably the most important of these intramolecular radical reactions for preparing tetrahydrofurans is that based on the oxidation of monohydric alcohols with lead tetra-acetate.[111] Like the hypobromite and hypoiodite reactions, this method has the practical advantage that unstable intermediates do not have to be prepared and isolated in a separate step. Evidence is available that, in apolar media, the mechanism of cyclic ether formation differs from that in the other procedures in that the carbon radical (**74**), which is probably paired with the triacetyl-lead radical, is oxidized to a carbenium ion (**76**) (step *e*) before cyclization occurs (step *f*). This mechanism appears to be followed especially in cases where the relative positions of the oxygen radical and δ-carbon atom are not rigidly fixed. It has been suggested that in rigid systems ring closure may involve a non-classical, bridged transition state and oxidative conversion of (**74**) into the cyclic ether may occur, therefore, without intervention of a carbenium ion intermediate.

The reaction provides an extremely useful route to tetrahydrofurans of varying complexity. Thus heptan-1-ol, when treated with lead tetra-acetate in boiling benzene, gives 2-propyltetrahydrofuran in 50% yield, with minor side products.[112] The reaction has been utilized extensively in the steroid series and also in simpler polycyclic systems. An indication of the power of the method is the conversion of 2-bicyclo[2,2,2]octanemethanol (**81**) to the tetrahydrofuran derivative (**82**) in 43% yield.[113]



(81)



(82)

A procedure seemingly related to the above radical processes, but involving cationic oxygen, has been described.[114] A hydroperoxide (**73**; X = OH) was found to undergo cyclization to a tetrahydrofuran type of ether in 5–10% yield on treatment with an arenesulphonyl halide, through attack by oxygen at a saturated carbon atom.

An unusual and potentially versatile synthesis of the tetrahydrofuran ring system involves reaction between tetracyanoethylene oxide and ethylene or acetylene, yielding 2,2,5,5-tetracyanotetrahydrofuran or 2,2,5,5-tetracyano-2,5-dihydrofuran respectively, in good yields.[115] The reaction could be regarded as a 1,3-dipolar addition between the unsaturated system and a carbonyl ylide formed by electrocyclic transformation of the tetracyanoethylene oxide.

(*ii*) *Reactions*

Ring-opening reactions of tetrahydrofuran and its higher homologues, in contrast to those of oxirans, nearly always require some form of acidic catalysis. Hydrogen halides produce either haloalcohols or dihaloalkanes with these cyclic ethers, depending on the precise reaction conditions and the reactivities of these acids in inducing ring scission increase in the order HCl < HBr < HI. Addition of a Lewis acid, such as zinc chloride, greatly aids ring-opening by hydrogen chloride. Other ring-cleavage reagents include inorganic or organic acid chlorides, acid anhydrides, phosphorus halides, titanium tetrachloride, antimony pentachloride, the Vilsmeier reagent *N*,*N*-dimethyl(chloromethaniminium) chloride, and organometallic derivatives such as tritylmagnesium bromide, tritylsodium–triphenylboron, and some germanium and silicon compounds.

It has been reported[116] that diborane cleaves tetrahydrofuran in 64 hours at 60 °C to yield tributylborate, and that at room temperature the same reaction occurs in about 16 weeks. However, the presence of small amounts of dissolved sodium borohydride effectively eliminates the reductive cleavage of the cyclic ether, and solution of diborane in tetrahydrofuran stabilized in this manner are commercially available. Unsymmetrically substituted ethers are cleaved with diborane by attack at the least substituted α-position, 2-methyltetrahydrofuran giving tri-(2-pentyl)borate. A similar reduction of tetrahydrofuran may be achieved using a mixture of lithium aluminium hydride and aluminium chloride. The cleavage of cyclic ethers with diborane in the presence of iodine provides a very useful route to iodoalcohols.[117]

Electrophilic ring-opening of tetrahydrofurans in the presence of an aromatic compound can lead to alkylation of the latter. Thus reaction of 2-methyltetrahydrofuran with excess of toluene and aluminium chloride afforded 4-(4-methylphenyl)pentan-1-ol and 1,6-dimethyl-1,2,3,4-tetrahydronaphthalene in a ratio of 8 : 1.[98]

The radical chemistry of cyclic ethers has been the subject of increasing interest in recent years.[40] As with acyclic ethers, radicals are formed by preferential loss of a hydrogen atom from an α-position, and towards t-butoxy radicals the ease of hydrogen abstraction varies with ring size according to the order $5 \approx 6 \gg 4 > 3$. 2-Chlorotetrahydrofuran and 2,5-dichlorotetrahydrofuran may be obtained in yields of 38 and 45%, respectively,[118] from the photochemical chlorination of tetrahydrofuran with one or two moles of chlorine, and in a related reaction 2-cyano derivatives predominate amongst the products formed on irradiation of tetrahydrofuran and tetrahydropyran with cyanogen chloride.[119]

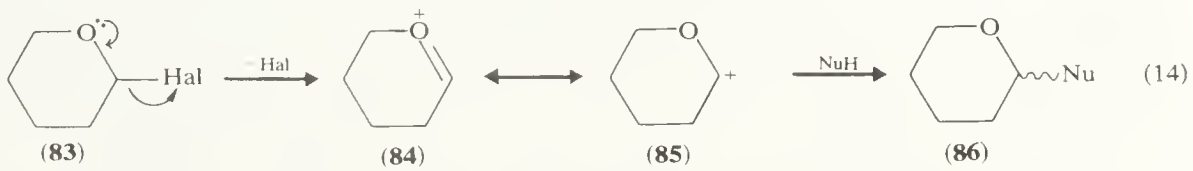
Further developments in this area of chemistry have arisen from the addition of radical

sources, in the form of peroxides or peroxy esters, to the reaction media. Thermal decomposition of t-butyl perbenzoate in tetrahydrofuran or tetrahydropyran in the presence of copper(I) ions affords 2-t-butoxy derivatives of the cyclic ethers.[120] By conducting the reaction in the presence of an alcohol, the alkoxy residue derived from that alcohol can be introduced into the α-position instead of the t-butoxy group. Interestingly, when the peroxy ester is decomposed photolytically below 35 °C in tetrahydrofuran in the presence of copper(I) ions, the 2-acyloxy derivative of the ether is formed.[121]

Addition of an alkene to radical reactions such as those above, to act as a radical trap, enables other useful transformations to be achieved. Tetrahydrofuran, with initiation by t-butoxy radicals, reacts with oct-1-ene at 135–150 °C to yield a small amount of 2-octyltetrahydrofuran, but the major product is dodecan-4-one which, it appears, arises by a process in which the first step is ring opening of the α-tetrahydrofuryl radical. An analogous result was found with tetrahydropyran.[122] The major product of treating 2-methoxytetrahydropyran with a peroxide catalyst is methyl valerate, caused by a similar ring-opening of the initially formed radical; in the presence of oct-1-ene the product was methyl tridecanoate, arising by radical addition to the alkene.[123]

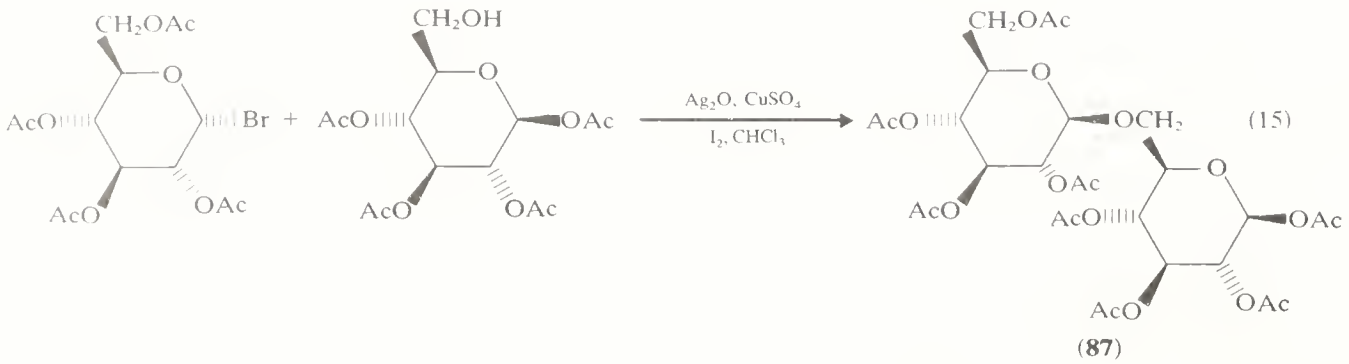
With an electron-deficient alkene such as maleic anhydride, 2-alkylation of tetrahydrofuran rather than ring-opening appears to predominate in radical-mediated reactions, and this might possibly reflect the enhanced reactivity of the alkene over that of oct-1-ene towards the α-tetrahydrofuryl radical.[124]

α-Haloethers are very much more reactive than haloalkanes in reactions involving displacement of halogen. Kinetic measurements on methyl chloromethyl ether indicate that the presence of the oxygen atom results in a rate increase, compared with chloromethane, of $\sim 10^{14}$ for reactions involving an S_N1 mechanism and $\sim 10^5$ for reactions involving an S_N2 mechanism.[125] It is to be expected therefore that α-halo cyclic ethers (**83**) (equation 14) will also readily undergo displacements with a nucleophilic species, NuH, to give (**86**), and that these reactions will tend to proceed by an S_N1 mechanism, especially in a polar medium. Both of these properties find a rationalization in the resonance stabilization that is possible in the oxocarbenium ion, (**84**)↔(**85**), shown in equation (14), and in the transition state for its formation.



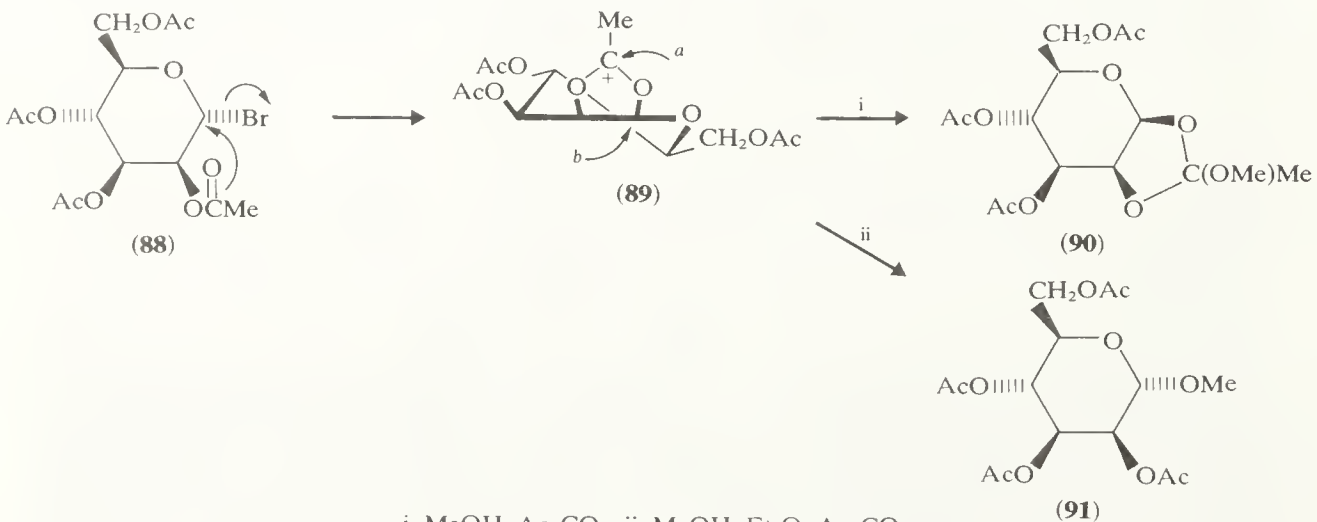
(**83**) (**84**) (**85**) (**86**) (14)

The facile replacement of halogen in α-haloethers is the basis of an important part of the chemistry at the anomeric centre in carbohydrates.[126] The most important uses of carbohydrate α-haloethers, which are termed glycosyl halides, are in the synthesis of simple and complex glycosides (equation 14; NuH = ROH) and of the nucleosides (equation 14; NuH = purine or pyrimidine). Many methods have evolved for the efficient coupling of such moieties, some of which involve the use of heavy metal salts, for example silver or mercury compounds, as acid acceptors. A glycosyl halide is usually used in the form of its acetylated derivative, and is nearly always prepared from a fully acetylated sugar. Two anomeric forms of glycosyl halides can exist, usually described as α- or β-derivatives, both of which have been prepared in many cases. As indicated in Section 4.4.2, a halogen substituent prefers to adopt an axial disposition with respect to a six-membered tetrahydropyran ring as a result of the anomeric effect, and the preparation of glycosyl halides under conditions of thermodynamic control — for example, using hydrogen halides — provides, predominantly, this anomeric form. The less-stable isomer must be prepared under conditions of kinetic control and this can sometimes be achieved by the action of aluminium chloride in cold chloroform on a suitable sugar derivative.



(87)

In general, with 1,2-*cis*-acylglycosyl halides, halide ions are displaced with inversion of configuration at C-1, as indicated in equation (15) in the preparation of β-gentiobiose octa-acetate (**87**). When a glycosyl halide possesses a 1,2-*trans* configuration, then the reaction products with alcohols depend markedly on the conditions used. For example, 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl bromide (**88**) gives a product containing about 80% of orthoesters (**90**) (Scheme 7) on treatment with methanol and silver carbonate, but if diethyl ether is used as diluent, methyl α-D-mannopyranoside tetra-acetate (**91**) is the major product. The formation of these two products can be explained by the intervention an acetoxonium ion (**89**) as an intermediate, which can undergo attack at *a* or *b* to give (**90**) or (**91**), respectively. In general, glycosides produced by use of silver oxide or silver carbonate as acid acceptor (Koenings–Knorr procedure) have the 1,2-*trans* configuration irrespective of the configuration of the glycosyl halide, provided the group at C-2 can participate in the displacement reaction. The observation that reactions between poly-*O*-acylglycosyl halides and heavy metal salts of purines and pyrimidines nearly always afford nucleoside derivatives with a *trans* arrangement of substituents about the C-1 to C-2 bond, regardless of the anomeric configuration of the glycosyl halide, can be understood in terms of a similar reaction mechanism.[127]



i, MeOH, Ag_2CO_3; ii, MeOH, Et_2O, Ag_2CO_3.

SCHEME 7

Studies into the solvolyses of glycosyl halides support the concept that where the halo and acyloxy groups at C-1 and C-2 are *trans* disposed, then reaction occurs with participation of the neighbouring group, and this factor influences not only the stereochemistry of the product but also accelerates its rate of formation.[128] However, it should be noted that, although tetra-*O*-acetyl-β-D-glucopyranosyl chloride is hydrolysed 10^4 times faster than the α-anomer, only part of the large rate difference can be ascribed to anchimeric assistance in the former compound; the higher initial-state free energy of the β-anomer is also an important factor.

The unsaturated cyclic ethers 3,4-dihydro-2*H*-pyran and 2,3-dihydrofuran are vinyl ethers and show the expected ability to undergo electrophilically initiated additions. Acid-catalysed addition of an alcohol to a vinyl ether affords an acetal and this can serve as a useful derivative for hydroxy group protection, as the alcohol may be regenerated by aqueous-acid treatment.[129] 3,4-Dihydro-2*H*-pyran has found considerable application as a protecting group in the synthesis of oligonucleotides, but it suffers from the disadvantage that, with chiral alcohols, diastereoisomeric acetals are produced. This type of problem may be avoided[129] by the use of the vinyl ether 4-methoxy-5,6-dihydro-2*H*-pyran; addition of an alcohol to this compound does not produce a new chiral centre.

Carbohydrate derivatives corresponding to these cyclic vinyl ethers are called glycals, and these compounds are of considerable synthetic importance as a result of the variety of selective addition reactions which they undergo, for example oxidation, hydration, hydrogenation, hydrohalogenation, halogenation, oxymercuration, and hydroformylation. Addition of nitrosyl chloride to glycals provides a valuable route to 2-amino-2-deoxy-sugars.[130]

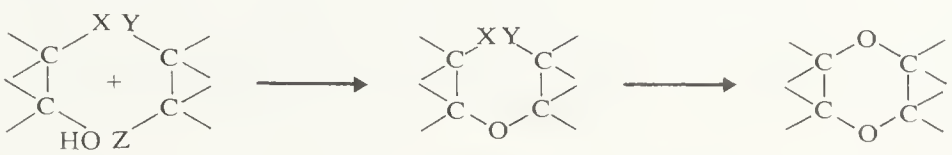
4.4.5 CYCLIC ETHERS CONTAINING MORE THAN ONE OXYGEN ATOM IN THE RING (EXCLUDING CYCLIC ACETALS)

4.4.5.1 1,4-Dioxan and 1,4-dioxepan

(*i*) *Synthesis*

The earlier literature on the chemistry of 1,4-dioxans has been summarized[131] and a monograph[44] on seven-membered heterocyclic compounds containing oxygen and sulphur which contains information on dioxepins, trioxepins, and related compounds has appeared. Methods of synthesis, and the reactions of many of these compounds, are contained in the treatise by Houben-Weyl.[98,99]

1,4-Dioxans are generally obtained (Scheme 8) by methods involving acid-catalysed dehydration of vicinal dihydroxyalkanes (**92**; X = OH + **93**; Y = Z = OH), by base-induced elimination of hydrogen halide from vicinal halohydroxyalkanes (**92**; X = Hal + **93**; Y = OH, Z = Hal), and by reaction of vicinal dihydroxyalkanes (**92**; X = OH) with vicinal dihaloalkanes (**93**; Y = Z = Hal) under basic conditions. The reactions proceed, presumably, through acyclic ether derivatives which themselves may act as synthetic precursors of 1,4-dioxans.



(**92**) (**93**)

SCHEME 8

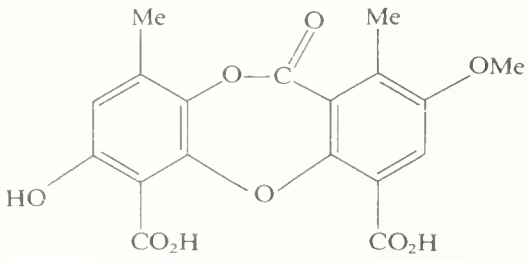
When prepared by the distillation of ethane-1,2-diol in the presence of sulphuric acid, 1,4-dioxan contains acetaldehyde and 2-methyl-1,3-dioxolan as impurities. Interestingly, distillation of propane-1,2-diol with sulphuric acid present does not afford 2,5- or 2,6-dimethyl-1,4-dioxan in any significant quantities, but 2-ethyl-4-methyl-1,3-dioxolan is produced by condensation between propane-1,2-diol and its dehydration product, propionaldehyde.[132]

An interesting route to 1,4-dioxans is based on the electrophilically initiated ring closure of allyl (2-hydroxyethyl) ethers and of diallyl ethers. With diallyl ether itself, and mercuric acetate as the cyclization agent, *cis*-2,6-bis(iodomethyl)-1,4-dioxan is obtained after appropriate work-up.[133] A particularly simple synthesis of the isomeric *trans*-2,5-bis(iodomethyl)-1,4-dioxan proceeds by the reaction of allyl alcohol with mercuric nitrate,

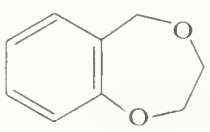
followed by treatment of the organomercury derivative so formed with potassium iodide and iodine.[134] *cis*- and *trans*-2,3-disubstituted 1,4-dioxans are obtained[135] in a related reaction between ethane-1,2-diol and butadiene in the presence of mercuric ions.

The dimerization of oxiran and its derivatives under acidic catalysis to form 1,4-dioxans is a long known reaction, and is used in the commercial preparation 1,4-dioxan.

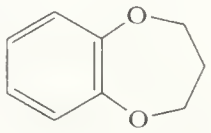
1,4-Dioxepans have, it seems, been very little studied, but their unsaturated derivatives, the dioxepins, are a better known class of compounds, especially those in which the heterocyclic ring is fused to a benzene nucleus. Thus a number of dibenzodioxepin derivatives occur in nature, usually in lichens and moulds; psoromic acid (**94**) is an example. In such derivatives the dioxepin ring is usually in the form of a cyclic lactone. The parent ring system in (**94**) may be synthesized by inducing an intramolecular esterification in 2-(2-hydroxyphenoxy)benzoic acid. The ring systems 2,3-dihydro-5*H*-1,4-benzodioxepin (**95**) and 3,4-dihydro-2*H*-1,5-benzodioxepin (**96**) may be prepared by reaction, in the presence of base, between *o*-hydroxybenzyl alcohol and 1,2-dibromoethane, and between catechol and 1,3-dibromopropane, respectively.



(**94**)



(**95**)



(**96**)

(*ii*) *Reactions*

A notable property of 1,4-dioxan is its ability to form addition compounds.[131] Examples of these are (D ≡ 1,4-dioxan): $D.Br_2$, $D.I_2$, $D.H_2SO_4$, $D.2H_3PO_4$, $D.SO_3$, D.2ICl, D.HalCOCOHal (Hal = Cl, Br), and $D.LiCl.H_2O$. The structures of some of these complexes have been investigated[136] by X-ray crystallographic techniques; in the case of the bromine[136] and oxalyl halide[137] adducts, the crystals contain chains of alternating 1,4-dioxan and acceptor molecules (bromine and oxalyl halide), in which each oxygen atom of every ether molecule is linked to one halogen atom, the second halogen of the acceptor molecule being linked to an oxygen atom of the next 1,4-dioxan molecule. In the crystals of the iodine monochloride adduct, each oxygen atom of a 1,4-dioxan ring is bonded to an iodine atom, and only van der Waals forces exist between chlorine atoms.[136] The symmetrical arrangement of oxygen atoms in the heterocyclic ring seems of importance for complex formation, as 1,3-dioxans do not show a similar general ability to form such adducts.

Some of the addition products of 1,4-dioxan have found synthetic application. The bromine adduct (m.p. 64 °C) finds use in the controlled bromination of reactive compounds, the diphosphate (m.p. 83–87 °C) in phosphorylation, and the sulphur trioxide adduct as a convenient sulphating agent. The formation of addition complexes between magnesium halides and 1,4-dioxan, which are insoluble in ethereal solution, was partly responsible for the proposal of the so called Schlenk equilibrium, to explain the constitution of Grignard reagents in solution.

1,4-Dioxan may be cleaved by treatment with acidic reagents. Treatment with hydrogen bromide at 25 °C leads to bis-(2-bromoethyl) ether in 39% yield.[138] Acyl halides in the presence of a Lewis acid such as titanium tetrachloride yield 2-acyloxyethyl chlorides, and acetic anhydride with ferric chloride affords bis-(2-acetoxyethyl) ether and 1,2-diacetoxyethane in low yields. Ring opening of 1,4-dioxan also occurs on its treatment with ethyl diazoacetate and hydrogen fluoride in ether solution to give ethyl 2-(2-fluoroethoxy)ethoxyacetate in 23% yield. In a similar type of reaction, using the complex acid

$HAlCl_4$, telomerization occurs leading to low molecular weight polymers, each chain having a chloro and an ethoxycarbonylmethyl end group.

A large number of halogenated 1,4-dioxans have been prepared, especially the chloro compounds, by direct halogenation of the parent ether under a variety of conditions.[131] Treatment of the cyclic ether with chlorine in carbon tetrachloride solution under reflux conditions affords[139] *cis*-2,3- and *trans*-2,3-dichloro-1,4-dioxans in the ratio of approximately 2:3, and the former derivative may readily be obtained from the reaction mixture by crystallization.

The *cis* isomer is thermodynamically unstable with respect to the *trans* isomer and isomerization is easily achieved by heating the former above 110 °C, or by treating it with aluminium chloride in benzene at room temperature. In the crystalline state the *trans* isomer has the chloro substituents axially disposed on the six-membered ring.[22] The *trans*-2,3-dibromo compound is obtained in 75% yield by heating the parent ether in refluxing carbon tetrachloride with bromine.[22,140] *trans*-2,5-Dichloro-1,4-dioxan is formed in 24% yield by chlorination of 1,4-dioxan at −5 to −10 °C in carbon tetrachloride solution.[22,131] The difference in the course of chlorination at low and high temperatures has been explained by supposing that, at the higher temperature, the initially formed 2-chloro-1,4-dioxan undergoes elimination of hydrogen chloride to give dihydro-1,4-dioxin, which then adds chlorine to afford the 2,3-dichloro derivative. At low temperature the elimination process is less favoured and the 2-chloro derivative undergoes chlorination at the 5-position of the ring. 2,2-Dichloro-1,4-dioxan may be obtained[139] by dehydrohalogenation of a 2,3-dichloro derivative followed by addition of hydrogen chloride to the resultant 2-chloro-5,6-dihydro-1,4-dioxin.

Tetrachloro-1,4-dioxans are formed by passing chlorine gas into the cyclic ether for a considerably longer period of time and at higher temperatures than are required for preparation of 2,3-dichloro compounds. The 2,3,5,6-tetrachloro-1,4-dioxans can exist in seven stereoisomeric forms, of which four form two enantiomeric pairs. An X-ray structure analysis shows that, in the crystalline state, the *trans,cisoid,trans* compound has all chlorine atoms in axial positions,[22] this remarkably large preference for an axial disposition of electronegative groups being explicable in terms of the anomeric effect (Section 4.4.2). Dehalogenation of *trans*-2,3-dichloro-1,4-dioxan and of isomers of 2,3,5,6-tetrachloro-1,4-dioxan, using magnesium iodide in the presence of magnesium metal, affords the unsaturated cyclic ethers dihydro-1,4-dioxin and 1,4-dioxin, respectively.[99] Addition of hydrogen chloride to dihydro-1,4-dioxin affords a ready synthesis of 2-chloro-1,4-dioxan.[131]

The benzo-fused derivatives of dihydro-1,4-dioxin and 1,4-dioxin can be prepared by base-induced reaction between catechol and dibromoethane, and by reaction of 2-halophenols with base, respectively. 2,3,7,8-Tetrachlorodibenzo[*b*,*e*]-1,4-dioxin, an extremely toxic substance, achieved notoriety in 1976 when quantities were accidentally released into the atmosphere near Seveso, Italy, from a chemical plant which was engaged in the preparation of 2,4,5-trichlorophenol. Inhabitants of the area surrounding the plant were required to evacuate their homes whilst decontamination was carried out.

4.4.5.2 Macrocyclic polyethers

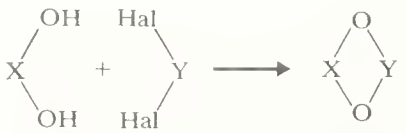
(i) Synthesis

A monograph[141] published in 1973, concerning metal complexes with organic ligands, deals in some detail with those macrocyclic and macrobicyclic compounds containing ether linkages which show a marked propensity for complexing alkali and alkaline-earth metal ions. It provides an excellent summary of the pertinent literature in this field prior to its publication date.

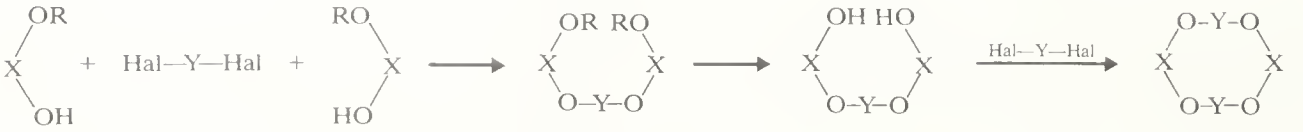
Macrocyclic polyethers have been known for a considerable time. Some early studies into the preparation of many-membered ring systems involved base-induced cyclizations, under conditions of high dilution, of mono-ω-haloalkyl ethers of hydroquinone, resor-

cinol, and other related dihydric phenols. Low yields of macrocyclic polyethers had also been obtained by reaction of bis(ω-haloalkyl) ethers of hydroquinone with hydroquinone. The cyclic, tetrameric condensation product from furan and acetone, and cyclic tetramers of oxiran and 2-methyloxiran, provide other early examples of cyclic polyethers.

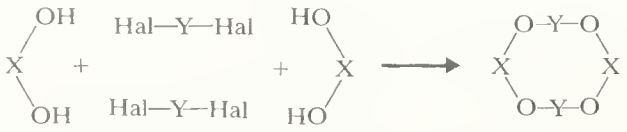
The discovery by Pedersen[142] that many macrocyclic polyethers show a remarkable tendency to form stable complexes with metal salts, especially those of the alkali or alkaline-earth metals, caused an enormous increase in interest in the chemistry of these compounds. Methods used by Pedersen and later workers to synthesize macrocyclic polyethers are represented in equations (16)–(20). In these syntheses the dihalo compounds $Y(Hal)_2$ may often be replaced by the disulphonate esters of the corresponding diols, that is $Y(OSO_2R)_2$, and the reactions are performed in the presence of a basic species in order to generate the alcoholate or phenolate, respectively, of the alcohol or phenol. The strategies behind the synthesis of ligand systems such as these and of more complex types have been discussed.[141]



(16)

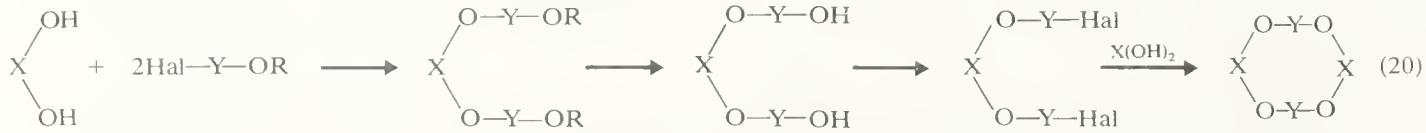


(17)



(18)

(19)



(20)

A remarkable feature of many of these cyclizations is that they often provide adequate to reasonable yields of products without recourse to high-dilution techniques. Reaction of triethylene glycol [2-(2-(2-hydroxyethoxy)ethoxy)ethanol] with triethylene glycol di-*p*-toluenesulphonate in 1,2-dimethoxyethane or in DMSO in the presence of potassium t-butyl alcoholate (equation 16) was reported[143] to give 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6*) in yields of 93 or 84%, respectively; lower yields of 30–60% were obtained on conducting the reaction in tetrahydrofuran. The operation of a template effect, resulting from coordination of reactants around potassium ions, was suggested to account for the relatively high yields obtained in these cyclizations, although it is likely that complexation is important only in the final ring-closure process. Notably, with tetrabutylammonium hydroxide as the base in tetrahydrofuran, the 18- and 21-membered cyclic ethers were obtained in greatly decreased yields, the majority of the starting

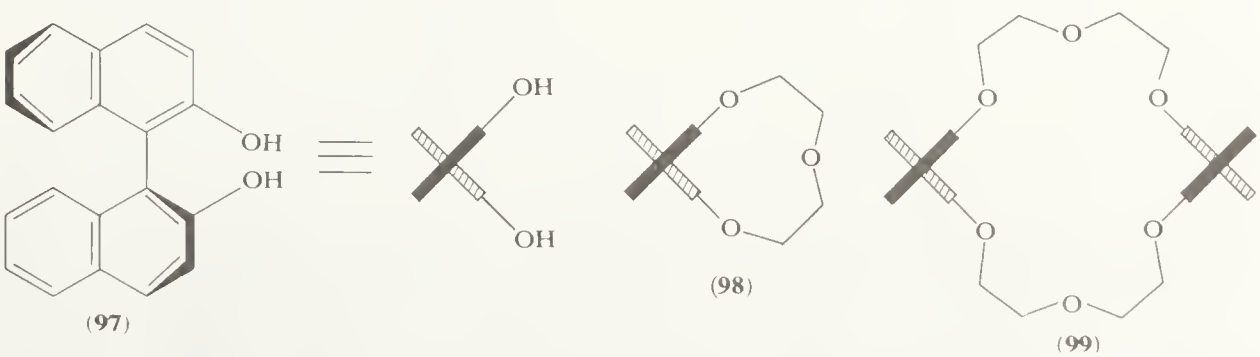
* The trivial 'crown' nomenclature was devised by Pedersen for convenience. The trivial names consist of, in order: (i) the number and kind of hydrocarbon rings (if any) fused to the macrocyclic polyether ring; (ii) the total number of atoms in the polyether ring; (iii) the class name 'crown'; and (iv) the number of oxygen atoms in the polyether ring. Although the 'crown' names do not define structure unequivocally, they will be used here to avoid the lengthy and, in many cases, extremely complicated names derived from the IUPAC rules, for compounds of other than the simple monocyclic type.

material polymerizing. Also noteworthy was the precipitation of only one half of the expected quantity of potassium *p*-toluenesulphonate in the 18-crown-6 synthesis using potassium t-butyl alcoholate as base, suggesting that in this case one molar equivalent of potassium ion is enveloped during cyclization. Related experiments[144] on the synthesis of simple macrocyclic polyethers containing repeating —CH_2CH_2O— units, using as reactants a diol and the di-*p*-toluenesulphonate of the same or another diol, as in equation (16), indicated that the ester should not be ethane-1,2-diol di-*p*-toluenesulphonate (which tends to undergo elimination), and it was found that reactions which might be expected to lead to 9- or 12-membered rings afforded instead products of twice these ring sizes, even under conditions of high dilution. Interestingly, competition experiments between a diol di-*p*-toluenesulphonate and several diols, with potassium t-butyl alcoholate as the base, indicated that there is a significant preference for the formation of a 21-membered ring ether over those with 15-, 18-, or 24-membered rings.

The stepwise method of synthesis indicated in equation (17) is the most versatile and affords, in general, the highest yields of cyclized products, but since it requires more operations than the method of equation (18), the latter may sometimes be preferable for practical reasons. The method indicated in equation (19) would appear to suffer the disadvantage that the halohydroxy compound is particularly suited to undergo intra- rather than inter-molecular cyclization, and indeed the former process was the basis of much of the early work on cyclic ether formation.

The synthesis indicated in equation (20) is a variation of that in equation (16), but it has been used by Cram and co-workers[145,146] to synthesize macrocyclic polyethers incorporating two different aromatic rings and to prepare cyclic polyethers possessing axial chirality.[146] Variations on the procedure of equation (20) have included the preparation of the species $X(OCH_2CH_2OSO_2C_6H_4Me)_2$ from the diol $X(OH)_2$ by conversion of the latter into its bis-allyl ether, which was then subjected sequentially to ozonolysis, reduction, and *p*-toluenesulphonylation.[147] An alternative and useful route for the synthesis of a 2-(*p*-toluenesulphonyloxy)ethyl ether derivative of an alcohol involves alkylation of the latter with ethyl chloroacetate, followed by lithium aluminium hydride reduction, then *p*-toluenesulphonylation.[148]

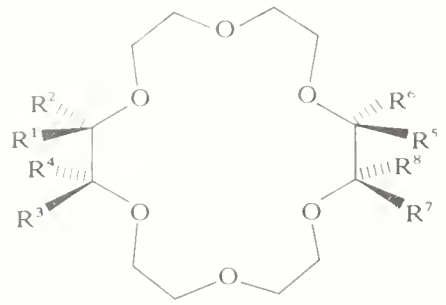
Undoubtedly one of the most significant developments in the study of macrocyclic polyether ligands has been the preparation of chiral crown ethers which have potential for chiral recognition towards enantiomeric 'guest' molecules. Cram and co-workers[149] have based their synthesis of such chiral 'hosts' on the 2,2′-dihydroxy-1,1′-binaphthyls which, owing to restricted rotation about the C-1—C-1′ bond, exist in enantiomeric forms. The (−)-(*S*)-form of the parent compound is depicted in formula (**97**). Reaction of diol (**97**) with diethyleneglycol di-*p*-toluenesulphonate in tetrahydrofuran containing potassium t-butyl alcoholate gave the cyclic ethers (**98**) and (**99**) in yields of 5% and 31% respectively. Such molecules may be classed as being conformationally chiral, as racemization occurs by rotation about a C—C single bond.



(**97**) (**98**) (**99**)

Chiral macrocyclic polyethers have also been produced by incorporating into the ring skeleton chiral sub-units which exhibit optical activity as a result of their configuration rather than their conformation. Thus *N*,*N*,*N*′,*N*′-tetramethyl-L-*threo*-tartaramide,[150] 1,4-

di-*O*-benzyl-L-threitol,[147] and 1,2:5,6-di-*O*-isopropylidene-D-mannitol,[147] which all contain α,β-diol groupings, have been transformed into the derivatives of 18-crown-6, (**100**), (**101**), (**102**) respectively, by elaboration of the necessary bridges between the two chiral units.

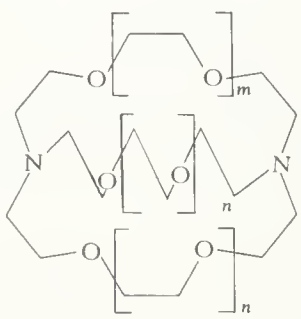


(**100**) $R^2 = R^3 = R^5 = R^8 = CONMe_2$
$R^1 = R^4 = R^6 = R^7 = H$

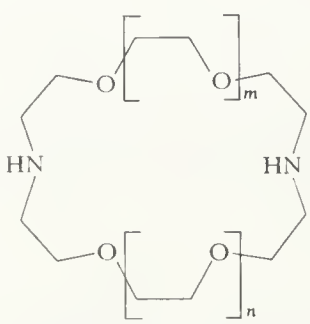
(**101**) $R^2 = R^3 = R^5 = R^8 = CH_2OCH_2Ph$
$R^1 = R^4 = R^6 = R^7 = H$

(**102**) $R^2 = R^3 = R^5 = R^8 = H$
$R^1 = R^4 = R^6 = R^7 = Me_2C$

An important advance in the study of the complexing abilities of oxygen-containing ring systems was made with the synthesis of the diazapolyoxa macrobicyclic compounds[151] of the type shown in formula (**103**). The bridgehead atom in these compounds is nitrogen, but any atom of valence three or higher can occupy this position. The preparation of such bicyclic systems is performed by reaction of a polyoxadiamine, $H_2NCH_2CH_2O(CH_2CH_2O)_mCH_2CH_2NH_2$, with a diacid dichloride, $ClCOCH_2O(CH_2CH_2O)_nCH_2COCl$, under conditions of high dilution, followed by reduction of the resulting macrocyclic diamide with lithium aluminium hydride to yield a macrocyclic diamine (**104**). Further reaction of (**104**) with the diacid dichloride leads to a bicyclic system, which, on reduction by diborane, yields (**103**). The synthetic route allows for the preparation of a variety of ligands which may differ in their cavity size and also in the nature of their ring heteroatoms.

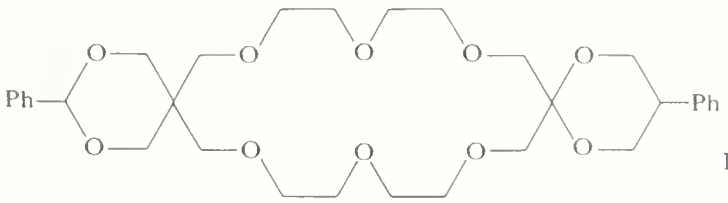


(**103**)

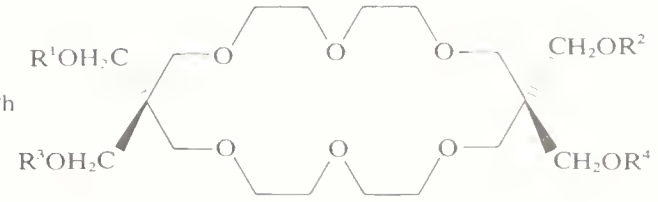


(**104**)

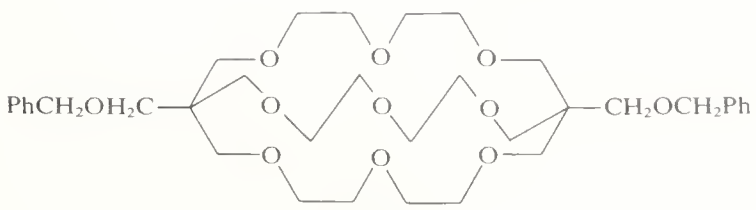
A macrobicyclic polyether has also been synthesized with carbon bridgeheads, starting from pentaerythritol,[152] which was converted into its mono-*O*-benzylidene derivative in the first step. This diol on reaction with diethylene glycol di-*p*-toluenesulphonate in the usual manner gave the macrocyclic ether (**105**) in 15% yield. The key reaction involved the controlled reductive cleavage of the acetal rings in this compound to yield a mixture of the diastereoisomeric diols, (**106**) and (**107**), one of which, presumably (**106**), underwent reaction with diethylene glycol di-*p*-toluenesulphonate to give the macrobicyclic compound (**103**) in 30% yield.



(**105**)



(**106**) $R^1 = R^2 = H$; $R^3 = R^4 = CH_2Ph$
(**107**) $R^1 = R^4 = H$; $R^2 = R^3 = CH_2Ph$



(**108**)

(ii) Complexing properties of macrocyclic polyethers

The most remarkable property of macrocyclic polyethers is their ability to form complexes with salts.[153] Pedersen and Frensdorff[142] noted that, of the 60 or so macrocyclic polyethers they had examined, the most effective complexing agents were amongst those containing five to ten oxygen atoms, each separated from the next by two carbon atoms. The compounds form 1:1 polyether–salt complexes in which the cation is encircled by the ring oxygen atoms, but 2:1 and 3:2 polyether–salt complexes are also known. That many alkali and alkaline-earth metal salts form complexes with these neutral ligands is especially noteworthy, as complexes of this type had rarely been observed, previously.

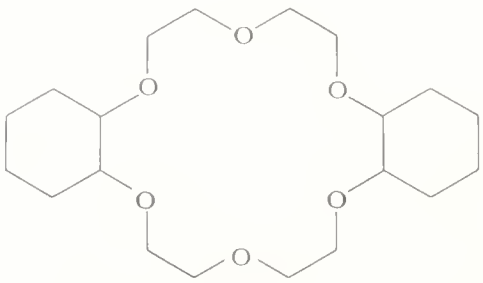
As a result of complex formation, ionic compounds may be solubilized in organic media, a dramatic demonstration of this being the dissolution of potassium permanganate in benzene[154] on the addition of dicyclohexyl-18-crown-6 (**109**). Stability constants of polyether–cation complexes have been measured by calorimetric, potentiometric, conductometric, and spectroscopic methods.[141] These constants might be expected to depend on ligand and ion parameters, and on the solvent.

Potentiometric measurements in methanol solution indicate[155] that with cyclic polyethers containing the $—CH_2—CH_2—O—$ repeating unit, the stability constants for each cation go through a maximum with increasing polyether ring size. The optimum ring size is 15–18 for Na^+, 18 for K^+, and 18–21 for Cs^+. There is a close correspondence between cation diameter and the 'hole' diameter, as measured from models, of the polyether ring of optimum size for complexing that cation. However, the increase in the stability constant for the K^+ ion with increase of polyether ring size from 24 to 30 suggests that in solution the larger ligand may wrap itself around the cation, as it does in the crystalline state (see later). Of the complexes of Na^+, K^+, and Cs^+ formed with the ligand of optimum ring size, the one from K^+ has the largest stability constant, an observation which can be rationalized as being the result of competition between complex formation and solvation. The intense electric field associated with a small cation ensures that the cyclic polyether must compete with strongly attracted dipolar solvent molecules, whereas with the largest cation the forces of attraction for solvent and polyether will be much lower. It should be noted that the order of complexing ability observed[155] for 18-crown-6 type ligands towards alkali metal ions in water and methanol solution, that is $K^+ > Na^+$ and Cs^+, is not followed in tetrahydrofuran. Measurements on ion pairs in carbanion alkali metal salts showed[156] that in this solvent Na^+ ions are more strongly complexed than Cs^+ and K^+ ions. Interestingly, in the strong donor solvent oxetan, favoured complexing of K^+ over Na^+ is again observed.

Complexes between a cyclic polyether and ions of similar charge and not greatly dissimilar diameters can differ enormously in their relative stabilities; the difference in

stability constants between Ca^{2+} and Pb^{2+} dicyclohexyl-18-crown-6 complexes is around 10^5, the complex with the latter ion being the stronger. This selectivity difference could have some potential in view of the toxicity of lead to some biological systems.

Increased stabilities of complexes are to be expected in transferring from a polar to a less-polar solvent. For complexes with dicyclohexyl-18-crown-6 (**109**), the K^+ and Na^+ ion stability constants are approximately 10^4 and 10^3 times higher, respectively, in methanol than in water.



(**109**)

In aqueous solution, macrobicyclic ethers of the type (**103**) show a much greater complexing ability for a given ion compared with monocyclic ethers of a comparable size. For example, (**103**; $m = 1, n = 1$) exhibits log K_s values (K_s = stability constant) of 3.9 for Na^+ and 5.4 for K^+ ions, which may be compared with corresponding values of <0.3 and 2.06 for 18-crown-6. The bicyclic ether complexes are formed by encapsulation of the cation within the cavity of the compound. These ligands appear better suited than the monocyclic ethers for exhibiting selectivity in ion complexing since changes in cavity size should affect more drastically the relative stabilities of complexes than changes in ring size. There is, not surprisingly, a correspondence between approximate cavity size and the diameter of the cation showing optimum complexing.

Pedersen's initial suggestion[157] that, in complexes between crown polyethers and metal salts, the metal cation lies in the central 'hole' of the polyether and is bound to it by ion–dipole interactions, has been substantiated in many cases by X-ray structure determinations.[141] Although the first complex to be studied (dibenzo-18-crown-6)$_3$(RbSCN)$_2$ did not have the postulated 'sandwich' structure (the stoichiometry results from an uncomplexed ligand in the crystal for every two complexed species), the rubidium ion was indeed found to be nearly equidistant from six coplanar oxygen atoms, and about 100 pm to one side of the mean plane through them. In (dibenzo-18-crown-6)NaBr.2H_2O, a sodium ion, for which there are two crystallographically distinct environments, lies similarly disposed with respect to the oxygen atoms although its displacement from their mean plane is less.[158] With the smaller ring-sized polyether benzo-15-crown-5, sodium iodide forms a 1:1 monohydrated complex,[159] with the sodium ion at 75 pm from the mean plane of the five oxygen atoms, and the water molecule coordinated to the metal ion, making a pentagonal-pyramid arrangement of oxygen atoms. Interestingly, the complex between benzo-15-crown-5 and potassium iodide has the formula (benzo-15-crown-5)$_2$KI, and crystal-structure determination[160] confirmed Pedersen's suggestion that such a complex may have a 'sandwich' structure. In this case the diameter of the metal ion (266 pm) is larger than the 'hole' (170–220 pm) and every potassium ion lies between two ligands, in each of which the oxygen atoms are approximately co-planar.

Seven configurational isomers of dicyclohexyl-18-crown-6 (**109**) are theoretically possible, of which four form two enantiomeric pairs. Two isomeric forms termed *A* and *B* have been isolated by hydrogenation of dibenzo-18-crown-6. The crystal structure of the barium thiocyanate complex of isomer *A* showed[161] the polyether to be the *cis,cisoid,cis* isomer and the barium ion to be coordinated by the six, nearly coplanar, oxygen atoms. Structure determination of the sodium bromide dihydrate complex of isomer *B* showed[162a] the ligand to have the *cis,transoid,cis* configuration, and the oxygen atoms to form a nearly planar ring around the sodium ion. The stereocontrolled syntheses of *trans*,

cisoid,trans-,[162b] (±)-*trans,transoid,trans*-,[162b] and (+)-*trans,transoid,trans*-dicyclohexyl-18-crown-6[162c] have been achieved.

With larger macrocyclic polyether rings the possibility exists for coordination of more than one metal ion by a ligand molecule, and also for encapsulation of an ion. The former possibility is observed in the (dibenzo-24-crown-8)$(KSCN)_2$ complex,[163] in which two potassium ions lie within one macrocyclic ring, displaced 66 pm to each side of the plane formed by the eight oxygen atoms. Two of the ring oxygen atoms are shared by both potassium ions. Dibenzo-24-crown-8 and two molecules of sodium 2-nitrophenolate afford a related complex[164] but, in this case, two ring oxygen atoms of the ligand are not involved in coordination, and the crown ring folds around the cations. With the larger ring compound dibenzo-30-crown-10, potassium iodide forms a 1:1 complex in which the potassium ion is completely enclosed by the ligand.[165] The oxygen atoms completely replace the hydration sphere of the cation, and the molecular configuration of the ligand resembles that of the seam on a tennis ball.

Crystal-structure determinations on alkali metal complexes of the diazahexaoxa macrobicyclic ligand (**103**; $m=1, n=1$) have shown[166,167] that in each case the metal ion is completely enclosed in the cavity of the ligand, a feature which is nicely illustrated by the stereoscopic drawings in the original papers. Perhaps the most remarkable of all of the encapsulated complexes is the crystalline compound (**103**; $m=1, n=1$)Na^+Na^-.[168]

Crown ethers find ever increasing application in synthetic organic chemistry. Their usefulness depends, essentially, on their ability to solvate cations in non-polar environments and thereby to render many ionic compounds soluble in non-polar, organic media. In addition, complexation of the cation prevents a close association between gegen ions, and this, together with the poor solvating power of non-polar aprotic media for anions, can lead to enhanced nucleophilicity and basicity of the anionic species. Potassium hydroxide, for example, may be dissolved in toluene in the presence of a molar equivalent of dicyclohexyl-18-crown-6 to form an approximately 0.3M solution in which sterically hindered esters of 2,4,6-trimethylbenzoic acid can be saponified readily, in contrast to their relative stability to the base in hydroxylic solvents.

Potassium permanganate may be dissolved in benzene in the presence of dicyclohexyl-18-crown-6 to afford purple solutions of concentration up to 0.06M, which can be used for the homogeneous oxidation of organic compounds.[154] It is not necessary, however, to pre-form the complex, and the oxidation may be carried out in the presence of a catalytic quantity of the cyclic polyether, which transfers the potassium permanganate into the organic layer by formation of a transient complex. Such a process is termed solid–liquid phase-transfer catalysis, and many examples of its application have been recorded. Potassium fluoride is solid-to-liquid phase-transferred into benzene or acetonitrile by 18-crown-6 and the 'naked' fluoride ion so produced is found to be a potent nucleophile and base.[169] The macrocyclic[170] and macrobicyclic[171] polyethers may be effective also as liquid–liquid phase-transfer catalysts, provided that their solubility properties ensure a partitioning between the two media; primary alkyl fluorides, chlorides, bromides, iodides, and cyanides are easily prepared in high yield by this method from the corresponding alkyl sulphonate and the appropriate alkali metal salt.

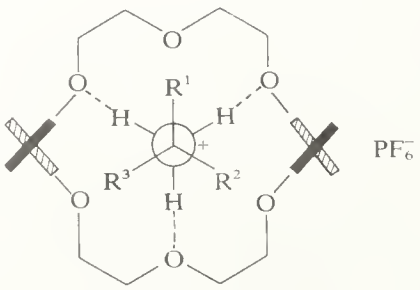
By its interaction in solution with the cation of an ionic compound, a crown ether may promote the formation of separated ion pairs, and thereby alter the course that a given reaction takes in its absence. For example, significant differences have been observed in the stereochemistry of carbanion[172] and β-elimination reactions[173] when they are conducted in the presence and absence of cyclic polyethers. Furthermore, a marked increase in the specific activity of potassium t-butoxide in DMSO occurs above a certain concentration of the base on the addition of 18-crown-6; this may be attributed to the polyether preventing ionic aggregation which occurs in its absence at moderate concentrations of the base.[174]

An important development in the study of the complexing properties of macrocyclic polyethers was initiated by Cram,[175] who formulated the concept of 'host–guest chemistry', in which a host molecule complexes preferentially with a species — the guest — by

recognizing in it an array of binding sites and steric features that complement those of the host. The motivation for such research stems from a desire to provide non-peptide, organic compounds that simulate enzyme behaviour, in particular the first step in enzymic catalysis, which involves the formation of a highly selective molecular complex containing a favourable orientation of reactive groups. Although metal ions may be regarded as 'guests', the latter term is usually reserved for organic species, which have more complex steric requirements and which generally offer a greater variety of bonding possibilities than simple ions.

A simple example of host–guest interaction is the solubilization of an arenediazonium tetrafluoroborate, $Ar—\overset{+}{N}\equiv N\ BF_4^-$, and benzoyl hexafluorophosphate, $Ph\overset{+}{C}\equiv O\ PF_6^-$, in a non-polar medium such as chloroform, by a macrocyclic polyether of suitable dimensions.[176] Variation in the structure of the guest and in the size of the macrocyclic ring, together with ^1H n.m.r. spectroscopic measurements, suggested that dissolution of the ionic species is caused by complexation, the linear $Ar—\overset{+}{N}\equiv N$ (or $Ph\overset{+}{C}\equiv O$) group inserting into the 'hole' of the cyclic polyether.

An outstanding property of many enzyme systems is the ability to differentiate between enantiomeric forms of an organic compound. This is, of course, a result of their own chiral nature, which means that an enzyme interacts differently with the two forms of a chiral substrate. Further developments in host–guest chemistry have involved attempts to synthesize relatively simple chiral hosts which may mimic this enzyme ability. Cram and co-workers have based their chiral hosts on 2,2′-dihydroxy-1,1′-binaphthyl (**97**), and two macrocycles derived from the (−)-(*S*)-enantiomer are depicted in formulae (**98**) and (**99**).



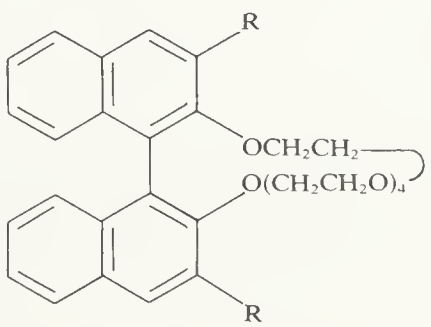
(**110**) $R^1 = Ph$, $R^2 = H$, $R^3 = Me$
(**111**) $R^1 = Ph$, $R^2 = Me$, $R^3 = H$
(**112**) $R^1 = Ar$, $R^2 = H$, $R^3 = COOMe$
(**113**) $R^1 = COOMe$, $R^2 = H$, $R^3 = CH_2Ph$

The ability of macrocyclic polyethers to form complexes with primary alkylammonium ions provided a strong impetus to study enantiomeric differentiation in compounds containing the $R—\overset{+}{N}H_3$ groups, especially in view of the fact that amino acids, in their *N*-protonated form, belong to this class. The (*S,S*) form of bisbinaphthyl-22-crown-6, which is shown in cross section in formula (**99**), was found[149] to extract preferentially the (*R*)-enantiomer of α-phenylethylammonium hexafluorophosphate into chloroform from an aqueous solution containing a racemic mixture of the salt. The ratio of the (*S,S*)-crown–(*R*)-ammonium salt complex (**110**) to that of the (*S,S*)-crown–(*S*)-ammonium salt complex (**111**) was approximately 2:1, a result which may be understood by an examination of the steric interactions in these complexes. In the ammonium–crown ether complexes it is assumed that the ammonium ion binds by means of dipole to ion forces associated with three O · · · H hydrogen bonds, and by three oxygen to nitrogen interactions (three-point binding model). By means of liquid–liquid chromatography, complete resolution of α-phenylethylamine was achieved,[177] through this selective complexation process. A solution of the (*S,S*)-host (**99**) in chloroform eluted the (*R*)-ammonium salt from a column containing the aqueous phase supported on Celite, before any of the

(*S*)-enantiomer appeared.* Two racemic α-amino-α-phenyl esters were also resolved by this technique, and in both cases the first eluted complex (**112**)* appeared to be the least sterically hindered on the basis of this 'three-point binding' model. However, it should be noted that in the complexes of (*S*,*S*)-host (**99**) with α-amino ester hexafluorophosphates, the guests in the favoured complexes do not always have related absolute configurations. For example, although (*S*,*S*)-host* (**99**) selectively complexes[177] (*S*)-methyl phenylglycinate salt to give complex (**112**; Ar = Ph), in the case of the methyl phenylalaninate salt,[146] the favoured complex (**113**) is formed with the (*R*)-enantiomer; this preference may be rationalized in terms of steric interactions in a 'four-point binding' model, in which the extra bonding interaction is between the carboxylic carbon atom and the closest ether oxygen atom. In addition, the introduction of methyl groups at the 3,3′-positions in (**99**) can, in some cases, increase the selectivity shown by the host between enantiomers,[146] and in others can reverse a selectivity for one enantiomer to a selectivity for the other one. Using the 3,3′-dimethyl derivative of the enantiomer of (**99**), that is the (*R*,*R*)-host, to extract racemic phenylglycine perchlorate salt from aqueous solution, it has been found[178] that enantiomeric differentiation is remarkably dependent on solvent polarity and extremely high chiral recognition may be achieved if certain chloroform–acetonitrile mixtures are used as the organic phase.

By the covalent attachment of chiral crowns of the type (**99**) to silica gel,[179] chromatographic supports may be prepared with which the resolution of racemic amine and amino ester salts may be performed through solid–liquid chromatography.

Cram and co-workers have investigated the effect of macrocyclic polyether structure on the association constants for the interaction of these hosts with alkylammonium guest compounds.[180] Amongst the many compounds they have prepared are those[181] of the series represented by (**114**). The (*S*)-diacid (**114**; R = $CH_2OCH_2CO_2H$) preferentially complexed[182] (*S*)-valine over its enantiomer by a factor of 1.3. Molecular models indicate that in such a favoured complex one of the carboxyl groups of the host might, in its ionized form, ion pair with the guest's ammonium group, which itself interacts with the ring-oxygen atoms of the polyether. The second carboxyl group of the host could provide a further point of bonding to the guest by hydrogen bonding with the carboxyl group of the latter. The enantiomer selectivity is readily understood from models; in the (*S*)–(*S*) complex, the alkyl group of valine points away from the naphthalene rings when the binding features described above are taken into account.



(114)

An example of an enzyme model showing stereoselectivity in catalysis, which can be rationalized in terms of a favourable guest–host fit, is provided[183] by the hydrolysis of enantiomeric *p*-nitrophenyl α-amino esters in the presence of the cyclic dithiol (**114**; R = CH_2SH). With L-amino ester salts in ethanol–dichloromethane solution, *p*-nitrophenol is liberated — presumably with the formation of a thioester as an intermediate — more quickly in the presence of the cyclic (*S*)-dithiol than the cyclic (*R*)-dithiol. The

* In the investigations reported in Ref. 177 the (*R*,*R*)-enantiomer of the host was actually used, and the more stable complex was formed with the (*S*)-ammonium salt of α-phenylethylamine. Similarly, (**112**) is the enantiomer of the more stable complex of the amino ester, reported in this paper. The configurations have been changed here to avoid unnecessary duplication of diagrams and to aid comparisons.

enantiomeric differentiation observed in this reaction improves with an increase in the bulk of the groups attached to the α-carbon atom of the guest molecule.

The diacid (**114**; $R = CH_2OCH_2CO_2H$) shows interesting selectivity towards alkaline earth metal ions. On hydrolyzing the diester (**114**; $R = CH_2OCH_2CO_2Me$) with a ten-fold excess of barium hydroxide containing 0.8% of strontium hydroxide, the strontium ion was scavenged[181] and was carried into chloroform, presumably as the crown ether complex, when the acid was isolated by solvent extraction.

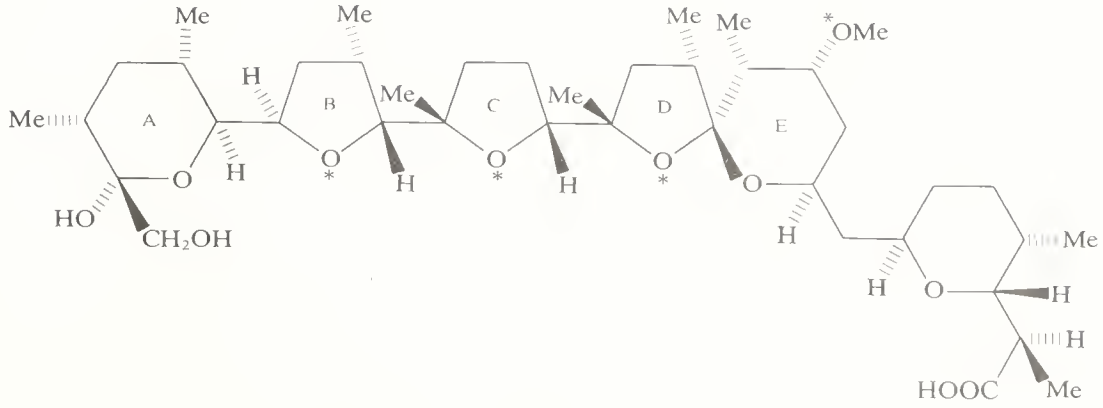
Chiral macrocyclic polyethers have been prepared from carbohydrate precursors. Carbohydrates are especially well suited for this type of synthesis as they usually contain —O—C—C—O— units in a variety of structural environments, and they provide a source of chirality. Stoddart and co-workers[147] have synthesized (**101**), (**102**), and some closely related derivatives, all of which dissolved alkali metal ions and alkylammonium salts in organic solvents. Compound (**102**) and 1,1′,4,4′-tetra-*O*-triphenylmethyl-2,2′:3,3′-bis-*O*-oxydiethylenedi-L-threitol (formula **101** with CH_2OCPh_3 replacing CH_2OCH_2Ph) differentiate between enantiomeric forms of α-phenylethylammonium hexafluorophosphate in complexation equilibria.[184] Significantly, chiral recognition was only observed when the substituent groups on the chiral macrocycle were bulky; compound (**101**) did not differentiate between the enantiomeric guest molecules. The favoured complexing of (**102**) with (*R*)-guest is readily rationalized on the basis of a three-point binding model. Selective complexation with one of the enantiomers of α-phenylethylammonium hexafluorophosphate was also observed in the case of two chiral macrocyclic polyethers derived from 1,2:5,6-di-*O*-isopropylidene-D-mannitol and the (*R*)- and (*S*)-forms of 2,2′-dihydroxy-1,1′-binaphthyl.[185]

Girodeau, Lehn, and Sauvage reported[150] that the macrocyclic polyether (**100**) forms a remarkably stable complex with Ca^{2+} ions in water; the stability constant of the complex at 25 °C is 100, whereas that for the interaction of dicyclohexyl-18-crown-6 with Ca^{2+} ions is approximately 3. Hydrolysis of (**100**) affords the corresponding tetracarboxylic acid,[186] which, as the tetracarboxylate, forms by far the most stable K^+ and NH_4^+ ion complexes reported to date for a macrocyclic polyether.

So far, this discussion on the complexing properties of polyethers has centred on synthetic ligands. However, a number of naturally occurring compounds having antibiotic properties are known which have the ability to form lipid soluble alkali and alkaline-earth ion complexes. Many of these contain cyclic-ether residues, whilst others, which will not be considered here, are neutral macrocycles with the ring composed of amide and ester linkages (for example, valinomycin). In the cyclic ether containing class, distinction may be made between the macrocyclic neutral molecules and the monobasic acids. The latter group is exemplified by nigericin (**115**), which was originally isolated[187] in 1951 along with two other acidic metabolites from unidentified *streptomyces*.* Interestingly, the solubility of the alkali salts of these metabolites in benzene and hot petroleum ether, and their insolubility in water, was noted at the time of their isolation, but the intriguing observation was not followed up. It was not until 17 years later that the structure of nigericin was elucidated by an X-ray crystal structure determination on its silver salt, which is isomorphous with the sodium salt. These results show that in the crystal one oxygen atom of the carboxylate anion is hydrogen bonded by the two hydroxy groups in ring A to produce a pseudomacrocyclic system, whilst the other oxygen atom of the anion is coordinated to the silver ion. The coordination sphere of the metal ion is completed by the ring-oxygen atoms in rings B, C, and D, and by the methoxy oxygen on ring E, which are marked with asterisks in (**115**). Nigericin favours complexation with potassium ions over sodium ions.

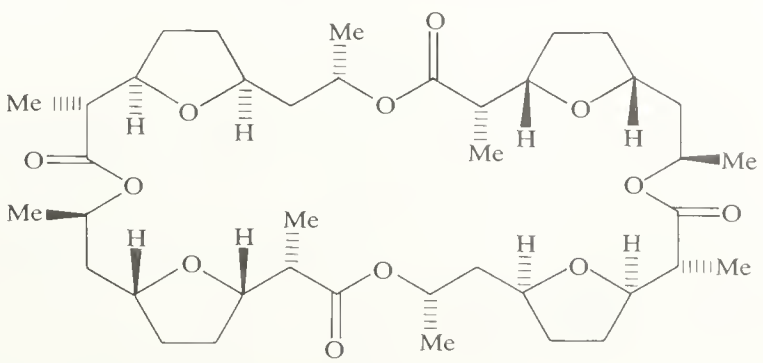
One of the neutral antibiotics containing cyclic ether residues is nonactin (**116**). The structure of this fungal metabolite, isolated from *actinomyces*, incorporates enantiomeric

* The antibiotics were originally given code numbers, and X-464 was later shown to be identical with nigericin, obtained by other workers from a streptomycete present in a Nigerian soil.



(**115**)

repeating units. Four units, two of each enantiomeric form, are joined through ester bonds to form the macrocycle. The alternating arrangement of the enantiomeric units means that the molecule possesses a four-fold alternating axis of symmetry, and thus is optically inactive. The compound is also classified as a macrotetrolide. Other members of this class of compounds have some of the methyl groups replaced by ethyl groups.



(**116**)

Nonactin complexes alkali metal ions in the sequence $Li^+ \ll Na^+$, $Cs^+ < Rb^+$, K^+. In the crystalline potassium thiocyanate complex[188] the ligand is wrapped around the potassium ion in a conformation resembling the seam of a tennis ball, in a similar manner to that found in the (dibenzo-30-crown-10)KI complex.[165] The potassium ion has a coordination sphere of eight oxygen atoms, composed of four from the tetrahydrofuran rings and four from the carbonyl groups.

The marked effects which these neutral and acidic antibiotics have on alkali-metal cation transport in respiring cell fragments, and on the cation permeability of natural and artificial membranes, is obviously a direct consequence of their ability to complex with certain metal cations.

References

1. 'Nomenclature of Organic Chemistry', Sections A and B (3rd edn.); Section C (2nd edn.), Butterworths, London, 1971.
2. J. D. Cox, *Tetrahedron*, 1963, **19,** 1175.
3. A. S. Pell and G. Pilcher, *Trans. Faraday Soc.*, 1965, **61,** 71.
4. A. Rosowsky, in 'The Chemistry of Heterocyclic Compounds', ed. A. Weissberger, Wiley, New York, 1964, vol. 19, part 1, chapter 1.
5. S. Searles, Jr., in 'The Chemistry of Heterocyclic Compounds', ed. A. Weissberger, Wiley, New York, 1964, vol. 19, part 2, chapter 9.
6. H. J. Geise, W. J. Adams, and L. S. Bartell, *Tetrahedron*, 1969, **25,** 3045.
7. M. Davis and O. Hassel, *Acta Chem. Scand.*, 1963, **17,** 1181.
8. W. J. Adams, H. J. Geise, and L. S. Bartell, *J. Amer. Chem. Soc.*, 1970, **92,** 5013.
9. J. F. Stoddart, 'Stereochemistry of Carbohydrates', Wiley-Interscience, New York, 1971.

10. F. A. Cotton and B. A. Frenz, *Tetrahedron*, 1974, **30,** 1587.
11. W. J. Lafferty, D. W. Robinson, R. V. St. Louis, J. W. Russell, and H. L. Strauss, *J. Chem. Phys.*, 1965, **42,** 2915.
12. J. B. Lambert, R. G. Keske, and D. K. Weary, *J. Amer. Chem. Soc.*, 1967, **89,** 5921.
13. G. A. Jeffrey and M. Sundaralingham, *Adv. Carbohydrate Chem.*, 1976, **32,** 353, and references quoted therein.
14. R. K. Harris and R. A. Spragg, *J. Chem. Soc.* (*B*), 1968, 684.
15. F. A. L. Anet and J. Sandstrom, *Chem. Comm.*, 1971, 1558.
16. H. S. Gutowsky and P. A. Temussi, *J. Amer. Chem. Soc.*, 1967, **89,** 4358.
17. J. Dale, *Tetrahedron*, 1974, **30,** 1683.
18. J. D. Dunitz, M. Dobler, P. Seiler, and R. P. Phizackerley, *Acta Cryst.*, 1974, **B30,** 2733.
19. R. U. Lemieux and S. Koto, *Tetrahedron*, 1974, **30,** 1933.
20. G. E. Booth and R. J. Ouellette, *J. Org. Chem.*, 1966, **31,** 544.
21. C. B. Anderson and D. T. Sepp, *J. Org. Chem.*, 1967, **32,** 607.
22. C. Romers, C. Altona, H. R. Buys, and E. Havinga, *Topics Stereochem.*, 1969, **4,** 39.
23. O. Eisenstein, N. T. Anh, Y. Jean, A. Devaquet, J. Cantacuzène, and L. Salem, *Tetrahedron*, 1974, **30,** 1717.
24. E. M. Arnett, in 'Progress in Physical Organic Chemistry', ed. S. G. Cohen, A. Streitweiser, and R. W. Taft, Wiley, New York, 1963, vol. 1, p. 223.
25. S. Searles, Jr., and M. Tamres, in 'The Chemistry of the Ether Linkage', ed. S. Patai, Wiley, New York, 1967, chapter 6.
26. M. Okada, K. Suyama, and Y. Yamashita, *Tetrahedron Letters*, 1965, 2329.
27. F. J. Cioffi and S. T. Zenchelsky, *J. Phys. Chem.*, 1963, **67,** 357.
28. D. E. McLaughlin, M. Tamres, S. Searles, Jr., and S. Nukina, *J. Inorg. Nuclear Chem.*, 1961, **17,** 112.
29. J. Le Brumant, M. Selim, and G. Martin, *Compt. rend.* (*B*), 1973, **276,** 335.
30. E. Lippert and H. Prigge, *Annalen*, 1962, **659,** 81.
31. G. Levy and P. de Loth, *Compt. rend.* (*C*), 1974, **279,** 331.
32. M. Tamres, S. Searles, Jr., and J. M. Goodenow, *J. Amer. Chem. Soc.*, 1964, **86,** 3934.
33. 'Solute–Solvent Interactions', ed. J. F. Coetzee and C. D. Ritchie, Dekker, New York, 1969.
34. R. G. Pearson, *J. Chem. Educ.*, 1968, **45,** 581, 643.
35. J. L. Down, J. Lewis, B. Moore, and G. Wilkinson, *J. Chem. Soc.*, 1959, 3767.
36. G. E. Coates, M. L. H. Green, P. Powell, and K. Wade, 'Principles of Organometallic Chemistry', Methuen, London, 1971, p. 54.
37. L. L. Chan and J. Smid, *J. Amer. Chem. Soc.*, 1968, **90,** 4654.
38. H. Normant, *Compt. rend.*, 1954, **239,** 1510.
39. E. C. Ashby, *Quart. Rev.*, 1967, **21,** 259.
40. R. J. Gritter, in 'The Chemistry of the Ether Linkage', ed. S. Patai, Wiley, New York, 1967, chapter 9.
41. G. Berti, *Topics Stereochem.*, 1973, **7,** 93.
42. J. G. Buchanan and H. Z. Sable, in 'Selective Organic Transformations', ed. B. S. Thyagarajan, Wiley, New York, 1972, vol. 2, p. 1.
43. N. R. Williams, *Adv. Carbohydrate Chem. Biochem.*, 1970, **25,** 109.
44. 'The Chemistry of Heterocyclic Compounds', ed. A, Rosowsky, Wiley, New York, 1972, vol. 26, chapters 1–9.
45. A. Casadevall, E. Casadevall, and M. Lasperas, *Bull. Soc. chim. France*, 1968, 4506.
46. K. D. Bingham, T. M. Blaiklock, R. C. B. Coleman, and G. D. Meakins, *J. Chem. Soc.* (*C*), 1970, 2330.
47. R. Villotti, C. Djerassi, and H. J. Ringold, *J. Amer. Chem. Soc.*, 1959, **81,** 4566.
48. H. B. Henbest, *Proc. Chem. Soc.*, 1963, 159.
49. B. Rickborn and S.-Y. Lwo, *J. Org. Chem.*, 1965, **30,** 2212.
50. J. C. Richer and C. Freppel, *Canad. J. Chem.*, 1968, **46,** 3709.
51. K. Marks and H. Kuczyński, *Roczniki Chem.*, 1965, **39,** 1259.
52. P. M. McCurry, Jr., *Tetrahedron Letters*, 1971, 1841.
53. D. H. R. Barton, D. A. Lewis, and J. F. McGhie, *J. Chem. Soc.*, 1957, 2907.
54. E. E. van Tamelen, *Accounts Chem. Res.*, 1968, **1,** 111.
55. E. Vogel, H.-J. Altenbach, and C.-D. Sommerfeld, *Angew. Chem. Internat. Edn.*, 1972, **11,** 939.
56. H. Newman, *Chem. and Ind.* (*London*), 1963, 372.
57. J. M. Williams, *Adv. Carbohydrate Chem. Biochem.*, 1975, **31,** 9.
58. D. A. Seeley and J. McElwee, *J. Org. Chem.*, 1973, **38,** 1691.
59. H. Neumann, *Chimia* (*Switz.*), 1969, **23,** 267.
60. W. G. Overend and N. R. Williams, *J. Chem. Soc.*, 1965, 3446.
61. E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, 1965, **87,** 1353.
62. C. E. Cook, R. C. Corley, and M. E. Wall, *J. Org. Chem.*, 1968, **33,** 2789.
63. R. E. Parker and N. S. Isaacs, *Chem. Rev.*, 1959, **59,** 737.
64. D. N. Kirk and M. P. Hartshorn, 'Steroid Reaction Mechanisms,' Elsevier, Amsterdam, 1968.
65. J. K. Addy and R. E. Parker, *J. Chem. Soc.*, 1963, 915.
66. G. Berti, F. Bottari, P. L. Ferrarini, and B. Macchia, *J. Org. Chem.*, 1965, **30,** 4091.
67. D. H. R. Barton, *J. Chem. Soc.*, 1953, 1027.
68. S. J. Angyal and P. T. Gilham, *J. Chem. Soc.*, 1957, 3691.

69. R. Fuchs and C. A. VanderWerf, *J. Amer. Chem. Soc.*, 1952, **74,** 5917.
70. E. L. Eliel and M. N. Rerick, *J. Amer. Chem. Soc.*, 1960, **82,** 1362.
71. T. Cohen and T. Tsuji, *J. Org. Chem.*, 1961, **26,** 1681.
72. M. P. Hartshorn, D. N. Kirk, and A. F. A. Wallis, *J. Chem. Soc.*, 1964, 5494.
73. A. C. Cope, M. M. Martin, and M. A. McKervey, *Quart. Rev.*, 1966, **20,** 119.
74. A. C. Cope, J. M. Grisar, and P. E. Peterson, *J. Amer. Chem. Soc.*, 1959, **81,** 1640.
75. D. N. Kirk, *Chem. and Ind. (London)*, 1973, 109.
76. G. Guroff, J. W. Daly, D. M. Jerina, J. Renson, B. Witkop, and S. Udenfriend, *Science*, 1967, **157,** 1524.
77. D. M. Jerina, J. W. Daly, and B. Witkop, *J. Amer. Chem. Soc.*, 1968, **90,** 6523.
78. G. Forsberg, *Acta. Chem. Scand.*, 1954, **8,** 135.
79. A. Rosowsky and D. S. Tarbell, *J. Org. Chem.*, 1961, **26,** 2255.
80. C. A. Grob and W. Baumann, *Helv. Chim. Acta*, 1955, **38,** 594.
81. S. Searles, Jr., R. G. Nickerson, and W. K. Witsiepe, *J. Org. Chem.*, 1960, **24,** 1839.
82. M. Bartók and J. Apjok, *Acta Univ. Szeged., Acta Phys. Chem.*, 1962, **8,** 133 (*Chem. Abs.*, 1963, **59,** 6337).
83. C. R. Noller, *Org. Synth. Coll. Vol.* 3, 1955, p. 835.
84. R. B. Clayton, H. B. Henbest, and M. Smith, *J. Chem. Soc.*, 1957, 1982.
85. P. W. Austin, J. G. Buchanan, and E. M. Oakes, *Chem. Comm.*, 1965, 374.
86. D. R. Arnold, *Adv. Photochem.*, 1968, **6,** 301.
87. A. Schönberg, 'Preparative Organic Photochemistry,' Springer-Verlag, Berlin, 1968, chapter 41.
88. N. C. Yang, M. Nussim, M. J. Jorgenson, and S. Murov, *Tetrahedron Letters*, 1964, 3657.
89. G. Büchi, C. G. Inman, and E. S. Lipinsky, *J. Amer. Chem. Soc.*, 1954, **76,** 4327.
90. J. M. Coxon and B. Halton, 'Organic Photochemistry,' Cambridge University Press, London, 1974.
91. C. H. DePuy and O. L. Chapman, 'Molecular Reactions and Photochemistry,' Prentice-Hall, New Jersey, 1972.
92. I. H. Kochevar and P. J. Wagner, *J. Amer. Chem. Soc.*, 1970, **92,** 5742.
93. N. C. Yang and W. Eisenhardt, *J. Amer. Chem. Soc.*, 1971, **93,** 1277.
94. O. L. Chapman and G. Lenz, in 'Organic Photochemistry,' ed. O. L. Chapman, Dekker, New York, 1967, p. 283.
95. J. G. Pritchard and F. A. Long, *J. Amer. Chem. Soc.*, 1958, **80,** 4162.
96. S. Searles, *J. Amer. Chem. Soc.*, 1951, **73,** 4515.
97. S. Searles, *J. Amer. Chem. Soc.*, 1951, **73,** 124.
98. 'Methoden der Organischen Chemie,' ed. E. Müller, Thieme, Stuttgart, 1965, vol. 6/3.
99. 'Methoden der Organischen Chemie,' ed. E. Müller, Thieme, Stuttgart, 1966, vol. 6/4.
100. V. J. Traynelis, W. L. Hergenrother, H. T. Hanson, and J. A. Valicenti, *J. Org. Chem.*, 1964, **29,** 123.
101. B. T. Gillis and P. E. Beck, *J. Org. Chem.*, 1963, **28,** 1388.
102. S. Soltzberg, *Adv. Carbohydrate Chem. Biochem.*, 1970, **25,** 229.
103. A. H. Haines and A. G. Wells, *Carbohydrate Res.*, 1973, **27,** 261.
104. J. D. Wander and D. Horton, *Adv. Carbohydrate Chem. Biochem.*, 1976, **32,** 15.
105. A. Kirrmann and N. Hamaide, *Bull. Soc. chim. France*, 1957, 789.
106. K. Heusler and J. Kalvoda, *Angew. Chem. Internat. Edn.*, 1964, **3,** 525.
107. M. Akhtar, *Adv. Photochem.*, 1964, **2,** 263.
108. D. H. R. Barton and J. M. Beaton, *J. Amer. Chem. Soc.*, 1961, **83,** 4083.
109. E. L. Jenner, *J. Org. Chem.*, 1962, **27,** 1031.
110. M. Akhtar, P. Hunt, and P. B. Dewhurst, *J. Amer. Chem. Soc.*, 1965, **87,** 1807.
111. M. Lj. Mihailović and R. E. Partch, in 'Selective Organic Transformations,' ed. B. S. Thyagarajan, Wiley, New York, 1972, vol. 2, p. 97.
112. V. M. Mićović, R. I. Mamuzić, D. Jeremić, and M. Lj. Mihailović, *Tetrahedron Letters*, 1963, 2091.
113. K. Kitahonoki and A. Matsuura, *Tetrahedron Letters*, 1964, 2263.
114. E. J. Corey and R. W. White, *J. Amer. Chem. Soc.*, 1958, **80,** 6686.
115. W. J. Linn, O. W. Webster, and R. E. Benson, *J. Amer. Chem. Soc.*, 1963, **85,** 2032.
116. J. Kollonitsch, *J. Amer. Chem. Soc.*, 1961, **83,** 1515.
117. G. F. Freeguard and L. H. Long, *Chem. and Ind. (London)*, 1964, 1582.
118. H. Gross, *Chem. Ber.*, 1962, **95,** 83.
119. E. Müller and H. Huber, *Chem. Ber.*, 1963, **96,** 2319.
120. G. Sosnovsky, *Angew. Chem. Internat. Edn.*, 1964, **3,** 269.
121. G. Sosnovsky, *Tetrahedron*, 1965, **21,** 871.
122. T. J. Wallace and R. J. Gritter, *J. Org. Chem.*, 1962, **27,** 3067.
123. E. S. Huyser, *J. Org. Chem.*, 1960, **25,** 1820.
124. R. L. Jacobs and G. G. Ecke, *J. Org. Chem.*, 1963, **28,** 3036.
125. P. Ballinger, P. B. D. de la Mare, G. Kohnstam, and B. M. Prestt, *J. Chem. Soc.*, 1955, 3641.
126. R. J. Ferrier and P. M. Collins, 'Monosaccharide Chemistry,' Penguin, Middlesex, England, 1972.
127. J. J. Fox and I. Wempen, *Adv. Carbohydrate Chem.*, 1959, **14,** 283.
128. B. Capon, *Chem. Rev.*, 1969, **69,** 407.
129. C. B. Reese, in 'Protective Groups in Organic Synthesis,' ed. J. F. W. McOmie, Plenum, London, 1973, chapter 3.
130. R. U. Lemieux and T. L. Nagabhushan, *Canad. J. Chem.*, 1968, **46,** 401.

131. C. B. Kremer and L. K. Rochen, in 'Heterocyclic Compounds,' ed. R. C. Elderfield, Wiley, New York, 1957, vol. 6, chapter 1.
132. E. Augdahl and O. Hassel, *Acta Chem. Scand.*, 1955, **9,** 172.
133. R. K. Summerbell, G. Lestina, and H. Waite, *J. Amer. Chem. Soc.*, 1957, **79,** 234.
134. R. K. Summerbell and J. R. Stephens, *J. Amer. Chem. Soc.*, 1954, **76,** 6401.
135. R. K. Summerbell and G. J. Lestina, *J. Amer. Chem. Soc.*, 1957. **79,** 3878.
136. O. Hassel, *Proc. Chem. Soc.*, 1957, 250.
137. E. Damm, O. Hassel, and C. Rømming, *Acta Chem. Scand.*, 1965, **19,** 1159.
138. A. B. Van Cleave and R. I. Blake, *Canad. J. Chem.*, 1951, **29,** 785.
139. R. K. Summerbell and H. E. Lunk, *J. Amer. Chem. Soc.*, 1957, **79,** 4802.
140. H. C. Dehm, *J. Org. Chem.*, 1958, **23,** 147.
141. 'Structure and Bonding', Springer-Verlag, Berlin, 1973, vol. 16: 'Alkali Metal Complexes with Organic Ligands'.
142. C. J. Pedersen and H. K. Frensdorff, *Angew. Chem. Internat. Edn.*, 1972, **11,** 16.
143. R. N. Greene, *Tetrahedron Letters*, 1972, 1793.
144. J. Dale and P. O. Kristiansen, *Acta Chem. Scand.*, 1972, **26,** 1471.
145. E. P. Kyba, M. G. Siegel, L. R. Sousa, G. D. Y. Sogah, and D. J. Cram, *J. Amer. Chem. Soc.*, 1973, **95,** 2691.
146. R. C. Helgeson, J. M. Timko, P. Moreau, S. C. Peacock, J. M. Mayer, and D. J. Cram, *J. Amer. Chem. Soc.*, 1974, **96,** 6762.
147. W. D. Curtis, D. A. Laidler, J. F. Stoddart, and G. H. Jones, *J.C.S. Chem. Comm.*, 1975, 833.
148. F. de Jong, M. G. Siegel, and D. J. Cram, *J.C.S. Chem. Comm.*, 1975, 551.
149. E. P. Kyba, K. Koga, L. R. Sousa, M. G. Siegel, and D. J. Cram, *J. Amer. Chem. Soc.*, 1973, **95,** 2692.
150. J. M. Girodeau, J. M. Lehn, and J.-P. Sauvage, *Angew. Chem. Internat. Edn.*, 1975, **14,** 764.
151. B. Dietrich, J. M. Lehn, J.-P. Sauvage, and J. Blanzat, *Tetrahedron*, 1973, **29,** 1629.
152. A. C. Coxon and J. F. Stoddart, *J.C.S. Chem. Comm.*, 1974, 537; *J.C.S. Perkin I*, 1977, 767.
153. J. J. Christensen, D. J. Eatough, and R. M. Izatt, *Chem. Rev.*, 1974, **74,** 351.
154. D. J. Sam and H. E. Simmons, *J. Amer. Chem. Soc.*, 1972, **94,** 4024.
155. H. K. Frensdorff, *J. Amer. Chem. Soc.*, 1971, **93,** 600.
156. K. H. Wong, G. Konizer, and J. Smid, *J. Amer. Chem. Soc.*, 1970, **92,** 666.
157. C. J. Pedersen, *J. Amer. Chem. Soc.*, 1967, **89,** 2495.
158. M. A. Bush and M. R. Truter, *J. Chem. Soc.* (*B*), 1971, 1440.
159. M. A. Bush and M. R. Truter, *J.C.S. Perkin II*, 1972, 341.
160. P. R. Mallinson and M. R. Truter, *J.C.S. Perkin II*, 1972, 1818.
161. N. K. Dalley, D. E. Smith, R. M. Izatt, and J. J. Christensen, *J.C.S. Chem. Comm.*, 1972, 90.
162. (a) D. E. Fenton, M. Mercer, and M. R. Truter, *Biochem. Biophys. Res. Comm.*, 1972, **48,** 10; (b) I. J. Burden, A. C. Coxon, J. F. Stoddart, and C. M. Wheatley, *J.C.S. Perkin I*, 1977, 220; (c) R. C. Hayward, C. H. Overton, and G. H. Whitham, *J.C.S. Perkin I*, 1976, 2413.
163. M. Mercer and M. R. Truter, *J.C.S. Dalton*, 1973, 2469.
164. D. L. Hughes, *J.C.S. Dalton*, 1975, 2374.
165. M. A. Bush and M. R. Truter, *J.C.S. Perkin II*, 1972, 345.
166. D. Moras, B. Metz, and R. Weiss, *Acta Cryst.*, 1973, **B29,** 383.
167. D. Moras, B. Metz, and R. Weiss, *Acta Cryst.*, 1973, **B29,** 388.
168. F. J. Tehan, B. L. Barnett, and J. L. Dye, *J. Amer. Chem. Soc.*, 1974, **96,** 7203.
169. C. L. Liotta and H. P. Harris, *J. Amer. Chem. Soc.*, 1974, **96,** 2250.
170. D. Landini, F. Montanari, and F. M. Pirisi, *J.C.S. Chem. Comm.*, 1974, 879.
171. M. Cinquini, F. Montanari, and P. Tundo, *J.C.S. Chem. Comm.*, 1975, 393.
172. J. N. Roitman and D. J. Cram, *J. Amer. Chem. Soc.*, 1971, **93,** 2231.
173. R. A. Bartsch, *Accounts Chem. Res.*, 1975, **8,** 239.
174. M. J. Maskornick, *Tetrahedron Letters*, 1972, 1797.
175. D. J. Cram and J. M. Cram, *Science*, 1974, **183,** 803.
176. G. W. Gokel and D. J. Cram, *J.C.S. Chem. Comm.*, 1973, 481.
177. L. R. Sousa, D. H. Hofman, L. Kaplan, and D. J. Cram, *J. Amer. Chem. Soc.*, 1974, **96,** 7100.
178. S. C. Peacock and D. J. Cram, *J.C.S. Chem. Comm.*, 1976, 282.
179. G. Dotsevi, Y. Sogah, and D. J. Cram, *J. Amer. Chem. Soc.*, 1975, **97,** 1259.
180. J. M. Timko, R. C. Helgeson, M. Newcomb, G. W. Gokel, and D. J. Cram, *J. Amer. Chem. Soc.*, 1974, **96,** 7097.
181. R. C. Helgeson, J. M. Timko, and D. J. Cram, *J. Amer. Chem. Soc.*, 1973, **95,** 3023.
182. R. C. Helgeson, K. Koga, J. M. Timko, and D. J. Cram, *J. Amer. Chem. Soc.*, 1973, **95,** 3021.
183. Y. Chao and D. J. Cram, *J. Amer. Chem. Soc.*, 1976, **98,** 1015.
184. W. D. Curtis, D. A. Laidler, J. F. Stoddart, and G. H. Jones, *J.C.S. Chem. Comm.*, 1975, 835.
185. W. D. Curtis, R. M. King, J. F. Stoddart, and G. H. Jones, *J.C.S. Chem. Comm.*, 1976, 284.
186. J. P. Behr, J. M. Lehn, and P. Vierling, *J.C.S. Chem. Comm.*, 1976, 621.
187. J. Berger, A. I. Rachlin, W. E. Scott, L. H. Sternbach, and M. W. Goldberg, *J. Amer. Chem. Soc.*, 1951, **73,** 5295.
188. M. Dobler, J. D. Dunitz, and B. T. Kilbourn, *Helv. Chim. Acta*, 1969, **52,** 2573.

4.5

Alkyl Aryl and Diaryl Ethers

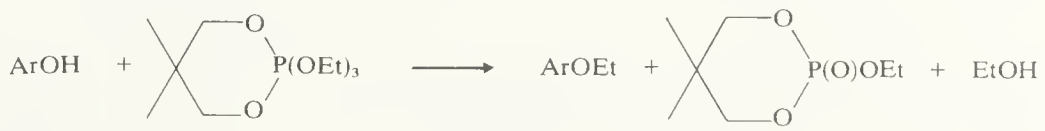
D. A. WHITING
University of Nottingham

4.5.1 SYNTHETIC METHODS 897
4.5.1.1 Alkyl aryl ethers 897
4.5.1.2 Diaryl ethers 898
4.5.1.3 Polymeric ethers 899
4.5.2 REACTIONS OF ARYL ALKYL AND DIARYL ETHERS 899
4.5.2.1 Ether cleavage 899
4.5.2.2 Reduction 901
4.5.2.3 Ring metallation 902
4.5.2.4 Coupling reactions 902
4.5.2.5 Rearrangements 904

4.5.1 SYNTHETIC METHODS

4.5.1.1 Alkyl aryl ethers

The usual method of preparing alkyl aryl ethers uses the phenol–base–alkyl (allyl, benzyl, propargyl) halide methods as discussed in Section 4.2.3.1, *e.g.* the phenol with potassium carbonate and potassium iodide in dry acetone or benzene and the appropriate halide. Hindered phenols can be *O*-alkylated by irreversible generation of the sodium salt using sodium hydride in DMF and alkylation of the salt with a reactive halide.



SCHEME 1

A method which does not require base catalysis has been used for ethyl ethers and, in principle, could be extended to others; this employs pentaethoxyphosphorane or its relatives[1] (Scheme 1). Phase-transfer catalysis can be employed with effect for the alkylation of phenols.[2] In this procedure a two-phase system, *e.g.* water–methylene chloride, is used: the phenol, a quaternary ammonium hydroxide in catalytic quantity, and the alkyl halide are added, and the phase equilibrium is maintained by efficient mixing. The situation is summarized in Figure 1. The phenol and quaternary hydroxide equilibrate with the quaternary ammonium phenoxide which is extracted into the organic phase where alkylation takes place. The quaternary ammonium halide re-equilibrates with its

hydroxide in the aqueous phase. The synthetic advantages are (i) the phenolate anion is less solvated in the organic phase, the alkylation rate is enhanced, the rate is less depressed by steric effects, and exclusive *O*-alkylation results; (ii) only the aqueous phase is basic, protecting the alkylating agent (halide, sulphate, *etc.*) from destruction through hydrolysis; and (iii) non-stoichiometric quantities of ammonium salt are used.

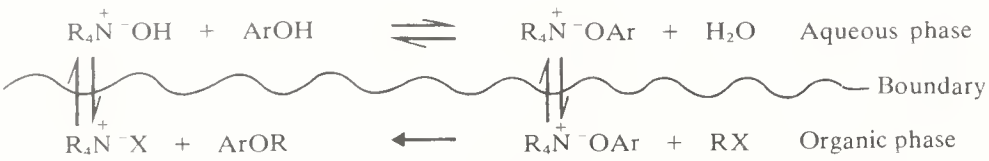
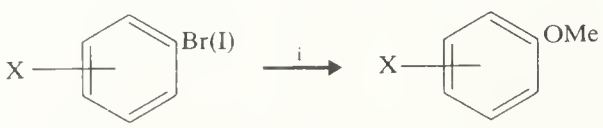


Figure 1

Reversal of the above reaction, *i.e.* using aryl halide and a metal alkoxide, is only of value if the aryl ring is substituted so as to stabilize the necessary anionic intermediate. Reactions involving arynes, *e.g.* the preparation of t-butyl phenyl ether from bromobenzene and potassium t-butoxide,[3] are rarely of synthetic value. The rate of replacement of halogen in *o*- and *p*-halogenonitrobenzenes is F > Cl > Br > I.[4] Suitably activated nitro groups may also be replaced and 3,5-dinitroanisole is formed (70%) from 1,3,5-trinitrobenzene and sodium methoxide.[5] For further comments, see Section 4.2.3. Alkoxide ions can effect displacement in diaryliodonium salts; radical traps, *e.g.* $Ph_2C{=}CH_2$, help to keep down competing radical processes, when aryl ethers can be obtained in fair yield:

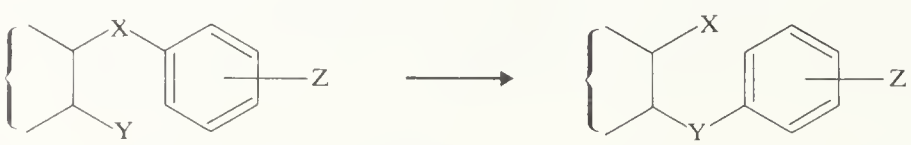
$$Ar_2\overset{+}{I}\,\overset{-}{B}F_4 + RONa \rightarrow ArOR + NaBF_4 + ArI$$

Replacement of halide ion in unactivated nuclei can be catalysed by cuprous iodide[6] (Scheme 2). However, reduction can intervene for sterically crowded halides. The Smiles rearrangement[7] is shown for a general case in Scheme 3. The best-documented examples have X = O, S, SO, or SO_2, and when Y = OH the reaction constitutes an ether synthesis.



i, NaOMe, CuI, collidine; X = R, RO, RO_2C

SCHEME 2



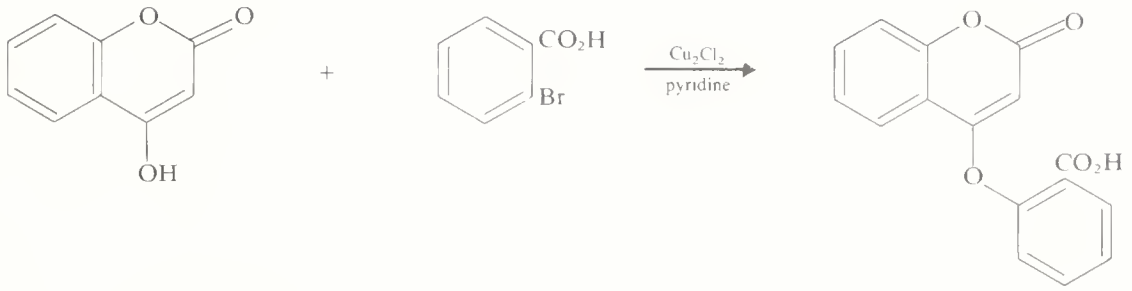
X = O, SO_2, SO, S; Y = OH, SH, NH_2, *etc.*

SCHEME 3

Moderately good yields of ethers can also be obtained by reaction of an aryl Grignard reagent and a perbenzoate ester (or dialkyl peroxide).[8] It is a useful method for aryl t-butyl ethers.

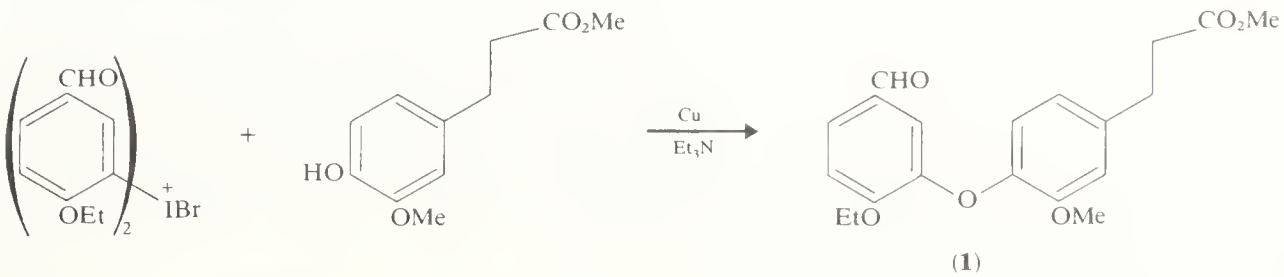
4.5.1.2 Diaryl ethers

Diaryl ethers can be prepared by heating an aryl bromide with alkali metal phenolate in the presence of copper powder. Free phenol and aryl bromide react in refluxing collidine over cuprous oxide[9] or other copper salts; a similar technique can be applied to yield aryl enol ethers (Scheme 4). Diaryliodonium salts[10] can also be subject to displacement by



SCHEME 4

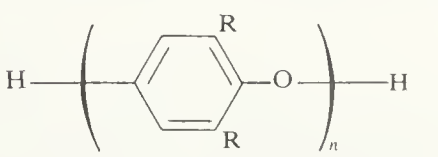
phenolates to afford ethers; this reaction in modified form provides a synthesis (see Scheme 5) of the diaryl ether (**1**), a key synthon in *Lunaria* alkaloid synthesis. Thermal decomposition of diaryl carbonates also gives diaryl ethers.[11]



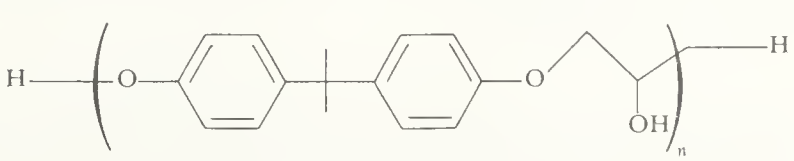
SCHEME 5

4.5.1.3 Polymeric ethers

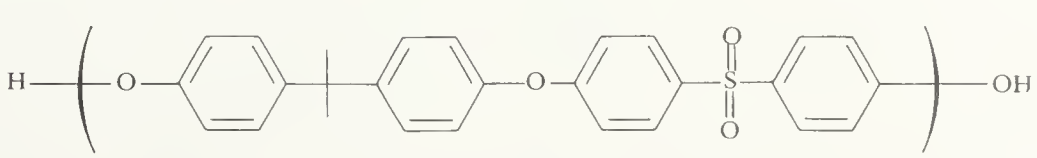
Polyaryl ethers of type (**2**) are prepared by air oxidation of hindered phenols using copper salt and amine catalysts, or by oxidation of bromophenols with ferricyanide.[12] Poly-(2,6-dimethyl-1,4-phenylene) ether (PPO) is used in the manufacture of insulating materials. Polyhydroxy ethers, or phenoxy resins, *e.g.* (**3**), are formed from dihydric phenols and epichlorohydrin (3-chloro-1,2-epoxypropane) in alkaline DMSO. The related polysulphones (**4**) are similarly prepared but using a dichlorodiphenyl sulphone instead of epichlorohydrin. Both polymers (**3**) and (**4**) are employed to manufacture useful plastics for food containers and electronic equipment.



(**2**)



(**3**)



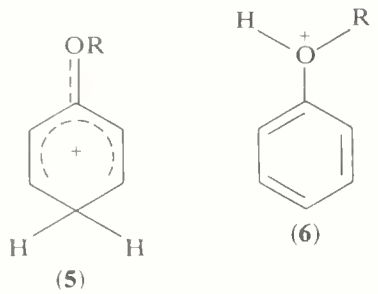
(**4**)

4.5.2 REACTIONS OF ARYL ALKYL AND DIARYL ETHERS

4.5.2.1 Ether cleavage

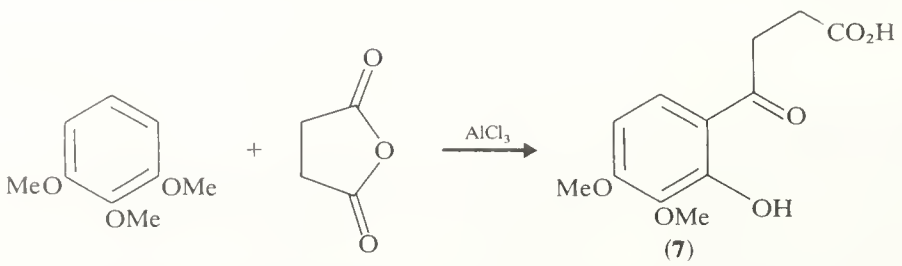
(i) Acid catalysed

Ethers are weak Lewis bases and are protonated in strongly acidic media. Protonation in aryl ethers may be at C and/or O giving ions (**5**) or (**6**); the n.m.r. spectra of these ions



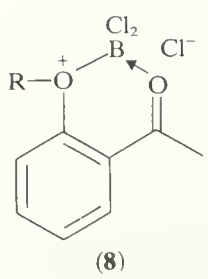
(5) (6)

have been measured.[13] Nucleophilic attack on the alkyl residue in (**6**) leads to ether cleavage; 'HSAB' theory suggests that an efficient reagent would be composed of a hard acid plus a soft base, and, in agreement, hydrogen iodide and hydrogen bromide have long been used for this purpose. The reaction with hydrogen iodide is the basis of the Zeisel determination of methyl aryl ethers. The hydrohalides of pyridine or aniline are also used to dealkylate phenol ethers under forcing conditions. Lewis acids, especially aluminium chloride, boron trichloride, and boron tribromide,[14] yield complexes with ethers which decompose to the free phenols. Aluminium chloride de-alkylates only at higher temperatures; a degree of selectivity is shown in that methoxy groups *ortho* to carbonyl groups are preferentially removed. Thus 1,2,3-trimethoxybenzene and succinic anhydride react by Friedel–Crafts acylation followed by selective demethylation to give the keto-acid (**7**)



(1)

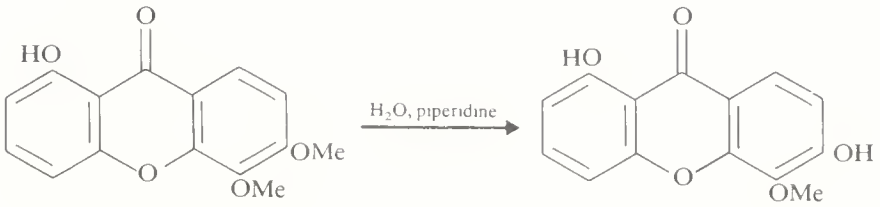
(equation 1). Boron trichloride is employed at temperatures near ambient to give selective demethylations, again preferring to react adjacent to the carbonyl group through an initial complex (**8**).[15a] Similarly, methylenedioxy groups[15b] have been cleaved without removing methoxy functions. Boron tribromide rapidly cleaves ethers even at −80 °C. 2,5-Dimethoxybenzaldehyde can be 5-demethylated by boron tribromide or 2-demethylated by boron trichloride.[15c]



(8)

(ii) Base catalysed

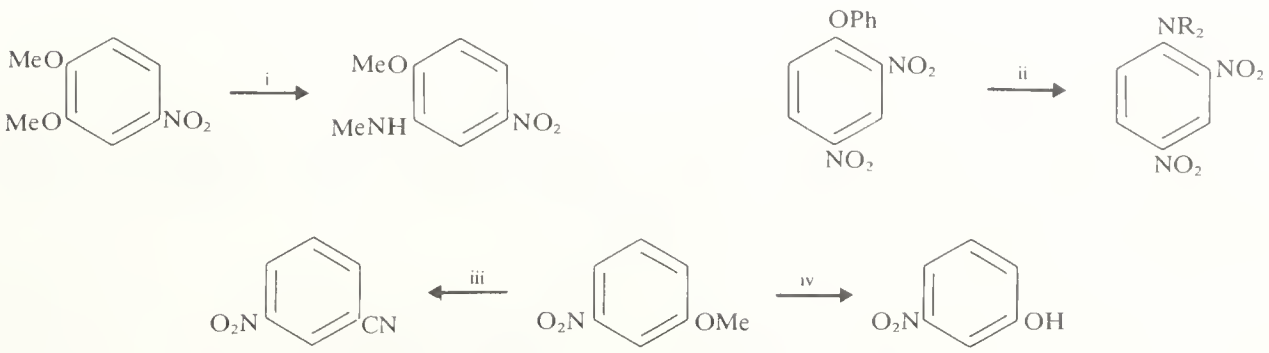
The usual comments apply to cleavage of the Ar—O bond by nucleophiles. Cleavage of the O—R bond can be achieved by good nucleophiles. Sodamide, lithium diphenylphosphide, and sodium or lithium thiolates[16a] have been employed. *p*-Methoxyaryl ketones may be viewed as vinylogous esters and such ethers are usually the most readily cleaved; hot aqueous piperidine suffices to demethylate the xanthone (**9**) at position-3 (equation 2).[16b] Methyl phenyl ethers have also been split using lithium iodide under essentially neutral conditions.[16c] Magnesium iodide etherate is also an effective reagent for demethylation. Some interesting examples of selective ether scission with lithium thiophenolate have been brought forward.[16d]



(9) (2)

(iii) Light catalysed

Various nitrophenyl alkyl ethers undergo photosubstitution reactions[17] in which the alkoxy group is displaced; a range of examples is shown in Scheme 6.



i, $MeNH_2$, $h\nu$; ii, R_2NH, $h\nu$; iii, ^-CN, $h\nu$; iv, ^-OH, $h\nu$.

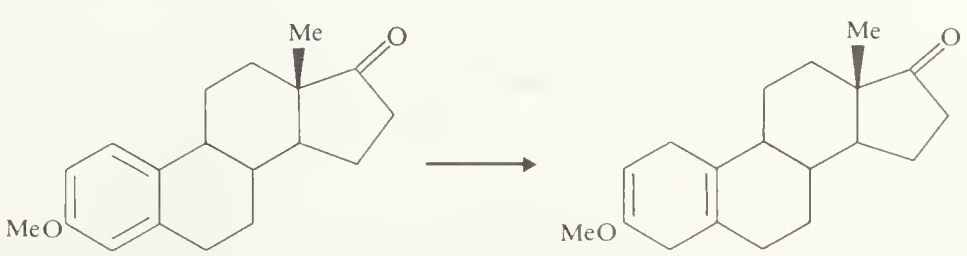
SCHEME 6

(iv) Oxidative and reductive

The dimethyl ethers of hydroquinones and catechols are oxidized to *p*- and *o*-quinones, respectively, in good yield by silver oxide in acidic dioxan; hydroxy and aldehyde functions need not interfere.[18] The general oxidation of aryl alkyl ethers has been reviewed.[18b] Reductive ether fission of ethers can be achieved with lithium and biphenyl (dilithiobiphenyl is the reagent).[19] The ready cleavage of allyl phenyl ethers by lithium is used to make allyl-lithium.

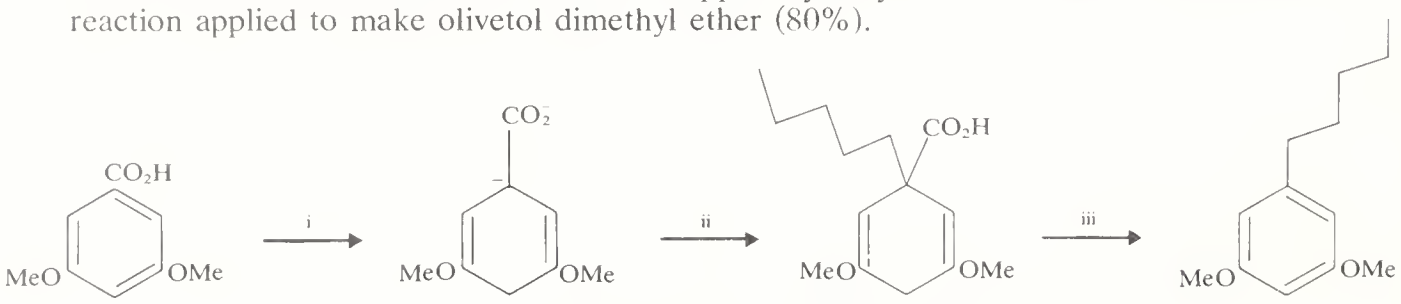
4.5.2.2 Reduction

The Birch reduction of aryl ethers by lithium or sodium metal in liquid ammonia relies on successive electron transfers from the metal to the aromatic substrate with protonation from an added alcohol (ammonia being insufficiently acidic) of the intermediate radical-anions/anions to form 1,4-diene enol ethers, which hydrolyse in aqueous acid to cyclohexanones.[20] This reaction has been widely used in synthesis, *e.g.* for steroid hormones. An interesting electrochemical equivalent reaction has been reported[21] — an example of its operation appears in Scheme 7.



SCHEME 7

The synthetic facility of Birch reduction has recently been extended by the introduction of reductive alkylation[22] in which an aromatic acid is reduced by lithium in liquid ammonia and the intermediate anion is trapped by alkyl halide. Scheme 8 shows this reaction applied to make olivetol dimethyl ether (80%).

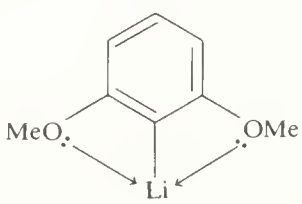


i, Li, NH_3; ii, n-$C_5H_{11}Br$; iii, $Pb(OAc)_4$, $Cu(OAc)_2$.

SCHEME 8

4.5.2.3 Ring metallation

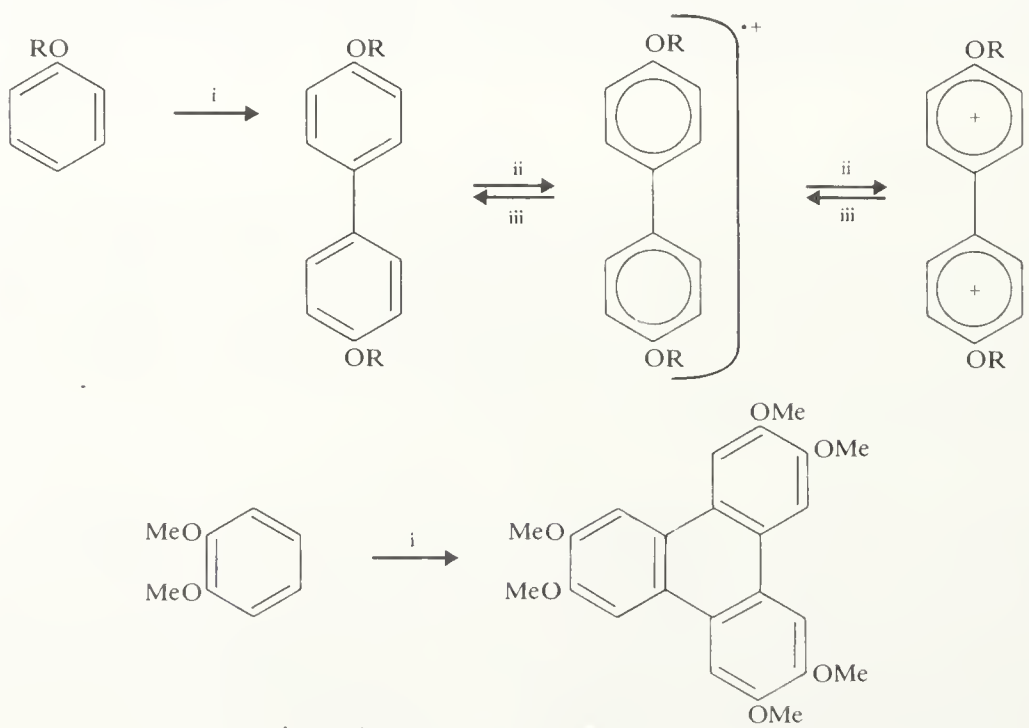
Aryl-lithium compounds can be formed selectively from aryl ethers when the metal occupies a coordinated position. Thus the compound (**10**) can be employed as a nucleophile to make 2-substituted resorcinol ethers.



(**10**)

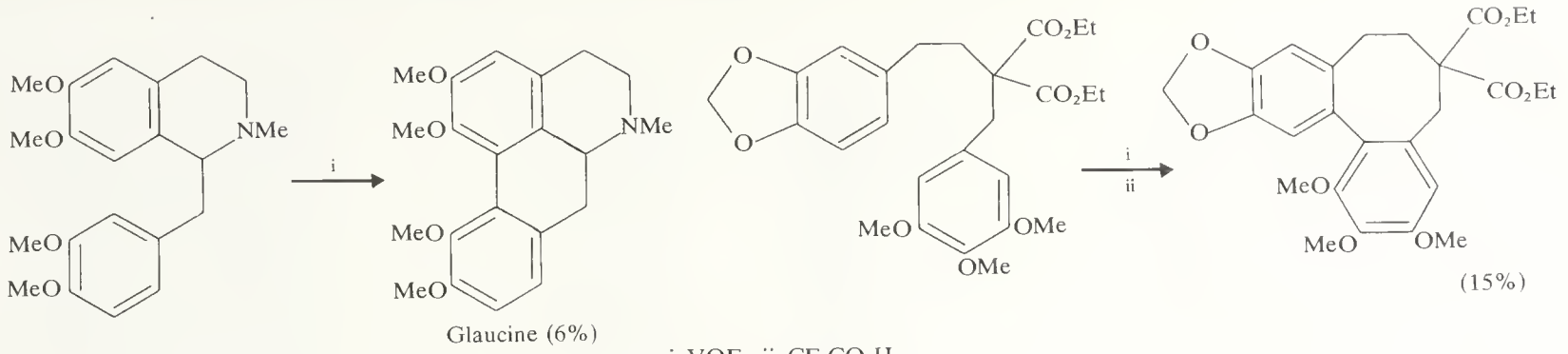
4.5.2.4 Coupling reactions

The aromatic nuclei of aryl ethers may be coupled by several methods,[23] both oxidative and non-oxidative. Thus, at the anode, aryl alkyl ethers couple to give biaryls. Strong acid media stabilize radical cation–dication products and prevent over-oxidation; reductive work-up may be required to obtain the biaryls. Scheme 9 shows examples of these



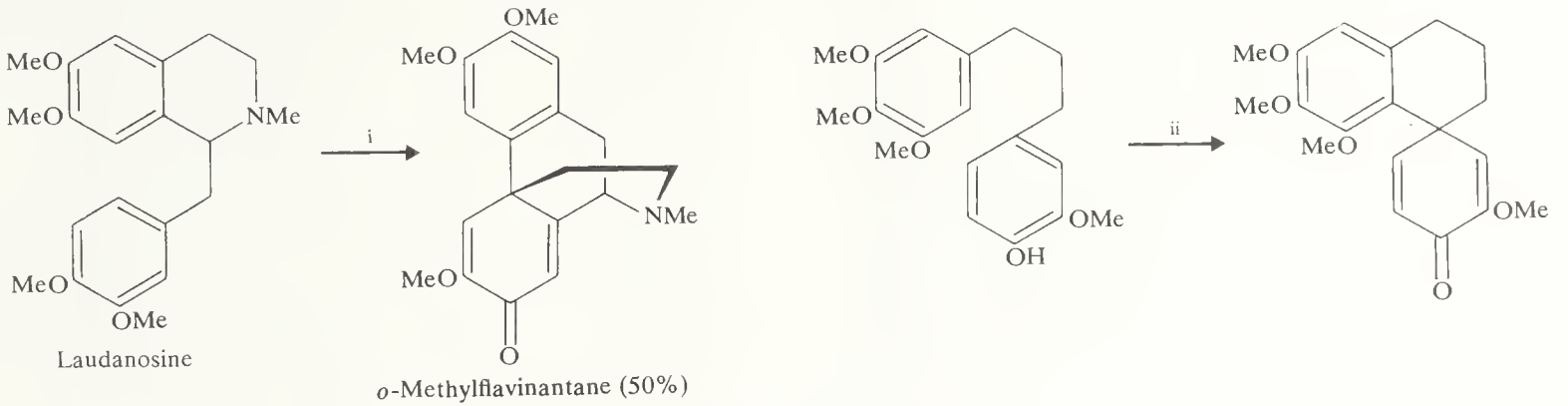
i, Anode, CF_3CO_2H; ii, $-e^-$; iii, $+e^-$.

SCHEME 9



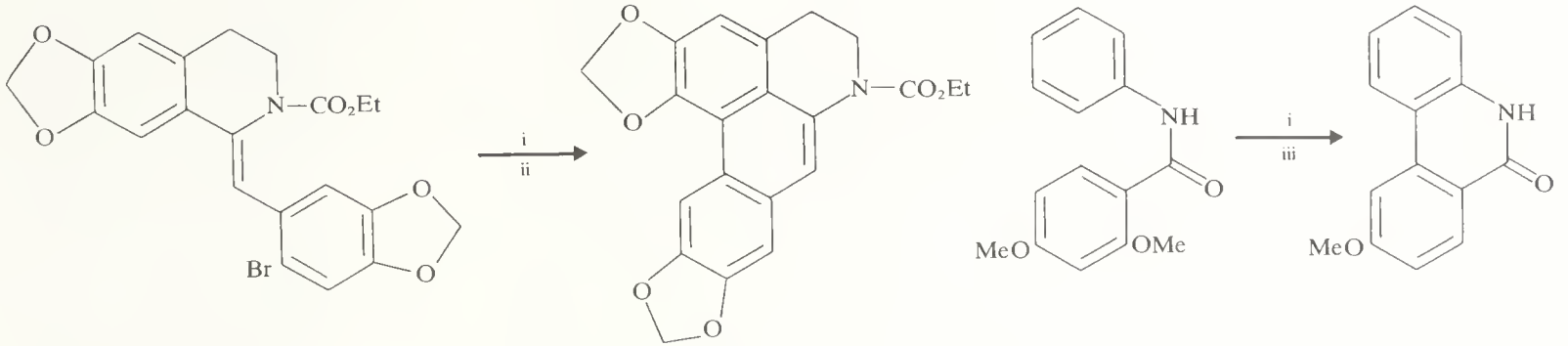
i, VOF_3; ii, CF_3CO_2H.

SCHEME 10



i, Anode, MeCN; ii, anode, MeCN, HBF_4.

SCHEME 11



i, $h\nu$; ii, $KOBu^t$; iii, –MeOH.

SCHEME 12

reactions;[23a–c] some intramolecular couplings to give biaryls are summarized in Scheme 10,[23d,e] and similar reactions leading to spiro-dienones in Scheme 11.[23f–h] Non-oxidative photo-couplings are illustrated in Scheme 12.[23i,j]

4.5.2.5 Rearrangements

Alkyl aryl ethers rearrange to alkyl phenols (Scheme 13) with various catalysts. Such reactions can be induced photochemically,[24] *e.g.* benzyl phenyl ether gives mainly *p*-benzylphenol and diphenyl ether provides *p*-hydroxybiphenyl; *o*- and/or *p*-alkyl phenols are also obtained by Lewis acid catalysis.[25] Both inter- and intra-molecular migrations have been thought to operate, the reaction being solvent and catalyst dependent. Bimolecular alkylation has been demonstrated for s-butyl phenyl ether with aluminium chloride, giving rise to *o*- and *p*-s-butylphenols with inversion of configuration; inverse addition of the reagent changes the mechanism to involve an ion-pair intermediate.

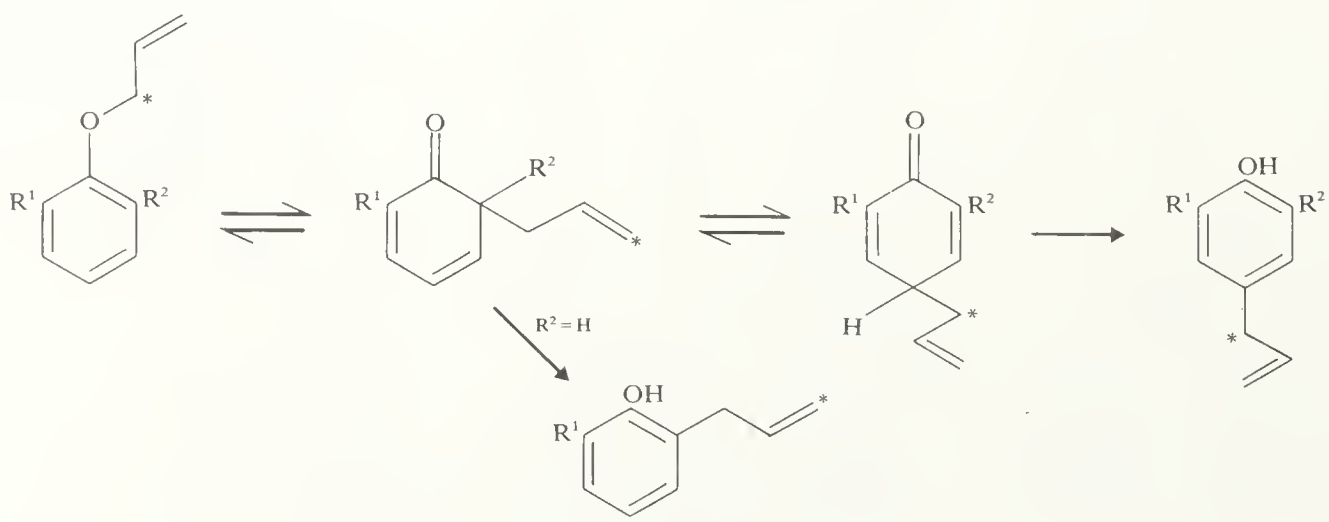
SCHEME 13

(i) Wittig rearrangement

Aryl benzhydryl ethers and others with relatively acidic hydrogens adjacent to the ether oxygen yield the isomeric carbinols on treatment with strong bases; a summary of the mechanistic investigations is available.[26]

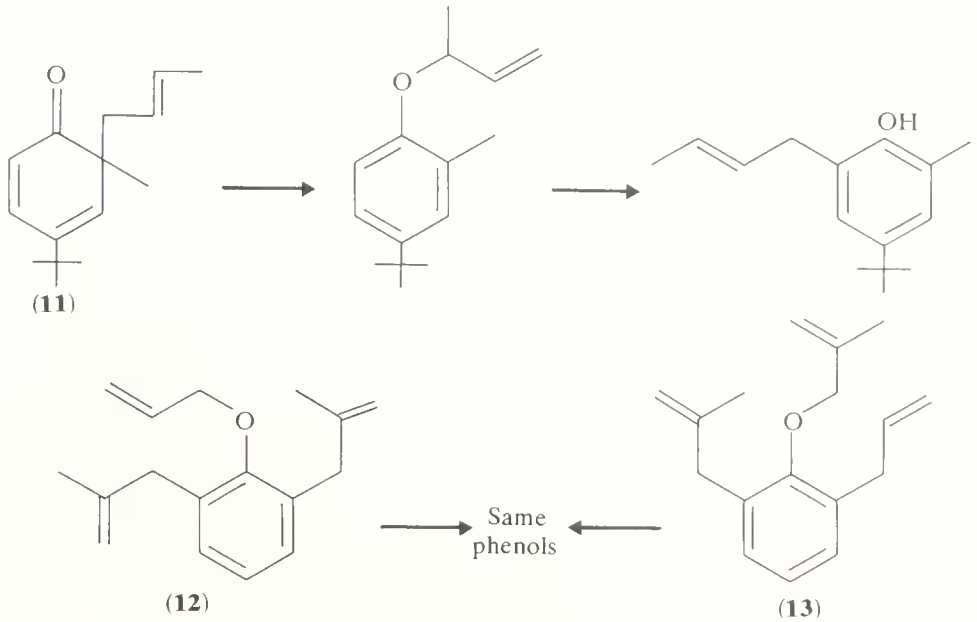
(ii) Claisen rearrangement

This rearrangement has received a great deal of attention, both as a useful synthetic tool and mechanistically as a reaction involving concerted [3,3]-sigmatropic shifts. Several general reviews are published,[27] and one deals in detail with reaction geometry;[27d] theoretical aspects are discussed in most of the many books and articles on pericyclic processes.



SCHEME 14

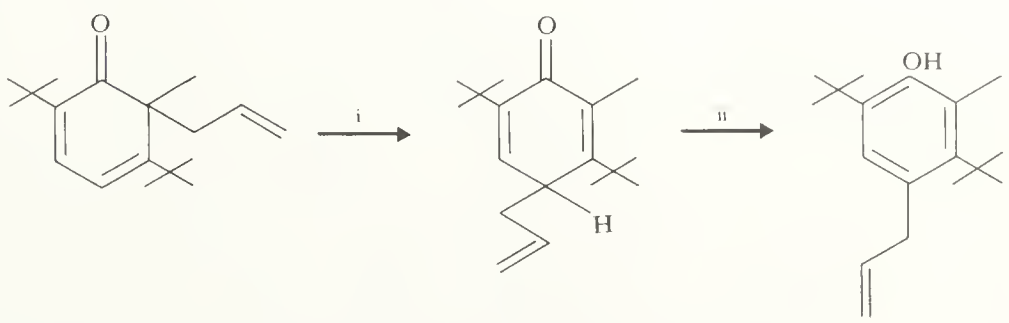
The basic reaction, discovered in 1912,[28] is shown in Scheme 14. The rearrangement is intramolecular, proceeding *via* cyclic transition states; no crossover products between different ethers are observed. The allyl groups invert in each individual [3,3]-migration. The intermediacy of dienones has been established by trapping with maleic anhydride.



(3)

(4)

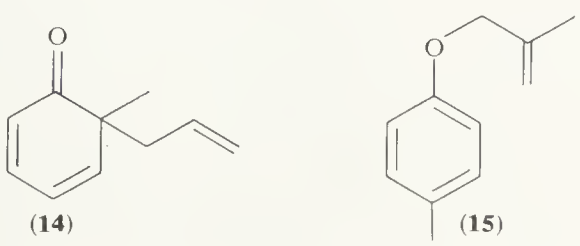
The first step is reversible: the synthetic dienone (**11**) undergoes the rarely directly observed rearrangement back to allyl ether and on to the free *ortho* position (equation 3).[29] Also, ethers (**12**) and (**13**) give the same products on heating (equation 4). *ortho*-Blocking groups are not essential for migration to the *para* position.[30] A *para*-substituted dienone has been isolated in the circumstance when the enolization following migration is relatively slow (Scheme 15).



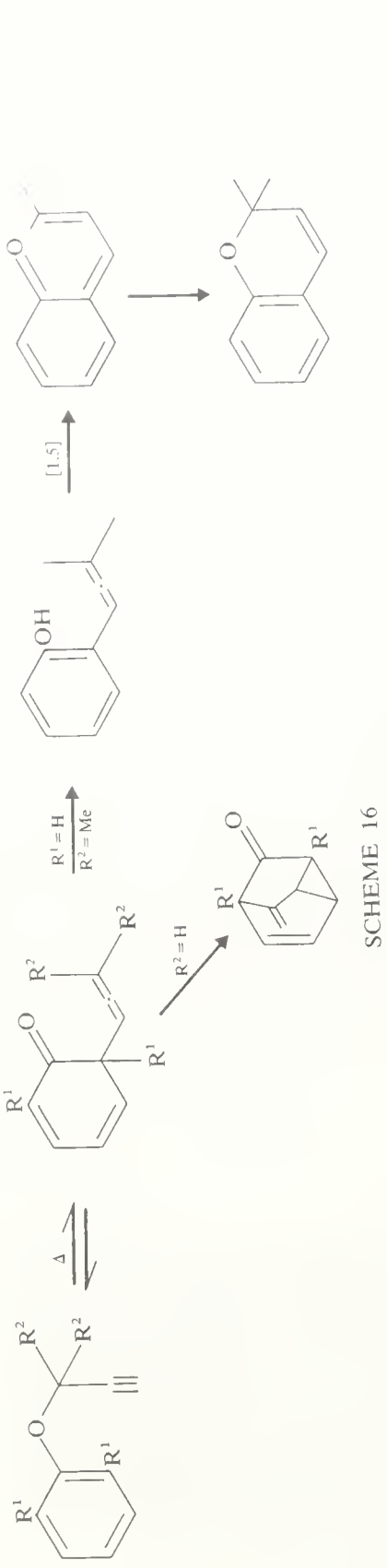
i, 110 °C, 5 min; ii, H^+ or ^-OH.

SCHEME 15

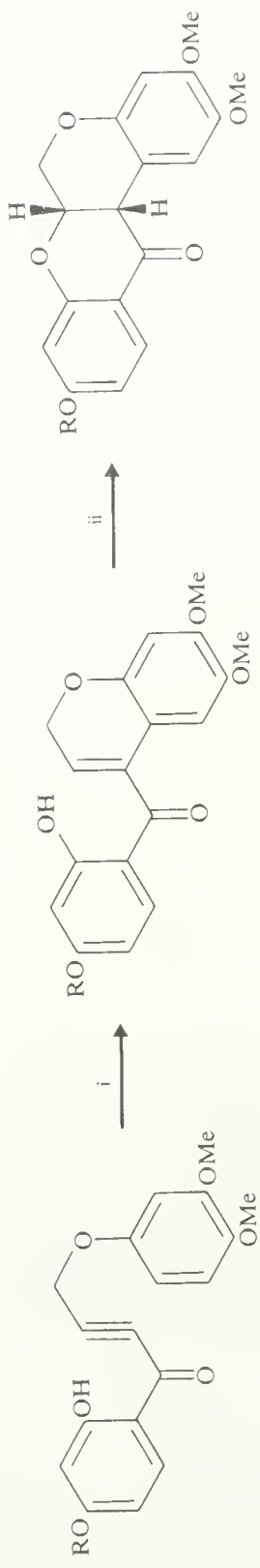
The Claisen rearrangement is catalysed by acids,[31] *e.g.* *o*-allylphenol is obtained from phenyl allyl ether at room temperature in trifluoroacetic acid, and by titanium(IV) salts in methylene chloride at −78 °C. Sigmatropic shifts of the dienone (**14**) with various catalysts have been examined. In trifluoroacetic acid, [3,3]-shifts occur *via* a charged-stabilized cyclic transition state, but with trifluoroacetic anhydride or acetic anhydride–sulphuric acid, [3,3]-, [1,2]-, and [3,4]-shifts all involve cationic intermediates. The methylallyl ether of *p*-cresol (**15**) undergoes light-induced rearrangement to the *ortho*, *meta*, and *para* products. The reaction involves dissociation into radical pairs; singlet pairs re-combine to give *ortho* and *para* products while triplet pairs give *meta*-substituted phenols.[32]



(14) (15)

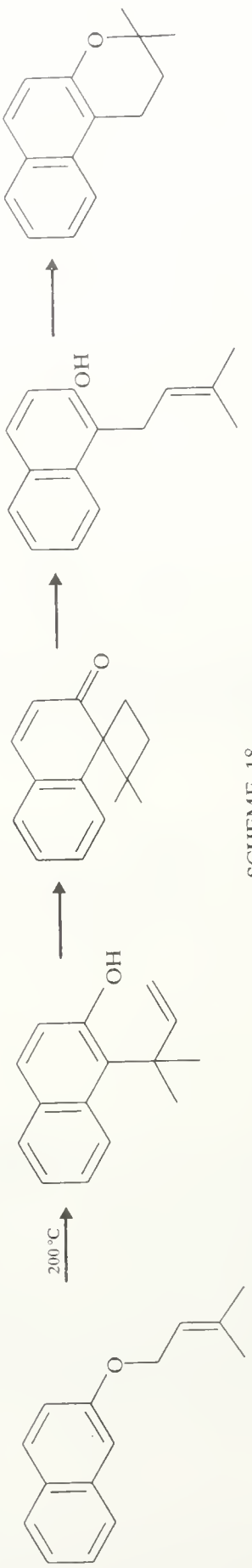


SCHEME 16



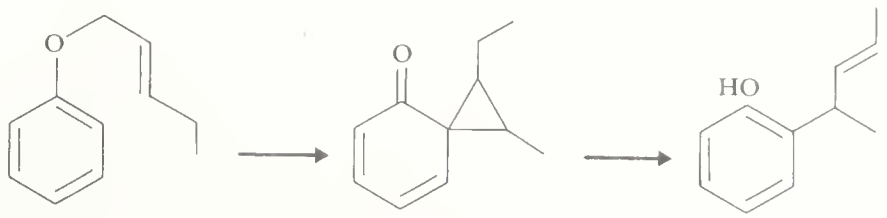
i, Δ; ii, NaOAc, EtOH.

SCHEME 17

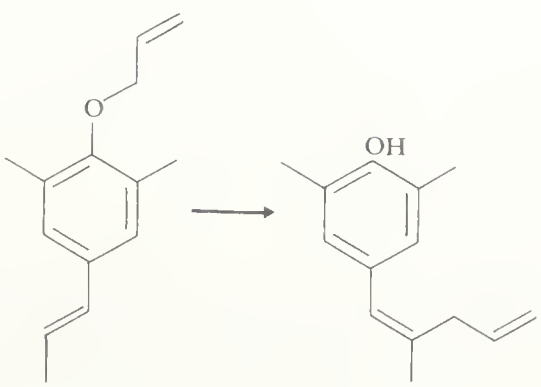


SCHEME 18

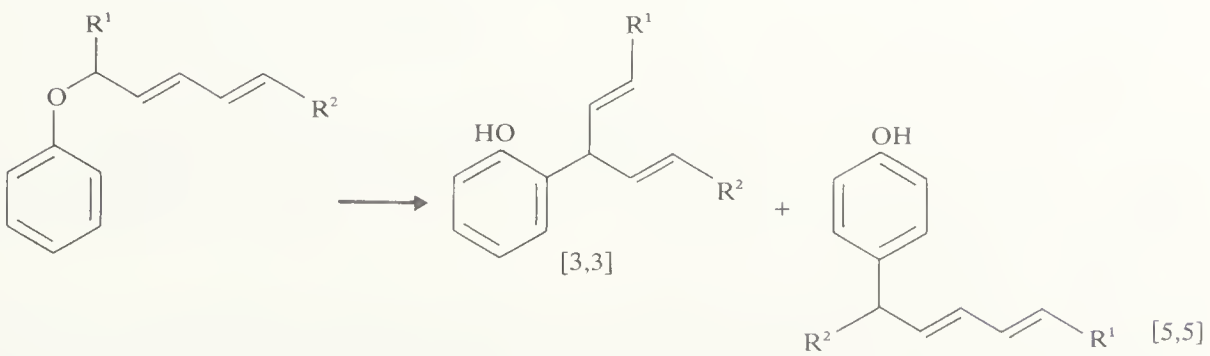
Propargyl ethers also participate in the Claisen rearrangement, leading ultimately to chrom-3-enes (Scheme 16);[33] allenic intermediates are implicated, and can be trapped. Such reactions have been shown to be silver ion catalysed[34] and have been put to good synthetic use, *e.g.* in rotenoid synthesis[35] (Scheme 17). The Claisen reaction can take an abnormal course[36] in certain substrates and a number of such reactions are illustrated in Schemes 18–21.



SCHEME 19



SCHEME 20



SCHEME 21

References

1. D. B. Denney and S. T. D. Gough, *J. Amer. Chem. Soc.*, 1965, **87,** 138.
1. (a) A. McKillop, J. C. Fiaud, and R. P. Hug, *Tetrahedron*, 1974, **30,** 1379; (b) E. V. Dehmlow, *Angew. Chem. Internat. Edn.*, 1974, **13,** 170; (c) J. Dockx, *Synthesis*, 1973, 441.
3. D. J. Cram, B. Rickborn, and G. R. Knox, *J. Amer. Chem. Soc.*, 1960, **82,** 6412.
4. B. A. Bolto, J. Miller, and V. A. Williams, *J. Chem. Soc.*, 1955, 2926.
5. F. Reverdin, *Org. Synth. Coll. Vol. 1*, 1941, 219.
6. R. G. R. Bacon and S. C. Rennison, *J. Chem. Soc.* (*C*), 1969, 308, 312, 1978.
7. T. S. Stevens and W. E. Watts, 'Selected Molecular Rearrangements', Van Nostrand Reinhold, London, 1973.
8. (a) S.-O. Lawesson and N. C. Yang, *J. Amer. Chem. Soc.*, 1959, **81,** 4230; (b) C. Frisell and S.-O. Lawesson, *Org. Synth.*, 1967, **41,** 91.
9. (a) R. G. R. Bacon and H. A. O. Hill, *J. Chem. Soc.*, 1964, 1108; (b) M. Darbarwar, V. Sundaramurthy, and N. V. Subba Rao, *Indian J. Chem.*, 1973, **11,** 850.

10. F. M. Beringer, A. Brierley, M. Drexler, E. M. Gindler, and C. C. Lumpkin, *J. Amer. Chem. Soc.*, 1953, **75,** 2708.
11. H. Witt, H. Holtschmidt, and E. Müller, *Angew, Chem. Internat. Edn.*, 1970, **9,** 67.
12. (a) A. S. Hay, *J. Polymer Sci.*, 1962, **58,** 581; (b) W. A. Batte, N. S. Chu, and C. C. Price in 'Macromolecular Syntheses', Wiley, New York, 1963, p. 76.
13. (a) D. M. Brouwer, E. L. Mackor, and C. McLean, *Rec. Trav. chim.*, 1966, **85,** 109, 114; (b) T. Birchall, A. N. Bourns, R. J. Gillespie, and P. J. Smith, *Canad. J. Chem.*, 1964, **42,** 1433.
14. J. F. W. McOmie and M. L. Watts, *Chem. and Ind. (London)*, 1963, 1658.
15. (a) F. M. Dean, J. Goodchild, L. E. Houghton, J. A. Martin, R. B. Morton, B. Parton, A. W. Price, and N. Somvichien, *Tetrahedron Letters*, 1966, 4153; (b) S. Teitel, J. O'Brien, and A. Brossi, *J. Org. Chem.*, 1972, **37,** 3368; (c) H. Ulrich, D. V. Rao, B. Tucker, and A. A. R. Sayigh, *ibid.*, 1974, **39,** 2437.
16. (a) G. I. Feutrill and R. N. Mirrington, *Tetrahedron Letters*, 1970, 1327; (b) B. Jackson, H. D. Locksley, I. Moore, and F. Scheinmann, *J. Chem. Soc. (C).*, 1968, 2579; (c) I. J. Harrison, *Chem. Comm.*, 1969, 616; (d) C. Hansson and B. Wickberg, *Synthesis*, 1976, 191.
17. (a) M. E. Kronenberg, A. van der Heyden, and E. Havinga, *Rec. Trav. chim.*, 1966, **85,** 56; (b) R. O. De Jongh and E. Havinga, *ibid.*, 1966, **85,** 275; (c) D. F. Nijhoff and E. Havinga, *Tetrahedron Letters*, 1965, 4199; (d) R. L. Letsinger and J. H. McCain, *J. Amer. Chem. Soc.*, 1966, **88,** 2884; 1969, **91,** 6425.
18. (a) C. D. Snyder and H. Rapoport, *J. Amer. Chem. Soc.*, 1972, **94,** 227; (b) O. C. Musgrave, *Chem. Rev.*, 1969, **69,** 499.
19. D. H. Eagle, *J. Org. Chem.*, 1963, **28,** 1703; J. Eisch and A. M. Jacobs, *ibid.*, 1963, **28,** 2145.
20. (a) A. J. Birch, *Quart. Rev.*, 1950, **4,** 69; (b) H. Smith, 'Chemistry in Non-aqueous Ionising Solvents', Interscience, New York, 1963, vol. I.
21. (a) R. A. Benkeser and E. M. Kaiser, *J. Amer. Chem. Soc.*, 1963, **85,** 2858; (b) R. A. Benkeser, E. M. Kaiser, and R. F. Lambert, *ibid.*, 1964, **86,** 5272; (c) A. F. Fentiman Jr. and R. H. Poirier, *Chem. and Ind. (London)*, 1966, 813.
22. A. J. Birch and J. Slobbe, *Tetrahedron Letters*, 1976, 2079.
23. (a) A. Ronlan and V. D. Parker, *J. Org. Chem.*, 1974, **39,** 1014; (b) A. Ronlan, K. Bechgaard, and V. D. Parker, *Acta Chem. Scand. (B)*, 1973, **27,** 2375; (c) K. Bechgaard and V. D. Parker, *J. Amer. Chem. Soc.*, 1972, **94,** 4749; (d) S. M. Kupchan, A. J. Liepa, V. Kameswaran, and R. F. Bryan, *ibid.*, 1973, **95,** 6861; (e) A. S. Kende and L. S. Liebeskind, *ibid.*, 1976, **98,** 267; (f) M. Sainsbury and R. F. Schmazi, *J.C.S. Chem. Comm.*, 1972, 718; (g) E. Kotani, F. Miyazaki, and S. Tobinaga, *ibid.*, 1974, 300; (h) L. L. Miller, F. R. Stermitz, and J. R. Falck, *J. Amer. Chem. Soc.*, 1973, **95,** 2651; (i) M. P. Cava, P. Stern, and K. Wakisaka, *Tetrahedron*, 1973, **29,** 2245; (j) Y. Kanaoka and K. Itoh, *J.C.S. Chem. Comm.*, 1973, 647.
24. (a) D. P. Kelly, J. T. Pinhey, and R. D. G. Rigbey, *Austral. J. Chem.*, 1969, **22,** 977; *Tetrahedron Letters*, 1966, 5953; (b) G. Sosnovsky and D. J. Rawlinson, in Houben-Weyl, 'Photochemie', 1975, vol. I, p. 687.
25. (a) M. J. S. Dewar and N. A. Puttmann, *J. Chem. Soc.*, 1960, 959; (b) P. A. Spanninger and J. L. von Rosenberg, *Chem. Comm.*, 1970, 795; *J. Amer. Chem. Soc.*, 1972, **94,** 1970, 1973; (c) M. J. S. Dewar and P. A. Spanninger, *J.C.S. Perkin II*, 1972, 1204.
26. (a) G. Wittig, H. Döser, and I. Lorenz, *Annalen*, 1949, **562,** 192; (b) D. L. Dalyrymple, T. L. Kruger, and W. N. White, in 'Chemistry of the Ether Linkage', ed. S. Patai, Interscience, New York, 1967.
27. (a) D. S. Tarbell, *Org. Reactions*, 1944, **2,** 1; (b) S. J. Rhoads, in 'Molecular Rearrangements', ed. P. de Mayo, Interscience, New York, 1963; (c) H. J. Shine, in 'MTP International Review of Science, Organic Chemistry, Series One', Butterworths, London, 1971, vol. 3, p. 65; (d) H.-J. Hansen and H. Schmid, *Chem. in Britain*, 1969, **5,** 111.
28. L. Claisen, *Ber.*, 1912, **45,** 3157.
29. B. Miller, *J. Amer. Chem. Soc.*, 1969, **91,** 2170.
30. J. Borgulya, H.-J. Hansen, P. Barner, and H. Schmid, *Helv. Chim. Acta*, 1963, **46,** 2444.
31. (a) U. Svanholm and V. D. Parker, *J.C.S. Chem. Comm.*, 1972, 645; (b) T. Mukaiyama, K. Narasaka, and E. Bald, *Chem. Letters*, 1975, 1041; (c) U. Widmer, J. Zsindely, H.-J. Hansen, and H. Schmid, *Helv. Chim. Acta*, 1973, **56,** 75.
32. W. Adam, H. Fischer, M.-J. Hansen, H. Heimgartner, H. Schmid, and H.-R. Waespe, *Angew. Chem. Internat. Edn.*, 1973, **12,** 662.
33. (a) J. Hlubucek, E. Ritchie, and W. C. Taylor, *Austral. J. Chem.*, 1971, **24,** 2347; (b) W. K. Anderson and E. J. La Voie, *J. Org. Chem.*, 1973, **38,** 3832; (c) J. Zsindely and H. Schmid, *Helv. Chim. Acta*, 1968, **51,** 1510.
34. U. Koch-Pomeranz, H.-J. Hansen, and H. Schmid, *Helv. Chim. Acta*, 1973, **56,** 2981.
35. H. Omokawa and K. Yamashita, *Agric. Biol. Chem. (Japan)*, 1973, **37,** 1717.
36. (a) D. R. Buckle and E. S. Waight, *Chem. Comm.*, 1969, 922; (b) E. N. Marvell, D. R. Anderson, and J. Ong, *J. Org. Chem.*, 1962, **27,** 1109; W. M. Lauer and T. A. Johnson, *ibid.*, 1963, **28,** 2913; (c) A. Nickon and B. R. Aaronoff, *ibid.*, 1964, **29,** 3014; (d) Gy. Fráter and H. Schmid, *Helv. Chim. Acta*, 1970, **53,** 269.

4.6

Peroxides

D. SWERN
Temple University, Philadelphia

4.6.1 ALKYL HYDROPEROXIDES, R—O—O—H 910
4.6.1.1 Autoxidation methods 910
4.6.1.2 Hydrogen peroxide reactions 913
4.6.1.3 Physical properties of hydroperoxides 916
4.6.1.4 Determination of hydroperoxides 917
4.6.1.5 Reactions of hydroperoxides 920
4.6.1.6 Economic aspects 924
4.6.2 DIALKYL PEROXIDES, R^1—O—O—R^2 924
4.6.2.1 Hydrogen peroxide and hydroperoxide reactions under acidic conditions 924
4.6.2.2 Hydrogen peroxide and hydroperoxide reactions under basic conditions 925
4.6.2.3 Hydroperoxides and metal ions under neutral conditions 926
4.6.2.4 Autoxidation methods 927
4.6.2.5 Miscellaneous 929
4.6.2.6 Physical properties of dialkyl peroxides 929
4.6.2.7 Determination of dialkyl peroxides 930
4.6.2.8 Reactions of dialkyl peroxides 931
4.6.2.9 Economic aspects 935
4.6.3 PEROXIDE POLYMERS AND COPOLYMERS 935
4.6.3.1 Autoxidation of polymerizable alkenes and dienes 936
4.6.3.2 Ketone peroxides 936
4.6.3.3 Physical and chemical properties 937
4.6.4 SAFETY AND HEALTH HAZARDS 937

Organic peroxides contain the peroxide functional group, —O—O—. Compounds with three or four connected oxygen atoms (trioxides and tetroxides, respectively) have recently been reported but they are unstable and have been identified only spectroscopically at low temperatures or from their degradation products; they will not be discussed in this chapter.

Two important classes of peroxides will be discussed: hydroperoxides (R^1—O—O—H) and dialkyl peroxides (R^1—O—O—R^2), where R^1 and R^2 are primary, secondary, or tertiary alkyl, cycloalkyl, and aralkyl groups. The peroxide function may be part of a ring or polymeric system, more than one peroxide group may be present in the compounds, and R^1 and R^2 may be the same or different, as in constitutionally symmetrical or unsymmetrical dialkyl peroxides, respectively.

4.6.1 ALKYL HYDROPEROXIDES, R—O—O—H

4.6.1.1 Autoxidation methods

The most general and widely used method for preparing hydroperoxides on a laboratory or commercial scale is the reaction of molecular (triplet) oxygen with alkanes bearing secondary and tertiary hydrogen atoms, aralkanes, alkenes, ethers, alcohols, and carbonyl compounds. Except in special cases the major disadvantage is the complexity of the reaction with the formation of unwanted by-products. The mechanism of autoxidation below 200 °C is best rationalized as a three-stage, free-radical chain reaction (equations 1–7).[1] Because $k_a \gg k_p$, termination at usual oxygen pressures is mainly by bimolecular interaction of alkylperoxy radicals.

Initiation: Free radical source $\xrightarrow{h\nu \text{ or } \Delta}$ $X^{\bullet} + XO_2^{\bullet}$ (1)

$RH + X^{\bullet}(\text{or } XO_2^{\bullet}) \xrightarrow{R_i} R^{\bullet} + XH \text{ (or } XO_2H)$ (2)

Propagation: $R^{\bullet} + O_2 \xrightarrow{k_a} RO_2^{\bullet}$ (3)

$RO_2^{\bullet} + RH \xrightarrow{k_p} RO_2H + R^{\bullet}$ (4)

Termination: $2\ RO_2^{\bullet} \xrightarrow{k_t} O_2 + RO_2R \text{ (or alcohols or carbonyl compounds)}$ (5)

$2\ R^{\bullet} \longrightarrow RR$ (6)

$RO_2^{\bullet} + R^{\bullet} \longrightarrow RO_2R$ (7)

(R_i is rate of initiation; k_a, k_p and k_t are specific rate constants for addition, propagation, and termination, respectively)

$$\frac{-d[O_2]}{dt} = -\frac{d[RH]}{dt} = \frac{d[RO_2H]}{dt} = k_p[RH](R_i/2k_t)^{1/2} \quad (8)$$

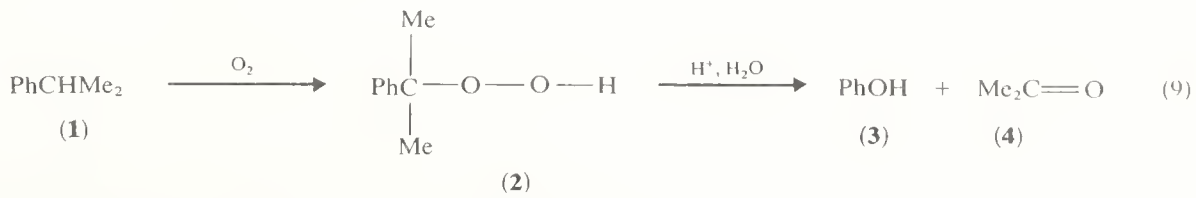
The rate expression for hydroperoxide formation and oxygen consumption, neglecting the formation of oxygen in the termination step, is given in equation (8).

The relative rates of autoxidation parallel the ease of rupture of the C—H bond and are related to the stability of the resulting radicals. For hydrocarbons, autoxidation rates increase in the order n-alkanes < branched alkanes < aralkanes ≈ alkenes < alkynes. The point of autoxidative attack is generally that producing the most stable radical. Initiating systems consist of free-radical sources (*e.g.* organic peroxides and bis-azonitriles), ultraviolet radiation, certain transition metals, or heat in the presence of oxygen.

(i) *Autoxidation of alkanes and aralkanes*

(*a*) *Thermal initiation.* Most alkanes and aralkanes can be autoxidized at 100–150 °C without added initiators, and many aralkanes give substantial yields of hydroperoxides at low temperatures. Such reactions typically show induction periods followed by increasingly rapid oxygen uptake and then finally they level off. The autocatalysis unquestionably derives from free-radical formation from decomposition of the hydroperoxides being produced; levelling off results when hydroperoxide formation and decomposition reach a steady state.

Since it is frequently easier to separate hydroperoxides from unreacted starting material than from decomposition products, autoxidations are usually carried to low conversions, although yields are frequently very high. A typical example is the autoxidation of cumene (**1**) to cumene hydroperoxide (**2**) which is carried out on a huge commercial scale, as (**2**) is readily decomposed with catalytic quantities of strong mineral acids to phenol (**3**) and acetone (**4**) in high yields (equation 9). The oxidation of (**1**) can be conducted in a homogeneous medium (neat or in a non-oxidizable solvent) or in aqueous emulsion. The hydroperoxide (**2**) is usually concentrated by extraction with concentrated aqueous base.



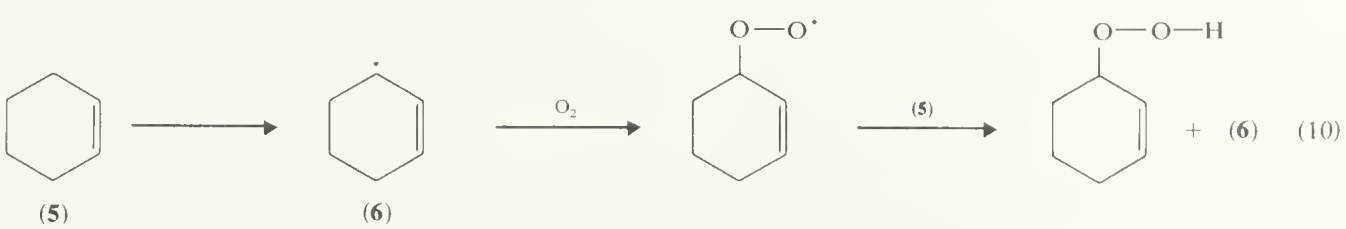
(9)

Autoxidation methods are most satisfactory for the preparation of tertiary hydroperoxides, but they can also be used to prepare secondary hydroperoxides and, in special cases, even primary hydroperoxides. Autoxidation methods are not generally recommended for the preparation of primary and secondary hydroperoxides. Aralkyl hydroperoxides are particularly easy to prepare by autoxidation because of the ease of formation of intermediate benzylic radicals.

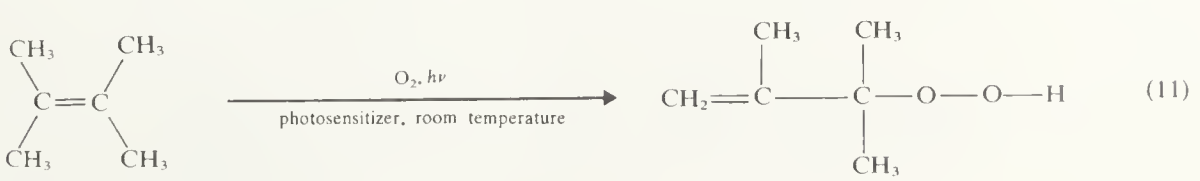
(*b*) *Initiation by metal ions.* Soluble salts of certain transition metal ions, chiefly iron, copper, manganese, and cobalt ions, are frequently used to accelerate autoxidations of alkanes and aralkanes. Although the metal ions produce more by-products than peroxide- or thermally-initiated reactions, many hydroperoxides have been prepared in 15–40% and even higher yields.[1] Cumene (**1**) and substituted cumenes, for example, at 100 °C give nearly quantitative yields of hydroperoxides up to 5% conversion with approximately 10^{-4} *M* Co^{2+} ion.[2] Most reactive aralkanes behave similarly.

(*ii*) *Autoxidation of alkenes*

Alkenes have two points of autoxidative attack, depending on whether or not photosensitizers are used. In their absence, an allylic C—H bond is attacked in a free-radical chain process (equation 10). The intermediate allylic radical may yield rearranged products usually involving the formation of the most stable peroxy radicals: mixtures of hydroperoxides are frequently obtained. With photosensitizers such as Rose Bengal or chlorophyll present an olefinic carbon is attacked, accompanied by rearrangement; singlet oxygen is the attacking species (equation 11).



(10)



(11)

Unlike free-radical autoxidations, the reaction in equation (11) is non-chain, and quantum yields may be as high as 1.0, although frequently they are lower. Hydroperoxide yields of 70–100% are reported for the oxidation shown, and that of but-2-ene, Δ^9-octalin, cyclohexylidenecyclohexane, trimethylethylene, and steroids. With simple alkenes and cycloalkanes, ease of oxidation and yields increase with increasing alkyl substitution of the double bonds; terminal olefins react slowly or not at all. Relative rates have been determined to be 1:450:3900:55000 for non-1-ene, methylcyclohexene, methylcyclopentene, and tetramethylethylene, respectively; different photosensitizers have little effect on this ratio. Similar results have been obtained in the absence of photosensitizers by using other singlet oxygen-generating methods.

(*iii*) *Autoxidation of ethers, alcohols, and carbonyl compounds*

Ethers (**7**) are readily autoxidized at room temperatures to α-hydroperoxy ethers (**8**) (equation 12).[1] The products are usually explosive and, on standing or on treatment with acids, they yield equally explosive dimeric and polymeric peroxides. Monomeric peroxides have been obtained not only from diethyl ether (**7**) but also from di-isopropyl, di-n-butyl, and di-isopentyl ethers, and tetrahydrofuran and dioxan, amongst others. Benzylic and allylic ethers also undergo autoxidation, but the intermediate hydroperoxides are too unstable to be isolated.

$$\underset{(7)}{CH_3CH_2OEt} \xrightarrow{O_2} \underset{(8)}{CH_3CH(OOH)OEt} \qquad (12)$$

Secondary alcohols similarly yield α-hydroperoxy alcohols (equation 13).[1] The hydroperoxide (**10**) from isopropanol (**9**) is easily hydrolysed to hydrogen peroxide and acetone. Autoxidation–hydrolysis of (**9**) is a commercial route to hydrogen peroxide; the acetone formed is reduced to (**9**), which is then reoxidized. The overall recycling sequence formally involves the conversion of oxygen and hydrogen to hydrogen peroxide.

$$\underset{(9)}{Me_2CHOH} \xrightarrow[Ph_2CO]{O_2,\, h\nu} \underset{(10)}{Me_2C(OH)OOH} \qquad (13)$$

Ketones are also autoxidized at the α-position but the hydroperoxides are quite unstable and only a few have been obtained in pure form and usually in poor yields.[1] Solutions of α-hydroperoxy ketones are normally obtained; reduction to α-hydroxy ketones establishes the structure of the precursor hydroperoxides. In a few instances, tertiary hydroperoxy ketones have been isolated, *e.g.* from di-isopropyl ketone (**11**) (equation 14), certain α,β-unsaturated ketones (**12**) (equation 15), and arylalkyl ketones (**13**) (equation 16). α-Hydroperoxy ketones exist as internally hydrogen-bonded species.[3]

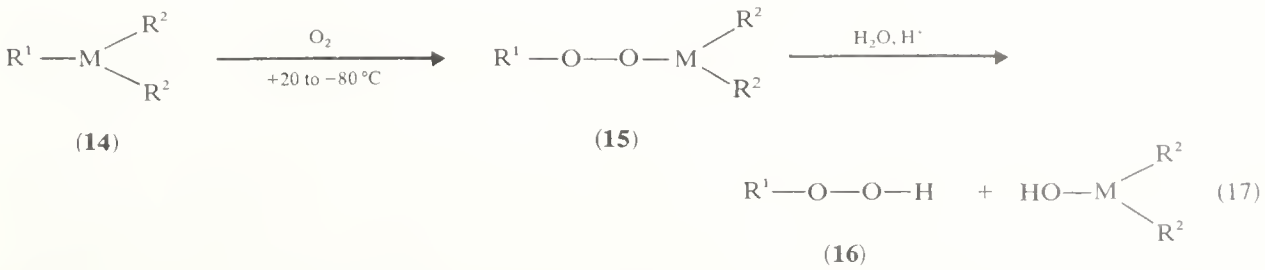
$$\underset{(11)}{Me_2CH{-}C(=O){-}CHMe_2} \xrightarrow{O_2} Me_2C(OOH){-}C(=O){-}CHMe_2 \qquad (14)$$

$$\underset{(12)}{Me_2CH{-}CH{=}CH{-}C(=O){-}Me} \xrightarrow{O_2} Me_2C(OOH){-}CH{=}CH{-}C(=O){-}Me \qquad (15)$$

$$\underset{(13)}{Ph_2CH{-}CHMe{-}C(=O){-}Ph} \xrightarrow{O_2} Ph_2CH{-}CMe(OOH){-}C(=O){-}Ph \qquad (16)$$

(iv) Autoxidation of organometallic compounds

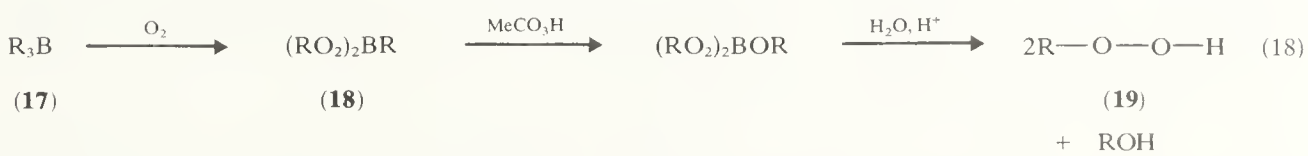
Organometallic compounds (**14**), $R—M\begin{<}$ (M = metal), are autoxidized (sometimes flammably) at low temperatures (+20 to −80 °C), perhaps by a free-radical pathway, to yield intermediate organometallic peroxides (**15**).[1] They may decompose with loss of peroxidic oxygen but those of lithium,[4] magnesium,[4] cadmium,[5] zinc,[4] and boron[6] can be hydrolysed to hydroperoxides (**16**), often in good yields (equation 17).



(**14**) (**15**) (**16**) (17)

The low temperature (−80 °C) oxidation and subsequent hydrolysis of Grignard reagents has been used to prepare tertiary hydroperoxides and also primary and secondary alkyl hydroperoxides normally not readily accessible by other methods.[4] Although hydroperoxide yields of up to 90% have been obtained from tertiary Grignard reagents and 55–65% yields from primary and secondary ones, yields are frequently much lower.

Organo-zinc and -cadmium reagents can be autoxidized at higher temperatures and frequently give excellent yields of hydroperoxides, including those derived from long-chain homologues.[6] Trialkylboranes (**17**), readily obtained from olefins, yield diperoxyboranes (**18**) on autoxidation; further oxidation with peroxy acids, followed by hydrolysis, gives 30–50% yields of hydroperoxides (**19**), based on starting olefin (equation 18). The major product is often the alcohol rather than (**19**).



(**17**) (**18**) (**19**) + ROH (18)

4.6.1.2 Hydrogen peroxide reactions[1]

Hydrogen peroxide and the hydroperoxy anion are excellent nucleophiles and they already contain the —O—O—H structure. Thus they are excellent reactants and are used frequently for the preparation of hydroperoxides by nucleophilic displacement reactions on suitable substrates (**20**) (equation 19).

(**20**) (19)

(X = OH, OR, OSO_2H, OSO_2R, halogen)

(**21**) (20)

(Y = C<, N—, O)

Hydrogen peroxide also adds to suitable unsaturated compounds (**21**), such as olefins, enamines, and carbonyl compounds, to yield hydroperoxides often in excellent yields (equation 20).

(*i*) *Hydroperoxides from alkyl sulphates and sulphonates*

Ethyl hydroperoxide, the first hydroperoxide to be isolated, was prepared by the reaction of diethyl sulphate with dilute alkaline hydrogen peroxide.[7] The reaction is also applicable to the preparation of homologous hydroperoxides but yields are low because of base-induced decomposition of the products.

The most reliable method for the preparation of primary and secondary hydroperoxides is the solvolysis of alkyl methanesulphonates (**22**) with alkaline hydrogen peroxide. Although yields are not high (25–40%) with secondary sulphonates, the starting materials are inexpensive and readily available. The C_3–C_{10}[8] and longer-chain[9] alkyl hydroperoxides (to C_{18}) are readily prepared in this way, as well as the unstable allyl hydroperoxide (equation 21).[10] As expected for an S_N2 reaction, almost complete inversion of configuration occurs.

$$\underset{\textbf{(22)}}{ROSO_2Me} + H_2O_2\ (30\%) \xrightarrow{KOH} R{-}O{-}O{-}H \qquad (21)$$

(R = C_3–C_{18} n-alkyl; allyl)

Tertiary hydroperoxides are obtained in good to excellent yields from 30% hydrogen peroxide and alkyl hydrogen sulphates, prepared *in situ* from tertiary alcohols or appropriate alkenes and approximately equimolar quantities of 70% or more concentrated sulphuric acid.[1] t-Butyl and t-pentyl hydroperoxides, higher homologues, and even tertiary acetylenic hydroperoxides (**23**) have been prepared in 70% yields in this way (equation 22). Large excesses of acid should be avoided in order to minimize acid-catalysed decomposition of the hydroperoxides.

$$H{-}C{\equiv}C{-}CMe_2OH \xrightarrow{H_2SO_4,\ H_2O_2} \underset{\textbf{(23)}}{H{-}C{\equiv}C{-}CMe_2O{-}O{-}H} \qquad (22)$$

(*ii*) *Hydroperoxides from alcohols and ethers*

Hydroperoxides are formed rapidly and in high yields from concentrated hydrogen peroxide (>70%) (CAUTION!), catalytic quantities of strong acids, typically sulphuric or perchloric acid, and alcohols that undergo S_N1 displacements involving carbenium (carbonium) ion intermediates (equation 23).[1] Alcohols bearing three alkyl or at least one aryl group on the carbinol carbon atom are best suited for conversion to hydroperoxides. The relative ease of the reaction parallels the order of carbenium ion stability:[11] $Me(Et)CHOH < Me_3COH < Ph(Me)CHOH < Ph_2CHOH < Ph_3COH$. ^{18}O-Labelled alcohols yield unlabelled hydroperoxides, as a mechanism involving the intermediacy of a carbenium ion requires. Certain esters[11] and ethers[12] that form carbenium ions readily behave similarly, and optically active alcohols yield racemic hydroperoxides largely plus only minor quantities of retention and inversion products (<10%).[13] In some instances, strong acid-catalysis is neither necessary (2,2,3-trimethylbutan-1-ol) nor desirable (1-methylcyclobutan-1-ol); in the latter case, acid-catalysed hydroperoxide decomposition is extremely facile.

$$R_3COH \xrightarrow{H^+\ catalyst} [R_3C]^+ + H_2O \xrightarrow{H_2O_2} R_3C{-}O{-}O{-}H + H^+ \qquad (23)$$

(*iii*) *Hydroperoxides from halides*

Reactive halides are the only types used, typically diaryl, triaryl, tertiary alkyl, allylic, or benzylic halides. Since the alcohols corresponding to the halides are usually more readily available and often equally reactive, there is ordinarily no advantage in using halides. The reaction has been most useful for the preparation of triaryl hydroperoxides and of hydroperoxides of Group IV elements other than carbon.[1]

(*iv*) *Hydroperoxides from alkenes, enamines, and carbonyl compounds*[1]

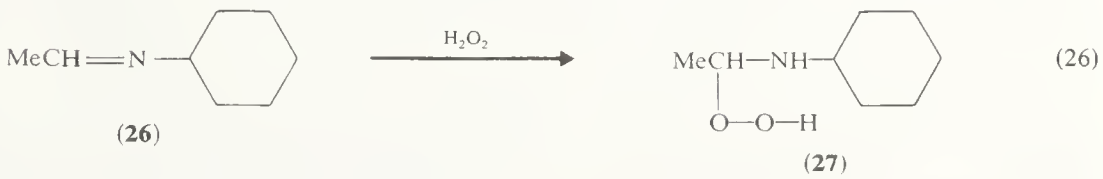
Alkenes with electron-donating groups attached to the double bond yield hydroperoxides on acid-catalysed reaction with hydrogen peroxide;[11] carbenium ions are intermediates. Typical preparations are those of t-pentyl hydroperoxide (**24**) (equation 24), and ethyl α-hydroperoxyethyl ether (**25**) (equation 25), but the reaction is generally applicable to electron-rich olefins.

$$Me_2C{=}CHMe \xrightarrow{H_2O_2,\ H^+} Me_2C(OOH){-}CH_2Me \quad (24)$$

(**24**)

$$CH_2{=}CHOEt \xrightarrow{H_2O_2,\ H^+} CH_3{-}CH(OOH)OEt \quad (25)$$

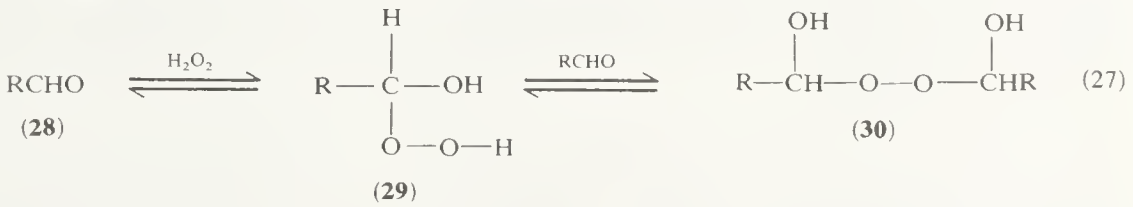
(**25**)



(26) (27) (26)

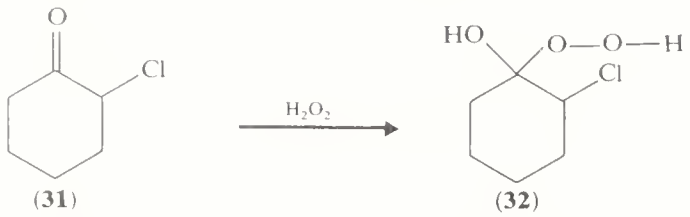
Imines (**26**) react readily with hydrogen peroxide and the products are usually bis-peroxides.[14] However, a number of α-hydroperoxy amines (**27**) have been prepared by the low-temperature addition of hydrogen peroxide to imines (equation 26).[15]

Hydrogen peroxide adds to the carbonyl group of aldehydes (**28**) and ketones to yield firstly α-hydroxyhydroperoxides (**29**), which then form bis-(1-hydroxyalkyl) peroxides (**30**) and more complex peroxides on reaction with more carbonyl compound (equation 27).[16] The reactions are thermodynamically controlled processes; equilibrium is attained in a few minutes without added catalysts and is reached much more rapidly with acid catalysis. Both (**29**) and (**30**) have been prepared from C_1–C_{11} aldehydes. Equimolar mixtures of hydrogen peroxide and aldehyde in ether yield (**29**) mainly if the solvent is evaporated at room temperature and mainly (**30**) at higher temperatures (CAUTION!). With the longer-chain aldehydes, (**29**) may crystallize from the reaction mixture.



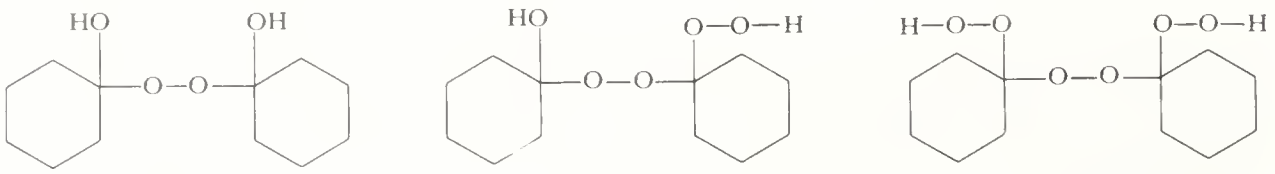
(**28**) (**29**) (**30**) (27)

The 1:1 addition products are rarely isolable from ketones and hydrogen peroxide. A noteworthy exception is the α-hydroxyhydroperoxide (**32**) from 2-chlorocyclohexanone (**31**) (equation 28).[17]



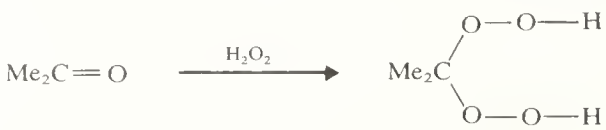
(31) (32) (28)

Cyclohexanone gives mainly a mixture of dimeric hydroxyperoxides (**33**), peroxyhydroperoxides (**34**), and peroxydihydroperoxides (**35**), each in turn predominating with increasing acidity; in addition, other more complex peroxides are also formed.[18] Acetone,



(33) (34) (35)

butan-2-one, and some cyclic ketones yield *gem*-dihydroperoxides (**36**); from acetone a 95% yield of (**36**) is reported with neutral hydrogen peroxide (equation 29).[19]



(36) (29)

Ordinarily, a vast array of products is obtained from solutions of ketones with hydrogen peroxide, especially if catalytic quantities of acids are present.[20] The equilibrium mixture contains linear and cyclic dimers, trimers, and tetramers, with or without free hydroxy or hydroperoxy groups. These products are often heat and/or shock sensitive. At least seven peroxides have been separated by chromatography and identified from the reaction of hydrogen peroxide (0.2 *M*), methyl ethyl ketone (0.2 *M*), and sulphuric acid (0.05 *M*) in ether at −5 °C.[20] Similar results are obtained from acidified hydrogen peroxide with diethyl ketone, cyclohexanone, acetone, 1,3-dichloroacetone, and di- and tri-ketones.[1]

4.6.1.3 Physical properties of hydroperoxides[1,21]

Most hydroperoxides are liquids but some are crystalline solids; typically they have slightly lower melting points and higher boiling points than the corresponding alcohols. Solubility of hydroperoxides in water and organic solvents parallels that of the corresponding alcohols. Except for the first two members of the homologous series of alkyl hydroperoxides, they are stable enough when pure to be distilled or melted below about 70 °C, but all should be handled with caution at higher temperatures as they may undergo rapid and explosive decomposition. Impurities, such as metal ions, dust, and inert particles, cause a profound and often mysterious decrease in stability. Hydroperoxides are slightly stronger acids than the corresponding alcohols and are sometimes separated as their alkali metal salts from neutral impurities, *e.g.*, alkanes, alkenes, alcohols, ethers, and carbonyl compounds.

(*i*) *Spectral characteristics*

(*a*) *Infrared.* Hydroperoxides have infrared absorptions in the 820–880 (—O—O— stretch), 3400–3600 (—O—H stretch), and 6900–7100 cm^{-1} (—O—H overtone) regions. In solution they exhibit two maxima in the O—H stretching region, a sharp peak due to

monomer, and a broad peak at higher wavelengths due to the hydrogen-bonded dimer. The monomer:dimer ratio can be determined by dilution studies.

(*b*) *Ultraviolet.* Hydroperoxides with no other absorbing functional groups have no distinctive absorptions in the ultraviolet. Energy is weakly absorbed below 300 nm ($\log \varepsilon$ is approximately 1 at 250 nm) and maxima are not observed above 200 nm.

(*c*) *Nuclear magnetic resonance.* Relatively little use has been made of ^{1}H n.m.r. spectroscopy with hydroperoxides.[1,21] Significant (0.3 p.p.m.) downfield chemical shifts are observed in the protons on α-carbon atoms of hydroperoxides compared with those in the corresponding alcohols.[22] Peak area and chemical shift of the labile proton in the —O—O—H group are dependent on concentration, solvent composition, and the rate of chemical exchange. A shift to higher field is observed upon dilution but it is less than that observed for the corresponding alcohols. The resonance line of protons β to the —O—O—H group is affected only slightly by solvent (0.02–0.08 p.p.m.). Although the chemical shifts of β-protons in alcohols and the corresponding hydroperoxides differ only slightly, modern ^{1}H n.m.r. spectrometers permit resolution of the small differences and, in selected cases, permit characterization and quantitative determination of the two species.

(*d*) *Mass spectra.* Limited mass spectral data are available on hydroperoxides. A study of isomeric pentyl, hexyl, and heptyl hydroperoxides suggests that initial ionization removes an electron from a non-bonding orbital of one of the peroxide oxygen atoms.[23] The C—O bond in hydroperoxides is more readily fragmented than in the corresponding alcohols. The order of stability of the molecular ions is tertiary>secondary>primary, and pentyl>hexyl>heptyl. Alkyl ions arise from the molecular ions by loss of $HO_2\cdot$.

4.6.1.4 Determination of hydroperoxides[24]

Hydroperoxides are determined by physical and instrumental methods, chemical reduction methods, and colorimetric and photometric methods.

(*i*) *Physical and instrumental methods*

(*a*) *Chromatography.* t-Alkyl hydroperoxides are the most stable members of this class; they can be determined by gas chromatography if they contain a maximum of about eight carbon atoms. Some primary and secondary alkyl and alkenyl hydroperoxides have also been purified and analysed by this technique. Gas chromatography is widely used for the analysis of mixed alcohols obtained by reduction of mixed hydroperoxides.

Adsorption and liquid–liquid partition chromatography are mild non-destructive techniques that have been used in the analysis of mono- and di-hydroperoxides and of hydroxyhydroperoxides. The column adsorbent is of prime importance in determining separation efficiency and hydroperoxide survival. Silicic acid and celite are frequently used but alkaline alumina is often too destructive.

Various paper chromatographic techniques have been used to separate classes of peroxides, including hydroperoxides, prior to analysis. The technique is mild and non-destructive and is recommended particularly for complex mixtures. A summary of the principal solvent systems for paper chromatographic separation of peroxides and R_f values has been published.[24]

Thin layer chromatography is now used in the separation and analysis of hydroperoxides, along with paper chromatography. Silica gel is the most widely employed adsorbent.

R_f Values with a variety of solvent systems have been reported for representative hydroperoxides.[24]

(*b*) *Polarography.* Hydroperoxides are readily reduced in a polarograph and they can be both qualitatively and quantitatively determined on a micro scale in aqueous or non-aqueous media.[21] Half-wave potentials have been tabulated for a series of saturated, unsaturated, and steroidal hydroperoxides. Polarography is better suited for distinguishing peroxide types than for identifying individual compounds.

(*ii*) *Chemical reduction methods*[24]

(*a*) *Iodometric methods.* Reduction of hydroperoxides by iodide ion is the most widely used and most generally applicable method for analysis of hydroperoxides. The scope, limitations, and controlling variables have been discussed[24] in detail.

Iodide ion reacts rapidly and stoichiometrically with hydroperoxides in acidic solution, liberating iodine which is determined by titration methods or colorimetrically. The major drawback to iodometry is that other classes of organic peroxides and hydrogen peroxide oxidize iodide ion; however, in the absence of interfering substances, hydroperoxides can be precisely and accurately determined by this method.

(*b*) *Stannous ion.* Reduction of hydroperoxides with stannous chloride and titration of the excess of stannous ion avoids the interference in the iodide methods by sulphur compounds that consume iodine. The method, although precise and accurate, is lengthy and complex and requires careful purging with nitrogen and the absence of other reducible peroxides.

(*c*) *Arsenite ion.* Reduction with arsenite ion is another useful hydroperoxide analytical method where there are interferences with iodide methods, presumably by sulphur compounds. The method has been used for determining hydroperoxides in petroleum products down to levels of less than 0.1 mequiv l^{-1}.

(*d*) *Ferrous ion.* Reduction by ferrous ion is useful for the quantitative analysis of easily reduced peroxides, particularly alkyl hydroperoxides formed in the development of fat rancidity and in other autoxidation processes. Unless ferrous ion reduction methods are conducted under carefully controlled conditions, results are irreproducible and inaccurate. Oxygen must be scrupulously excluded, solvent effects are serious and not understood, and chain reactions may consume peroxide without oxidizing ferrous ion. In spite of these difficulties, ferrous ion methods are used in the colorimetric determination of traces of peroxides where absolute values are not required.

(*e*) *Organic phosphines.* Tertiary phosphines reduce virtually every type of organic peroxide except the most unreactive ones. Hydroperoxides, as well as other easily reduced peroxides, are rapidly reduced and can be determined in the presence of dialkyl peroxides that are frequently formed in the preparation of hydroperoxides by displacement reactions.

(*f*) *Catalytic hydrogenation.* Rates of hydrogenation with palladium black in acetic acid have been used to differentiate between and characterize organic peroxides, but the

method is now rarely used. Hydroperoxides are reduced quantitatively in a few minutes; peroxy esters and dialkyl peroxides are substantially less reactive, and dimeric and trimeric ketone peroxides still less so. The chief utility of catalytic reduction in peroxide analysis is the preparation of stable reduction products for proof of structure.

(*g*) *Lithium aluminium hydride.* All classes of peroxides are reduced by lithium aluminium hydride. Organic hydroperoxides are smoothly reduced at room temperature to the corresponding alcohols with the evolution of two moles of hydrogen per mole of hydroperoxide; other peroxides form one mole of hydrogen per mole. Interference by other reducible groups limits the utility of this reductant. Sodium borohydride does not have this drawback, but it has received limited use to date.

(*iii*) *Colorimetric and photometric methods*

These methods are used to determine trace levels of peroxides, typically in rancid fats and other autoxidized natural products, and in estimating peroxides in vinyl polymerization systems.

(*a*) *Ferrous methods.* One of the most precise and sensitive methods uses the oxidation of ferrous thiocyanate. Although there are many drawbacks, good absolute accuracy can be obtained by careful control of reaction variables and calibration with an independent method.

(*b*) *Aromatic diamines.* The best aromatic diamine reagents are *N*,*N*′-diphenyl-*p*-phenylenediamine and 4,4′-diaminodiphenylamine, the oxidation of which produces highly absorbing blue dyes (molar absorptivity $1–5\times10^4$ l mol^{-1} cm^{-1} at 700 and 640 μm, respectively). The method is not specific for hydroperoxides.

(*c*) *Leuco Methylene Blue.*[24–26] This reagent is not only one of the most sensitive colorimetric reagents (molar absorptivity 8×10^4 l mol^{-1} cm^{-1}), but it has an almost constant molar response for all reactive peroxide classes. Its main drawback — the preparation and storage of the dye in benzene solution — can be avoided by protecting the reagent solution from light, oxygen, and water in a dispensing burette over platinized asbestos, where it may be reduced with hydrogen before use, thus maintaining its analytical quality.

N-Benzoyl leuco Methylene Blue is more stable and it can be stored in benzene solution in the presence of air, but it reduces peroxides slowly and it is light-sensitive. Molar absorptivity values of about 1.5×10^5 l mol^{-1} cm^{-1} at 622 μm, approximately twice that of leuco Methylene Blue, have been reported.

(*d*) *Iodide methods.*[24] Colorimetric estimation of iodine, either directly or indirectly, extends the range of peroxide analyses by iodide reduction considerably below that practically possible by volumetric procedures. Tri-iodide ion is the species most frequently determined; it forms quantitatively at iodide:iodine ratios of 5 or above.[27] Tri-iodide ion has a molar absorptivity of about 2.3×10^4 l mol^{-1} cm^{-1} in acetic acid–chloroform with a maximum at 362 μm, although in practice none of the methods use measurements at the absorption peak. In one recommended procedure,[28] hydroperoxides have been estimated with good precision and accuracy in the 1–10 p.p.m. range in organic solvents.

4.6.1.5 Reactions of hydroperoxides

(i) Heterolytic reactions[1]

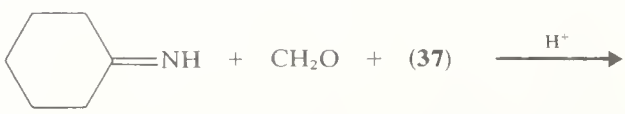
Hydroperoxides, and their anions in particular, are excellent nucleophiles due in large measure to the facile polarizability of the unshared electrons on the peroxy group (the so-called α-effect).[29] Hydroperoxides are widely used for the preparation of dialkyl peroxides by nucleophilic displacement on halides, sulphates, sulphonates, and epoxides, or by reaction with carbenium ions.

Hydroperoxides add to certain olefins (equations 30 and 31), vinyl ethers (equation 32), and imines (equation 33) in the presence of strong acids, but the temperature must be well controlled to minimize acid-catalysed thermal decomposition of starting materials and products.

$$Me_2C{=}CH_2 + Me_3CO_2H \xrightarrow[0\text{–}50\,^\circ C]{H^+} Me_3C{-}O{-}O{-}CMe_3 \quad (30)$$
(37)

$$PhC(Me){=}CH_2 + (37) \xrightarrow[0\text{–}50\,^\circ C]{H^+} PhCMe_2{-}O{-}O{-}CMe_3 \quad (31)$$

$$CH_2{=}CHOEt + (37) \xrightarrow{H^+} CH_3CH(OEt){-}O{-}O{-}CMe_3 \quad (32)$$



(33)

Carbonyl groups of aldehydes and ketones react with hydroperoxides under neutral conditions and, even more rapidly, with acid catalysts (equations 34 and 35). Ketones form *gem*-peroxides (**38**). The reactivity of hydroperoxides towards acetaldehyde decreases in the order α-tetralyl > t-butyl > α-cumyl > diphenylmethyl.[30]

$$MeCHO + (37) \longrightarrow MeCH(OH){-}O{-}O{-}CMe_3 \quad (34)$$

$$Me_2CO + (37) \rightleftharpoons Me_2C(OH){-}O{-}O{-}CMe_3 \longrightarrow Me_2C(O{-}O{-}CMe_3)_2 \quad (35)$$
(38)

Acyl halides or anhydrides react with hydroperoxides to form peroxy esters (equation 36). The acid formed is either neutralized by base (*e.g.* pyridine, sodium hydroxide) or removed by vacuum evaporation. Sulphonyl halides behave similarly and yield peroxysulphonates.

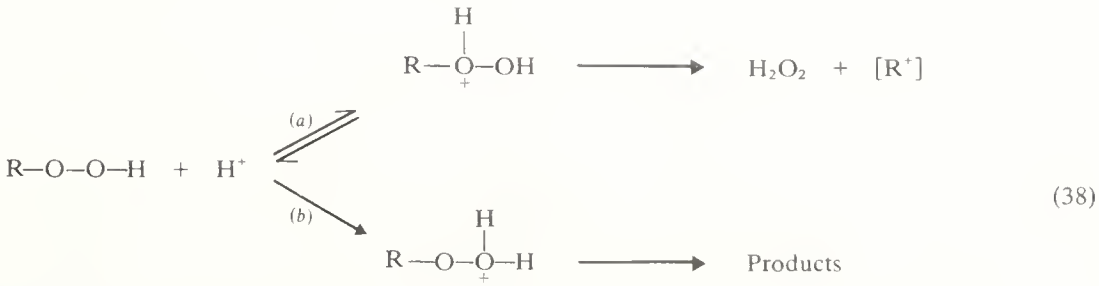
$$R^1C(=O)X + R^2{-}O{-}O{-}H \longrightarrow R^1C(=O){-}O{-}O{-}R^2 + HX \quad (36)$$
(X = Halogen, acyloxy)

$$R^1N{=}C{=}O + R^2{-}O{-}O{-}H \longrightarrow R^1NH{-}C(=O){-}O{-}O{-}R^2 \quad (37)$$

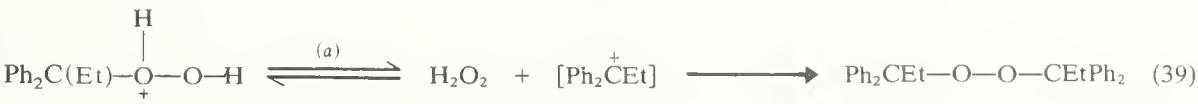
Hydroperoxides add nucleophilically to ketens and isocyanates to yield peroxy esters or peroxy carbamates, respectively (equation 37).

Electrophilic attack by a proton can occur at either oxygen atom of a hydroperoxide (equation 38). Hydroperoxides with strongly electron-donating groups follow pathway (*a*) and form hydrogen peroxide plus a carbenium ion species.[31] The latter may react with hydroperoxide to form a peroxide (equation 39). Pathway (*b*) leads to non-reversible

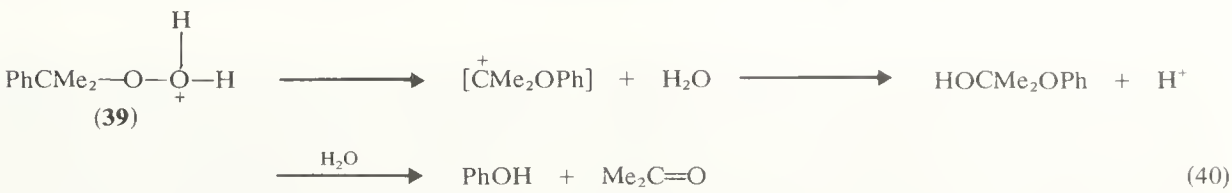
—O—O— heterolysis accompanied by rearrangement and cleavage; this transformation tends to obscure pathway (*a*). The conversion of cumene, *via* its protonated hydroperoxide (**39**), to phenol and acetone is a large-scale application of the operation of pathway (*b*) (equation 40). Acid-catalysed heterolysis by pathway (*b*) depends on the ability of an alkyl or aryl group to undergo a 1,2-shift from carbon to oxygen in concert with the departure of the water molecule. The alkyl oxygen atom may have an incipient positive charge, although the alkyloxonium ion never has a free existence,[32] and anchimeric effects are quite important in the —O—O— bond-breaking step.[33] Relative group migratory aptitudes are cyclobutyl>aryl ≫ vinyl > H > cyclopentyl ≈ cyclohexyl ≫ alkyl.



(38)



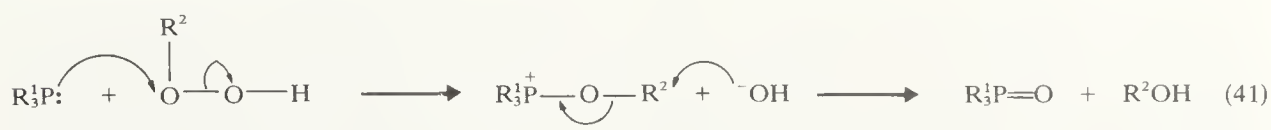
(39)



(40)

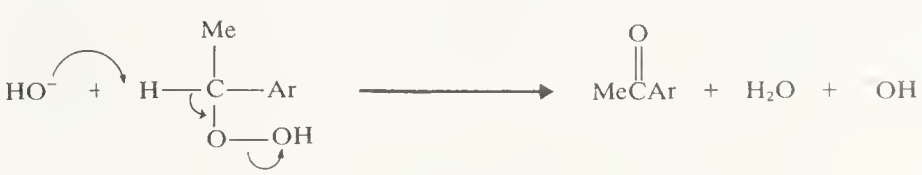
t-Butyl hydroperoxide yields isobutene and hydrogen peroxide — pathway (*a*) — or acetone and methanol — pathway (*b*) — depending upon reaction conditions.[34]

Nucleophiles, such as trivalent phosphorus compounds, thioethers, and amines, attack hydroperoxides and rapid —O—O— heterolysis occurs, often quantitatively (equation 41). The reaction with a phosphine is undoubtedly more complex than shown. Thioethers react similarly, yielding sulphoxides and the alcohol corresponding to the hydroperoxide. The reaction of hydroperoxides with amines is exceedingly complex and radicals are certainly involved. Thus if thiols are also present they are oxidized to disulphides. Polymerizations and hydrocarbon autoxidation are accelerated by the amine–hydroperoxide reaction. It is believed, however, that —O—O— heterolysis is the initial step, but that conclusion is still equivocal.[35]



(41)

(R^1 = alkyl, alkoxy, aryl, aryloxy)

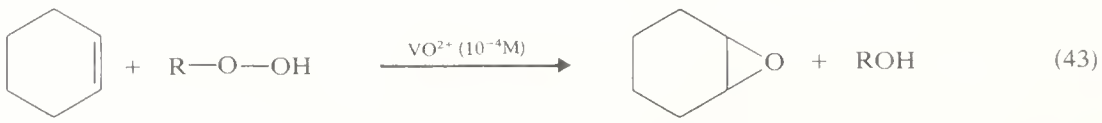


(42)

Hydroperoxides with an α-hydrogen react with bases and undergo heterolytic cleavage (equation 42).[36] A significant kinetic isotope effect, $k_H/k_D = 3.9$, is observed when the α-hydrogen is replaced by deuterium.

Olefins are epoxidized in high to quantitative yields by hydroperoxides, typically t-butyl and α-cumyl hydroperoxides, in the presence of complexes or salts of molybdenum,

vanadium, chromium, or tungsten (equation 43).[1,37] Although the mechanism of the reaction is not entirely clear, several factors indicate a nucleophilic displacement process by the C=C bond preceded by hydroperoxide–metal ion complexation. Metal ions, such as Co^{2+}, Fe^{2+}, Mn^{2+}, Ni^{2+}, Ce^{4+} ions, that induce free-radical chain decomposition of hydroperoxides give little or no epoxides. Epoxidation rates are increased by electron-donating substitutents on the double bond and electron-withdrawing substituents on the hydroperoxide, and are decreased with increased solvent polarity, analogous to the situation which pertains in the peroxy acid epoxidation of olefins. The reaction has evoked extensive industrial interest, especially among petroleum companies that have access to large quantities of easily hydroperoxidized hydrocarbons, such as isobutane and cumene.



(43)

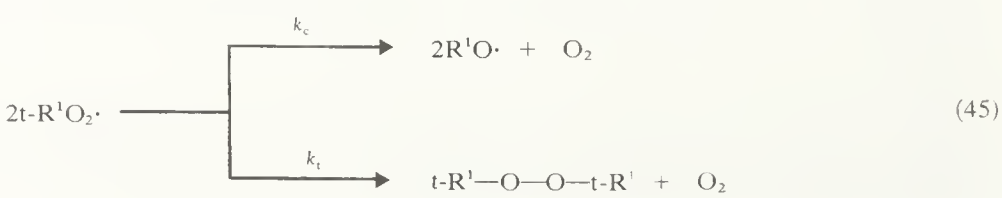
Under similar conditions, hydroperoxides efficiently oxidize amines to amine oxides,[38] and sulphides to sulphoxides and sulphones.[39]

(*ii*) *Homolytic reactions*

Four general types of homolytic reactions will be considered: free radical abstraction, radical displacements on the peroxy group, thermal decomposition, and reactions with metal ions.

(*a*) *Free radical abstraction* (*radical-induced decomposition*). Tertiary hydroperoxides react with radicals generated at low temperatures (20–60 °C), typically from peroxy esters, azo compounds, or hypochlorites; a chain reaction takes place (equations 44 and 45).[40] The chain length is determined by the ratio k_c/k_t. The overall mechanism is more complex than that shown and involves the intermediacy of tetroxides.[41] Alkoxy radical cleavage competes with hydrogen abstraction, and other side reactions occur when autoxidizable solvents, such as alkanes, are used; both of these factors reduce the chain length.

(44)

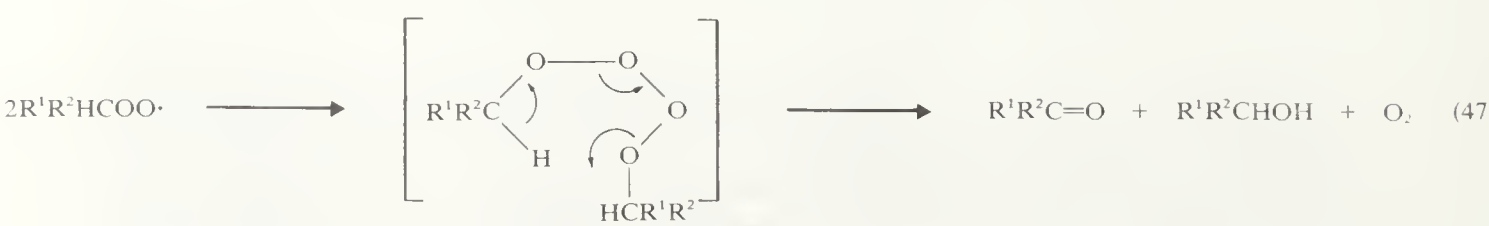


(45)

(k_c and k_t are specific rate constants for a chain process and termination, respectively)

Primary and secondary hydroperoxides also undergo radical-induced decomposition, but a chain reaction is not observed in the presence of free radical initiators.[42] Termination on every interaction of primary or secondary radicals conforms to a cyclic decomposition pathway (equations 46 and 47). A deuterium isotope effect, $k_H/k_D = 1.3–1.7$, is

(46)



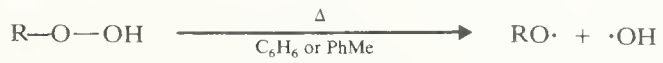
(47)

observed.[43] Above 100 °C, however, peroxide-induced decomposition of secondary hydroperoxides exhibits short chains, due perhaps to some C—H cleavage.

(*b*) *Radical displacements on —O—O—.* Thermodynamically, it would seem preferable for alkyl radicals to attack the relatively weak —O—O— bond rather than abstract hydrogen. These reactions are not facile ones, as chain-transfer constant measurements have shown, but they offer a reasonable explanation for the production of cyclic ethers by intramolecular radical displacements in autoxidations of certain hydrocarbons at or above 275 °C (equation 48).[44,45]

(48)

(*c*) *Thermal decomposition.* Unimolecular homolysis has been studied in the liquid or gas phase (180–220 °C) by using low concentrations of hydroperoxides in benzene or toluene (equation 49). Homolysis is assessed by determining the yield of biphenyl or bibenzyl, respectively. In dilute solutions or in the gas phase, induced decomposition pathways are minimized.



(49)

Solvent-assisted homolysis causes a ten- to twenty-fold increase in overall decomposition rates, especially at lower temperatures. When induced decomposition is suppressed, either by addition of a suitable inhibitor (phenyl-α-naphthylamine) or styrene, decomposition kinetics are essentially first order.

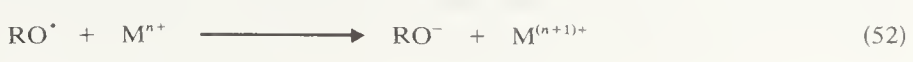
In solvents, decomposition rates are greater and activation energies lower than predicted for unimolecular homolysis. Decomposition rates roughly parallel ease of autoxidation of the solvent and suggest that both C—H and —O—O— bond breaking are occurring.

Hydroperoxide homolysis is assisted by many kinds of species, such as olefins, aldehydes, ketones, acids, alcohols, amines, sulphur compounds, aralkanes, trace metals, halide ions, another molecule of hydroperoxide, monomers, and many others.[1] Molecularly assisted homolysis has complex kinetics, first or second order in hydroperoxide and first order in monomer and/or solvent. Homolysis studies are often irreproducible and are not really understood.

(*d*) *Reactions with metal ions.* The decomposition of hydroperoxides by minuscule quantities of transition metal ions, such as Co^{2+}, Mn^{2+}, Fe^{2+}, and Cu^{+} ions, is rapid at or below room temperature.[46,47] In unreactive solvents the reactions can be rationalized as shown in equations (50) and (51). Radical chain decomposition competes with these processes (equation 52). t-Butyl hydroperoxide with catalytic quantities of Co^{2+} or Mn^{2+} ions, for example, yields about 95% oxygen plus t-butyl alcohol, and di-t-butyl peroxide by induced decomposition (equation 45). Metal ions differ considerably in their abilities to effect the reactions in equations (50)–(52), a result probably influenced in part by the counter-ions or by complexing ligands.[47]

(50)

(51)



(52)

In suitably constituted hydroperoxides, cleavage of the alkoxy radicals and recombination is a synthetically useful reaction (equations 53 and 54). Final products may be derived from radicals by dimerization, hydrogen abstraction, reaction with counter-ions or solvents, or telomerization with added monomers. In solvents that readily undergo hydrogen abstraction, good yields of dialkyl peroxides can be obtained (equation 55).

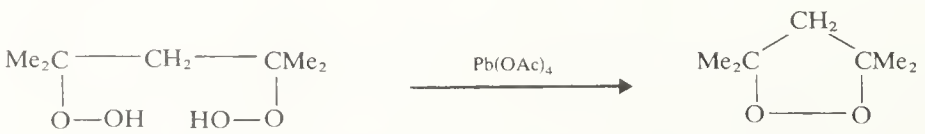
$$PhCMe_2O{-}OH \xrightarrow{Fe^{2+}} PhCMe_2O\cdot \longrightarrow PhC(=O)Me + Me\cdot \qquad (54)$$

$$R^1H + R^2O{-}OH \xrightarrow{M^{n+}} R^1{-}O{-}O{-}R^2 \qquad (55)$$

(R^1H = cumene, alkenes, tetrahydrofuran, nitriles, cyclohexane)

Kinetics of metal ion-catalysed decomposition of hydroperoxides are complex, irreproducible and not understood; initial rates are usually first order in RO_2H but show considerable variation (0–3) in metal ion.

Lead tetra-acetate reacts with 1,3- or 1,4-dihydroperoxides to produce cyclic peroxides (equation 56).[48] Cumene hydroperoxide yields dicumyl peroxide in low yield; since acetophenone and cumyl alcohol are the major products, a free radical-induced decomposition is probable.



(56)

4.6.1.6 Economic aspects

The most important industrial process involving hydroperoxides is the preparation of phenol and acetone by the acid-catalysed decomposition of cumene hydroperoxide (**39**) (equation 40); it has become the major route to phenol.[49]

Epoxidation of olefins by hydroperoxides in the presence of catalytic quantities of complexes or salts of molybdenum, vanadium, chromium, or tungsten has recently become industrially important;[49] ethylbenzene and t-butyl hydroperoxides are the oxidants of choice. The process is of interest to manufacturers of petrochemicals as ethylbenzene hydroperoxide is obtained from benzene and ethylene, and t-butyl hydroperoxide from isobutane or isobutene. A current large-scale industrial process is the preparation of propene oxide from propene.

A compilation of the physical properties of hydroperoxides with references to the preparation of individual compounds is available.[1]

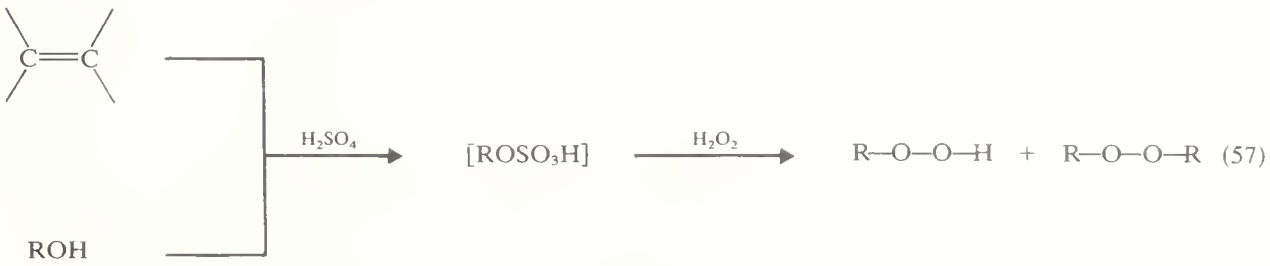
4.6.2 DIALKYL PEROXIDES, $R^1{-}O{-}O{-}R^2$ [50]

4.6.2.1 Hydrogen peroxide and hydroperoxide reactions under acidic conditions

(i) Alkyl sulphate intermediates

Alkenes or alcohols yield dialkyl peroxides on reaction with hydrogen peroxide in moderately concentrated sulphuric acid (equation 57).[50] The intermediate alkyl sulphates need not be isolated. Although a mixture of hydroperoxide and dialkyl peroxide is

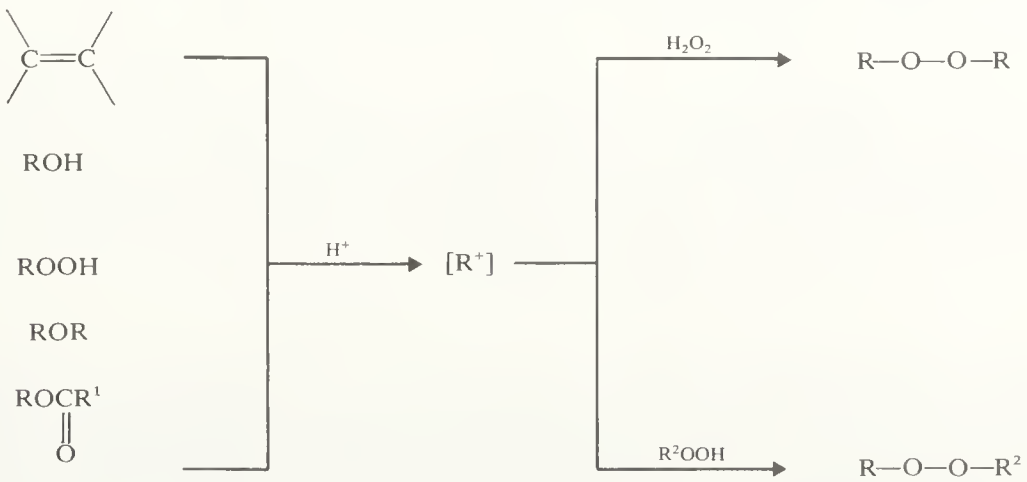
obtained, the latter can be favoured by adjusting the ratio of starting materials. Product separation is accomplished by solvent extraction of the dialkyl peroxide from an aqueous solution of an alkali metal salt of the hydroperoxide or, in favourable cases, by distillation (CAUTION) or chromatography. The procedure is best suited for the preparation of constitutionally symmetrical t-dialkyl peroxides. Constitutionally unsymmetrical peroxides are prepared similarly but a hydroperoxide, usually t-butyl or cumyl hydroperoxide, is used instead of hydrogen peroxide.



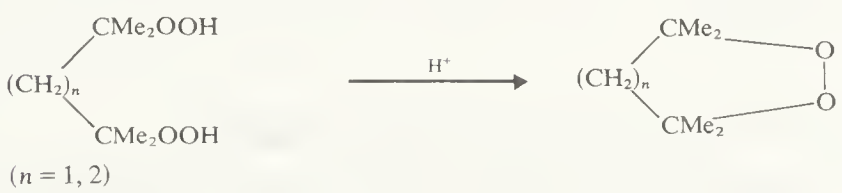
(57)

(*ii*) *Carbenium ion intermediates*

Tertiary or resonance-stabilized carbenium ions, formed by the reaction of catalytic quantities of strong acids on alkenes, alcohols, hydroperoxides, ethers, or esters, readily alkylate hydrogen peroxide or hydroperoxides (equation 58). Constitutionally symmetrical and unsymmetrical dialkyl peroxides can be prepared in this way. Diols and suitably constituted dihydroperoxides yield cyclic dialkyl peroxides (equation 59). Carbenium ion rearrangements are complicating factors in certain cases and lead to mixtures of products.



(58)



(59)

($n = 1, 2$)

4.6.2.2 Hydrogen peroxide and hydroperoxide reactions under basic conditions

(*i*) *Alkyl sulphate or sulphonate intermediates*

The most practical method for preparing low molecular weight primary and secondary dialkyl peroxides, albeit in low to moderate yields, is the alkylation of hydrogen peroxide by dialkyl sulphates in the presence of strong bases; the products are constitutionally symmetrical dialkyl peroxides (equation 60). Constitutionally unsymmetrical dialkyl

peroxides are obtained by alkylating hydroperoxides similarly. A drawback to this method is base-induced decomposition of starting materials and products.

$$(RO)_2SO_2 + H_2O_2 \xrightarrow{^-OH} ROOR \qquad (60)$$

The most general procedure for preparing primary and secondary dialkyl peroxides is the base-catalysed displacement by hydrogen peroxide or hydroperoxides on an alkyl methanesulphonate.[50] Yields are sometimes low but the method is relatively safe and reproducible, and starting materials are readily available. 1,2-Dioxan, a cyclic dialkyl peroxide, is prepared in 30% yield by this route starting with the bis(methanesulphonate) of butane-1,4-diol (**40**) (equation 61).

$$\underset{(\mathbf{40})}{MeSO_3(CH_2)_4SO_3Me} + H_2O_2 \xrightarrow{KOH} \text{(1,2-Dioxan)} \qquad (61)$$

(ii) Other nucleophilic displacements

Sodium or potassium salts of tertiary hydroperoxides react readily with primary, secondary, allylic, and benzylic halides to yield constitutionally unsymmetrical dialkyl peroxides (equation 62). Four- and six-membered cyclic dialkyl peroxides can also be prepared in this way (equations 63 and 64). Recently, the reaction of primary and secondary trifluoromethanesulphonates with the potassium salt of t-butyl hydroperoxide and sodium bicarbonate was shown to be a facile method for the preparation of unsymmetrical peroxides in 30–80% yields.[50a]

$$Me_3C{-}O{-}OK + Me_2CHBr \longrightarrow Me_3C{-}O{-}O{-}CHMe_2 + KBr \qquad (62)$$

$$Me_2C(OH){-}CHBrMe \xrightarrow{^-OH} Me_2C(O{-}O){-}CHMe \qquad (63)$$

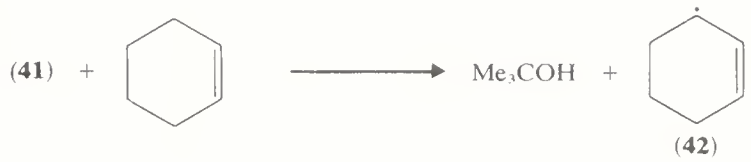
$$BrCH_2CH{=}CHCH_2Br \xrightarrow[^-OH]{H_2O_2} \text{(1,2-Dioxen)} \qquad (64)$$

A number of hydroperoxides have been alkylated by diazomethane;[51] the reaction appears to be general for the preparation of constitutionally unsymmetrical methyl alkyl peroxides. More recently, other diazoalkanes, such as diazo-ethane, -propane, -isopropane, and -isobutanes, have been used to alkylate cumyl hydroperoxide; 40–65% yields have been reported.[52]

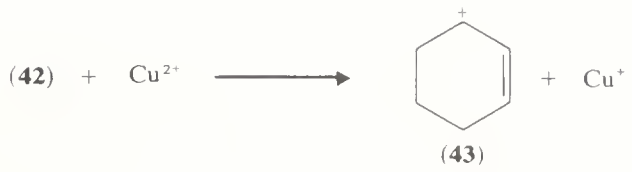
4.6.2.3 Hydroperoxides and metal ions under neutral conditions

Radical-induced decomposition of hydroperoxides, catalysed by certain metal ions in an oxygen-poor system and in solvents that readily form radicals (benzylic or allylic typically), is a convenient route to constitutionally unsymmetrical dialkyl peroxides.[50] The major reaction is probably not coupling of radicals but carbenium ion attack on ROOH (equations 65–68).[53] Cuprous salts are best but cobalt and manganese salts, lead tetra-acetate, and rhodium complexes can be used. Ketones (equation 69) or amines (equation 70) can also be used as substrates.

$$\underset{(\mathbf{37})}{Me_3CO{-}OH} + Cu^+ \longrightarrow \underset{(\mathbf{41})}{Me_3CO\cdot} + Cu^{2+} + {}^-OH \qquad (65)$$

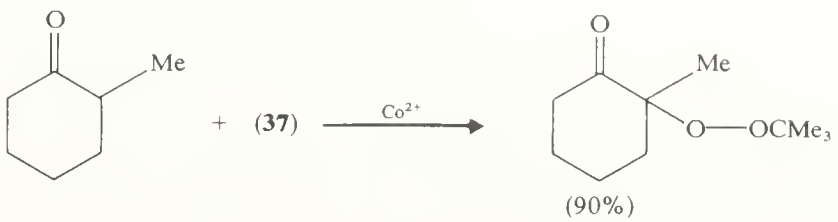


(66)

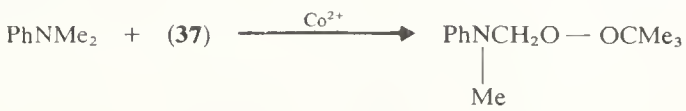


(67)

(68)



(69)



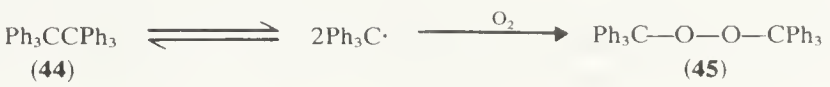
(70)

4.6.2.4 Autoxidation methods

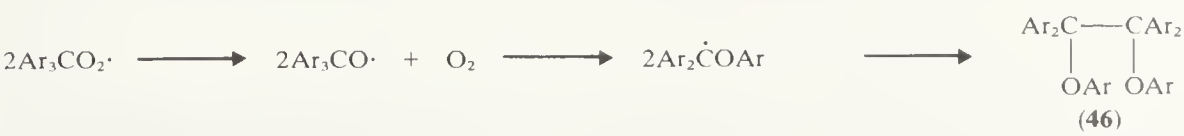
The preparation of monomeric dialkyl peroxides by autoxidation of hydrocarbons is considerably more restricted in scope than the synthesis of hydroperoxides. The method is best suited for the preparation of peroxides derived from highly stable intermediate free radicals.

(*i*) *Stable free radicals*

Solutions of hexaphenylethane (**44**) and other hexa-arylethanes rapidly absorb oxygen at ambient temperatures; bis(triphenylmethyl) peroxide (**45**) forms in almost quantitative yield (equation 71). Penta-arylethanes usually require higher temperatures (70–120 °C) for dissociation into free radicals. Other compounds that have been converted to peroxides in this way are triphenylmethane, 9-phenylanthrone, alkyl bixanthyl derivatives (but not bixanthyl), 2,4,6-tri(t-butyl)phenol, and isobutane (in the presence of hydrogen bromide).



(71)

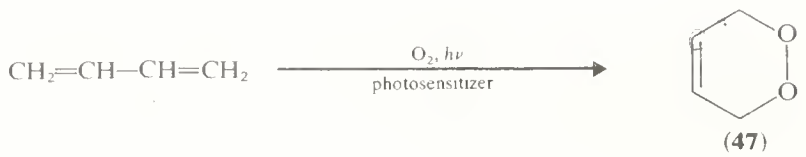


(72)

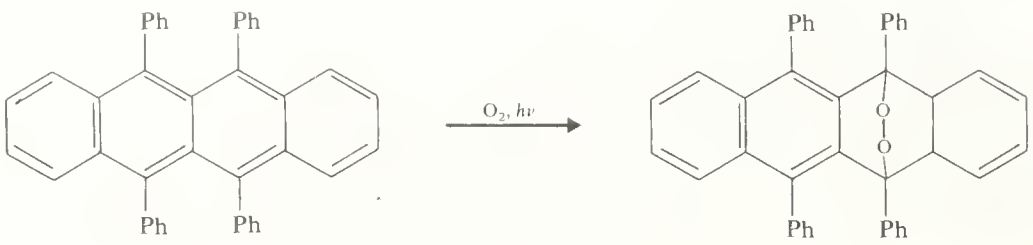
The autoxidation reaction (equation 71) is more complex than shown and, for clean conversions to peroxide, requires that the appropriate radical combination reaction be faster than rearrangement that leads finally to pinacol ethers (**46**) (equation 72).

(ii) Epiperoxides and transannular peroxides[50,54,55]

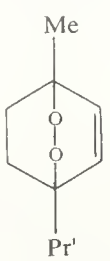
Conjugated dienes react with oxygen to give copolymeric peroxides usually, but photosensitized autoxidation proceeds by 1,4-addition of singlet oxygen in many cases, although yields of monomeric peroxides may be low. Buta-1,3-diene, for example, yields 1,2-dioxen (**47**) (equation 73). This reaction also takes place at high dilution with many cyclic compounds containing conjugated aryl or vinyl groups, typically rubrene (**48**) (equation 74), α-terpinene, cyclopentadiene, cyclohexadiene, cycloheptadiene, and furan. Ascaridole (**49**), a naturally occurring epiperoxide, is a major component (60–80%) of the oil of chenopodium and is reported to have anthelmintic properties.



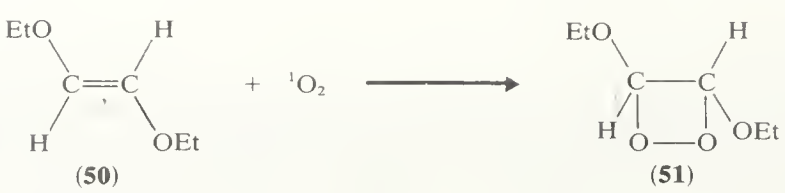
(47) (73)



(48) (74)



(49)



(50) (51) (75)

Singlet oxygen also adds to isolated double bonds with strongly electron-donating substitutents, such as 1,2-diethoxyethylene (**50**) giving the 1,2-dioxetan (**51**) (see equation 75).[56] In this way, *cis*- and *trans*-(**50**), tetramethoxyethylene, *p*-dioxen, and 1,3-dioxole have been converted to 1,2-dioxetans that are stable enough at low temperatures to be characterized. In other cases the intermediacy of unstable dioxetans has been inferred from the decomposition products.

(iii) Organometallic peroxides

Organometallic peroxides can be prepared by autoxidation of organometallic compounds of zinc, cadmium, boron, lead, antimony, and arsenic.[57] Typical peroxides prepared in this way are di(ethylperoxy)zinc, di(n-butylperoxy)cadmium, di(t-butylperoxy)-boron, and di(methylphenylbromoarsenic) peroxide.

4.6.2.5 Miscellaneous

Alkylperoxysilanes react with alcohols to yield constitutionally unsymmetrical dialkyl peroxides (equations 76 and 77).[57]

$$(R^1OO)_4Si + 4R^2OH \longrightarrow 4R^1OOR^2 + Si(OH)_4 \quad (76)$$

$$Me_3SiOOR^1 + R^2OH \longrightarrow R^1OOR^2 + Me_3SiOH \quad (77)$$

Trifluoromethyl peroxide (**52**) has been prepared in 90% yield by the high-pressure reaction of trifluoromethyl hypofluorite with carbonyl fluoride (equation 78).[58] Photolysis of fluoroformyl peroxide gives (**52**) in about 50% yield (equation 79).[59]

$$CF_3OF + COF_2 \underset{}{\overset{250\text{–}300\,^\circ C}{\rightleftharpoons}} \underset{(\mathbf{52})}{CF_3OOCF_3} \quad (78)$$

$$3FCOOCF \xrightarrow{h\nu} (\mathbf{52}) + 4CO_2 \quad (79)$$

Addition of hydrogen peroxide and mercuric acetate (**53**) to terminal olefins (**54**) yields mercury-containing hydroperoxides (equation 80).[50] Substituting t-butyl hydroperoxide (**37**) for hydrogen peroxide yields dialkyl peroxides (**55**) from which the mercuric acetate moiety can be removed by mild reduction or displacement (equation 81).[60]

$$\underset{(\mathbf{54})}{RCH{=}CH_2} + \underset{(\mathbf{53})}{Hg(OCMe)_2} + H_2O_2 \longrightarrow \underset{OOH}{\underset{|}{RCHCH_2HgOCMe}} \quad (\mathbf{55}) \quad (80)$$

$$(\mathbf{53}) + (\mathbf{54}) + (\mathbf{37}) \longrightarrow \underset{OOCMe_3}{\underset{|}{RCHCH_2HgOCMe}} \xrightarrow{NaBH_4} \underset{OOCMe_3}{\underset{|}{RCHMe}} \quad (50\text{–}60\%) \quad (81)$$

$$\underset{OOCMe_3}{\underset{|}{RCHCH_2HgOCMe}} \xrightarrow{Br_2} \underset{OOCMe_3}{\underset{|}{RCHCH_2Br}}$$

4.6.2.6 Physical properties of dialkyl peroxides[21,50]

Dialkyl peroxides (low molecular weight members) are liquids or low melting solids (below 100 °C), although some melt above 150 °C, usually with extensive decomposition. Melting points vary with rate of heating and the presence of minor impurities (decomposition catalysts); thus some published values may be unreliable. Severe explosions have occurred with dimethyl and diethyl peroxides, and occasionally with dipropyl peroxides. Dialkyl peroxides, especially di-tertiary ones, are the most stable class of organic peroxides.

(i) Spectral characteristics[21]

(a) Infrared. Dialkyl peroxides have a weak to moderately strong —O—O— stretching absorption band in the 820–890 cm^{-1} region. Complete infrared spectra of a number of dialkyl peroxides have been published.[21,50]

Di-t-butyl peroxide has a strong —O—O— absorption band at 874 cm^{-1} (t-butyl hydroperoxide, 847 cm^{-1}). The large torsional angle in di-t-butyl peroxide about the —O—O— bond constrains the molecule toward planarity, thereby diminishing the intensity of the —O—O— stretching vibration.

(*b*) *Ultraviolet.* As with most peroxides that contain no special ultraviolet absorbing groups, dialkyl peroxides show only weak absorption at 300–320 nm, which slowly increases at shorter wavelengths.

(*c*) *N.m.r.* Recent studies [21,22] have compared the chemical shifts of hydrogens α or β to the —O—O— group with those in the analogous alcohols. The α-protons in peroxides are shifted to lower fields (0.2–0.5 p.p.m.) and thus are readily distinguished, but the downfield shift of β-protons is much less (0.02–0.03 p.p.m.).

(*ii*) *Torsional angle*[21]

Dipole moment measurements on di-t-butyl peroxide in solution lead[21,61] to a calculated torsional angle, ϕ, of 123° about the —O—O— bonds; it is somewhat greater than those in hydrogen peroxide and dimethyl peroxide. The magnitude of ϕ has been explained as a steric effect of the two large t-butyl groups imposing a high rotational barrier about the —O—O— bond. This feature of —O—O— bonding leads to optical antipodes in cyclic peroxides.

4.6.2.7 Determination of dialkyl peroxides[24]

Dialkyl peroxides can be analysed by physical and instrumental methods as well as by chemical reduction procedures. Dialkyl peroxides are the most stable class of organic peroxides and chemical methods based on reduction procedures must take this into account.

(*i*) *Physical and instrumental methods*

(*a*) *Gas chromatography.* Primary, secondary, and tertiary dialkyl peroxides, usually $<C_{10}$ to avoid excessive decomposition, have been purified and/or analysed by gas chromatography. Di-t-butyl peroxide, for example, can be determined with a relative precision of ±0.3%; gas chromatography is the method of choice for this peroxide.[62] Gas chromatography can also be used as a pyrolytic decomposition technique for dialkyl peroxides; separation of volatile decomposition products serves both to identify and determine them quantitatively.

(*b*) *Liquid and column chromatography.* Liquid and column chromatography are useful for the separation and analysis of peroxides; dialkyl peroxides are the least readily adsorbed.[63] Normal and reverse-phase paper chromatography have been used to separate dialkyl peroxides from other classes.[24]

Thin layer chromatography has been used to separate and detect dialkyl peroxides in mixtures of various peroxides.[24] Dialkyl peroxides have the highest R_f values. The technique is used more frequently as a qualitative rather than a quantitative tool and it is extremely sensitive.

(*c*) *Electrometry.*[21,24] Dialkyl peroxides are more difficult to reduce polarographically than the other major peroxides, and conventional supporting electrolytes and solvents cannot be used for analysis. The negative potential range can be extended to −2.5 V (*vs.* saturated calomel electrode), well beyond the usual practical limit of −2.0 V, by using quaternary ammonium salts, typically tetraethylammonium bromide or chloride, and DMF as the solvent. In such systems, dialkyl peroxides can be readily determined but considerably more research is required before dialkyl peroxides can be routinely determined electrometrically.

(*ii*) *Chemical reduction methods*

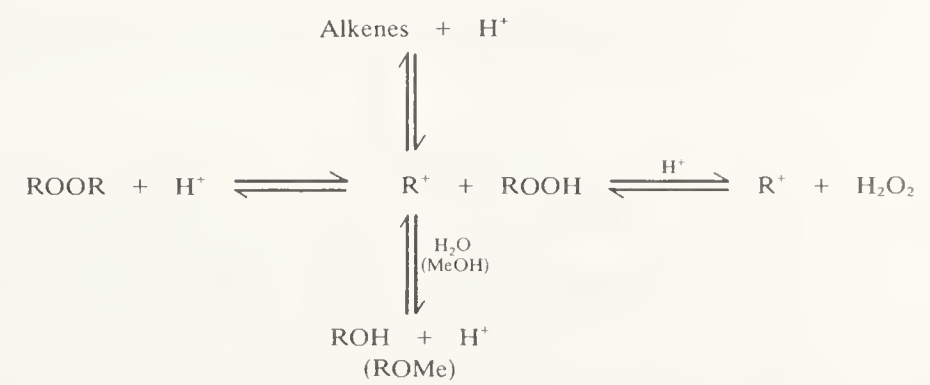
(*a*) *Iodide methods.*[24] Iodometric methods can be effectively used for the determination of peroxides that are difficult to reduce, provided more vigorous reducing conditions are employed than in the case of hydroperoxides already discussed. Reduction usually requires strong acids and elevated temperatures in the presence of sodium or potassium iodide.[64] The major side reaction is dehydration of certain alcohols followed by reduction of the olefins produced. α-Methylstyrene and α,α-dimethylbenzyl alcohol, for example, are reduced promptly and quantitatively; styrene and α-methylbenzyl alcohol are reduced more slowly and incompletely. Recommended iodide reduction procedures for specific dialkyl peroxides are available.[24]

(*b*) *Organic phosphine methods.*[24] Every class of organic peroxide is reported to be quantitatively reduced by tertiary phosphines.[65] Dialkyl peroxides are reduced rapidly at room temperature. Thus alkyl hydroperoxides can be readily determined in the presence of dialkyl peroxides,[65] and mixtures of easily reduced peroxides can be differentiated from the sluggishly reducible dialkyl peroxides.[66] Oxygen must be rigorously excluded in the phosphine methods.

4.6.2.8 Reactions of dialkyl peroxides

(*i*) *Heterolytic reactions*

(*a*) *Reactions with acids.*[50] Dialkyl peroxides react with strong mineral acids, activating a series of equilibrium processes (equation 82), especially if R^+ is a resonance-stabilized cation. In concentrated sulphuric acid, for example, di-t-butyl peroxide slowly yields polyisobutene, but in 50% methanolic sulphuric acid it produces high yields of t-butyl methyl ether. Trityl peroxide, on the other hand, when dissolved in sulphuric acid and the solution quenched in ice, yields triphenylcarbinol (92%) and no phenol or benzophenone. In media (hydrocarbons) that do not stabilize carbenium ions, however, t-butyl peroxide decomposes with rearrangement (equation 83).



(82)

$$Me_3C{-}O{-}O{-}CPh_3 \xrightarrow[H^+]{C_6H_6} Me_3COH + Ph_2C{=}O + PhOH \qquad (83)$$

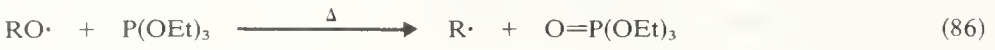
(*b*) *Reactions with bases.*[50] Primary and secondary dialkyl peroxides are sensitive to strong bases. The low yields obtained in the preparation of those peroxides can be ascribed to competing elimination and further condensations (equation 84). Reaction with base is second order and exhibits a primary deuterium isotope effect of about 6.

(84)

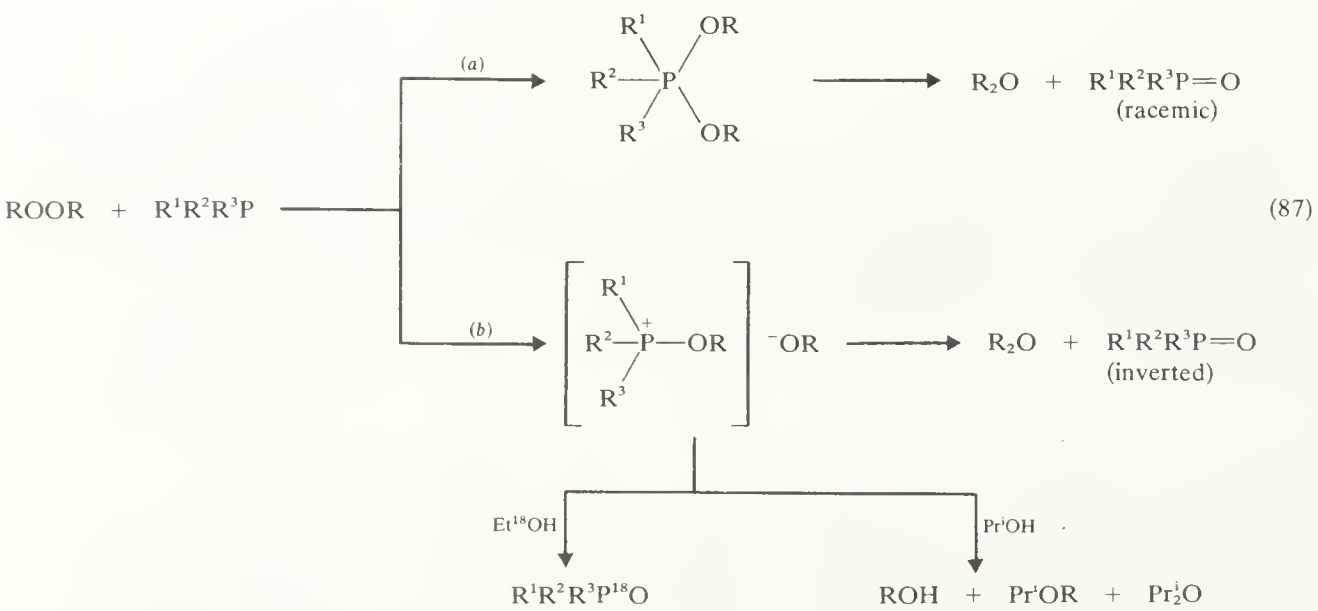
(85)

Many dialkyl peroxides react smoothly with phenylmagnesium bromide or phenyllithium in ether *via* S_N2 displacement on the —O—O— bond (equation 85). The reaction with di-t-alkyl peroxides is more complex and is both temperature and solvent dependent. With alkyl Grignard reagents, di-t-butyl peroxide undergoes competing elimination and etherification reactions; the ratio of these reactions depends on the Grignard reagent used. Some products derived from free radical intermediates are also observed and may become the major ones if a trace of manganous chloride is present.[67]

(*c*) *Reactions with organophosphorus compounds.*[50] Tertiary dialkyl peroxides do not undergo facile room-temperature oxygen abstraction observed with trialkyl phosphines or phosphites and hydroperoxides (equation 41). Di-t-butyl and dicumyl peroxides react only at temperatures at which —O—O— homolysis occurs (equation 86). Primary dialkyl peroxides, in contrast, undergo a slow displacement reaction at room temperature. Products are solvent dependent and their formation can be rationalized by pentacoordinate (pathway *a*) and phosphonium ion (pathway *b*) intermediates (equation 87).



(86)



(87)

(*ii*) *Homolytic reactions*

(*a*) *Thermolysis of the —O—O— bond.* Dialkyl peroxides decompose homolytically in the liquid or vapour phase at 100–180 °C. The reaction is one of the most convenient and

reliable sources of free radicals for initiating chain and other homolytic processes (equation 88).[68] Decompositions are almost invariably first order and little, if any, radical-induced decomposition or other side reactions accompany homolysis. An enormous body of rate data exists for both vapour and liquid decompositions.[50]

$$R^1OOR^2 \xrightarrow[\text{liquid or vapour phase}]{100\text{–}180\ ^\circ C} R^1O\cdot + \cdot OR^2 \qquad (88)$$

The fate of the alkoxy radicals initially formed depends on many factors (the environment, the temperature, the constitution of R, *etc.*) and several competing processes intervene. These include radical–radical combination or disproportionation, radical abstractions from or addition to available substrates, and alkoxy radical cleavage. In the vapour phase, for example, di-t-butyl peroxide (**56**) yields acetone and ethane as major products, as well as methane, methyl ethyl ketone, isobutene oxide, and other minor products (ethers and carbon monoxide) (equations 89–93). Dimethyl peroxide yields mainly methanol and carbon monoxide in a 3:1 ratio from $CH_3O\cdot$ disproportionation and successive attacks by it on formaldehyde and ·CHO. Other primary dialkyl peroxides yield aldehydes and alcohols along with carbon monoxide, formaldehyde, hydrocarbons, hydrogen, and carbon dioxide. Secondary dialkyl peroxides yield ketones mainly.

$$\underset{\textbf{(56)}}{Me_3COOCMe_3} \xrightarrow{\Delta} 2Me_3CO\cdot \longrightarrow \underset{\textbf{(57)}}{2Me_2C{=}O} + 2Me\cdot \qquad (89)$$

$$2Me\cdot \longrightarrow C_2H_6 \qquad (90)$$

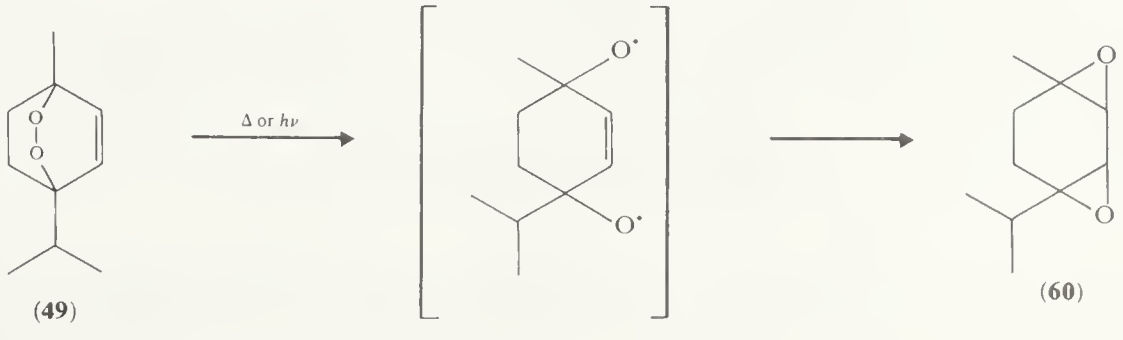
$$Me\cdot + \textbf{(57)} \longrightarrow CH_4 + \underset{\textbf{(58)}}{MeC(=O)CH_2\cdot} \qquad (91)$$

$$\textbf{(58)} + Me\cdot \longrightarrow MeC(=O)CH_2Me \qquad (92)$$

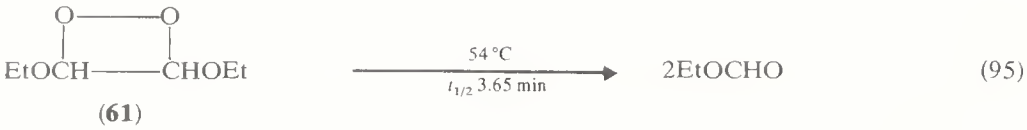
$$Me_3CO\cdot + R\cdot \longrightarrow \left[\begin{array}{l} Me_2CO\cdot \\ \quad | \\ \quad CH_2\cdot \end{array}\right] + RH \longrightarrow \underset{\textbf{(59)}}{\begin{array}{l} Me_2C \\ \quad \diagdown O \\ \quad \quad | \\ \quad \quad CH_2 \end{array}} \qquad (93)$$

In solution, many more reactions can occur. With di-t-butyl peroxide (**56**) the t-butanol:acetone ratio varies predictably, increasing as the hydrogen atom donating ability of the solvent increases. Ethane is formed only in trace amounts; methane and solvent dimers or addition products predominate.

Ascaridole (**49**) and other non-aromatic endoperoxides[69] form diepoxides (**60**) from intermediate diradicals (equation 94). 1,2-Dioxetans (**61**), stable enough to be isolated, readily undergo —O—O— and —C—C— bond cleavage (equation 95).

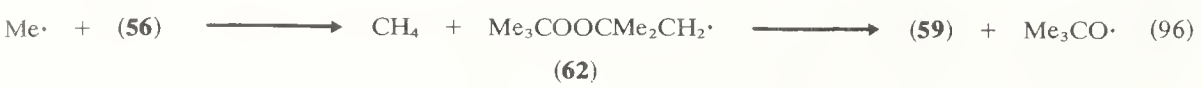


(49) (60) (94)



(61) (95)

(*b*) *Radical-induced decomposition.* Dialkyl peroxides exhibit two main types of radical-induced decomposition: hydrogen atom abstraction and S_H displacement on the —O—O— bond. One example of the former is attack by a methyl radical on di-t-butyl peroxide (**56**) in the vapour phase to yield methane and the radical (**62**), which goes on to form epoxide (**59**) and the t-butoxy radical (equation 96).[70] Chlorine atoms attack di-t-butyl peroxide (**56**) much more readily; a small quantity of hydrogen chloride is sufficient to produce a chain reaction accounting for all the decomposition (equations 97 and 98). Primary and secondary dialkyl peroxides are even more susceptible to self-induced decomposition.



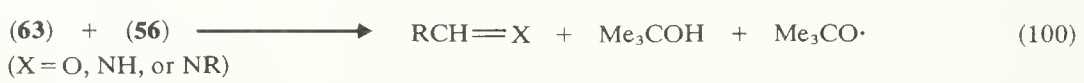
(96)

(97)

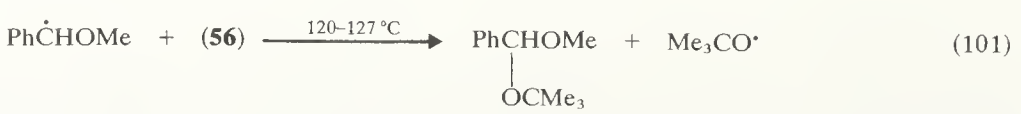
(98)

S_H-Type displacement reactions occur when peroxides are decomposed in certain solvents, notably primary and secondary alcohols, amines, and benzyl ethers. At 125–130 °C, di-t-butyl peroxide (**56**) decomposes two to five times as fast in such solvents as in a tertiary alcohol, tertiary amine, or alkyl ether analogue (equations 99 and 100). In benzyl ether solvents, the products are derived from carbon-radical displacement on the —O—O— bond (equation 101).

(99)

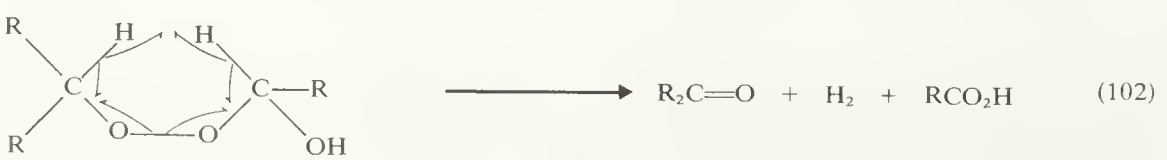


(100)

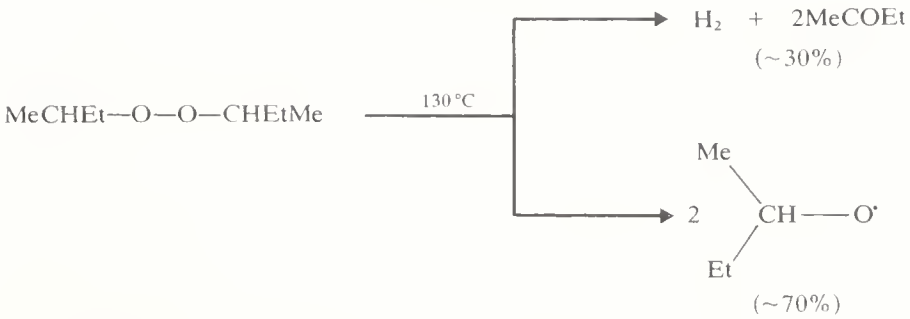


(101)

(*c*) *Hydrogen formation from dialkyl peroxides.* The production of hydrogen when certain peroxides are heated in inert solvents to temperatures sufficient for —O—O— homolysis occurs with hydroxymethylene peroxide [$HOCH_2$—O—O—CH_2OH], all alkylidene peroxides [RCH(OH)—O—O—CH(OH)R; RCH(OR)—O—O—CH(OR)R], semialkylidene peroxides [R_2CH—O—O—CH(OH)R], and secondary dialkyl peroxides. The key constitutional requirement for obtaining 30–80% yields of hydrogen, in competition with normal homolysis, is a hydrogen atom on each of the α-carbon atoms. A concerted mechanism has been proposed to account for the formation of hydrogen and other products (equation 102).[71] A primary isotope effect, $k_H/k_D = 4–5$, is observed. Simple dialkyl peroxides, such as s-butyl peroxide, behave similarly but homolysis (70%) predominates over hydrogen formation (30%) (equation 103).[72]



(102)



(103)

(*d*) *Oxygen formation from dialkyl peroxides.* Pyrolytic cleavage at the C—O bond, although uncommon, occurs when the driving force is rearomatization. Endoperoxides, such as those from anthracene, rubrene, or 9,10-diphenylanthracene, yield oxygen virtually quantitatively when pyrolysed neat at 60–150 °C.

(*e*) *Catalytic decomposition by metal ions.* Some of the reactions are complex but they can be classified roughly into three categories:

1. Metal ions that readily reduce alkoxy radicals produce alcohols, among other products (equation 104). The same reaction occurs with di-t-butyl peroxide (**56**) and Cu^+ ions, but the yield of acetone is much reduced over that in the absence of metal ion. In benzaldehyde solution at 130 °C in the presence of a trace of cuprous chloride, (**56**) yields t-butyl benzoate (83%) (equations 105–107). In the absence of the metal the major product is 1,2-diphenylethylene glycol dibenzoate.

$$Et—O—O—Et \xrightarrow{Fe^{2+}} MeCHO + EtOH \quad (104)$$

$$(\mathbf{56}) + Cu^+ \longrightarrow Me_3CO\cdot + [Me_3COCu]^{+\cdot} \quad (105)$$

$$PhCHO + Me_3CO\cdot \longrightarrow Me_3COH + Ph\dot{C}{=}O \quad (106)$$

$$Ph\dot{C}{=}O + [Me_3COCu]^{+\cdot} \longrightarrow PhC(=O)OCMe_3 + Cu^+ \quad (107)$$

2. Tertiary alkoxy radicals that cleave rapidly yield alkenes.
3. With oxidizing ions, typically Cu^{2+} ions, primary and secondary dialkyl peroxides give mixtures of alcohols and carbonyls.

The catalytic effect of metals on decomposition of di-t-alkyl peroxides is only modest, in contrast to the effect on hydroperoxides. Rate enhancements with copper salts at 110–140 °C, for example, range from three- to ten-fold.

4.6.2.9 Economic aspects

Dialkyl peroxides are used to a limited extent as radical initiators in the polymerization and copolymerization of vinyl and diene monomers, as cross-linking agents for polyhydrocarbons, rubbers, and elastomers, and as curing agents for resins and elastomers, among many miscellaneous applications.

4.6.3 PEROXIDE POLYMERS AND COPOLYMERS[50]

Polymeric alkyl peroxides have the general structural formula $(—\overset{|}{\underset{|}{C}}—\overset{|}{\underset{|}{C}}—O—O—)_n$; they are frequently referred to as polyperoxides, poly(alkylene) peroxides, or alkene–oxygen copolymers.

4.6.3.1 Autoxidation of polymerizable alkenes and dienes

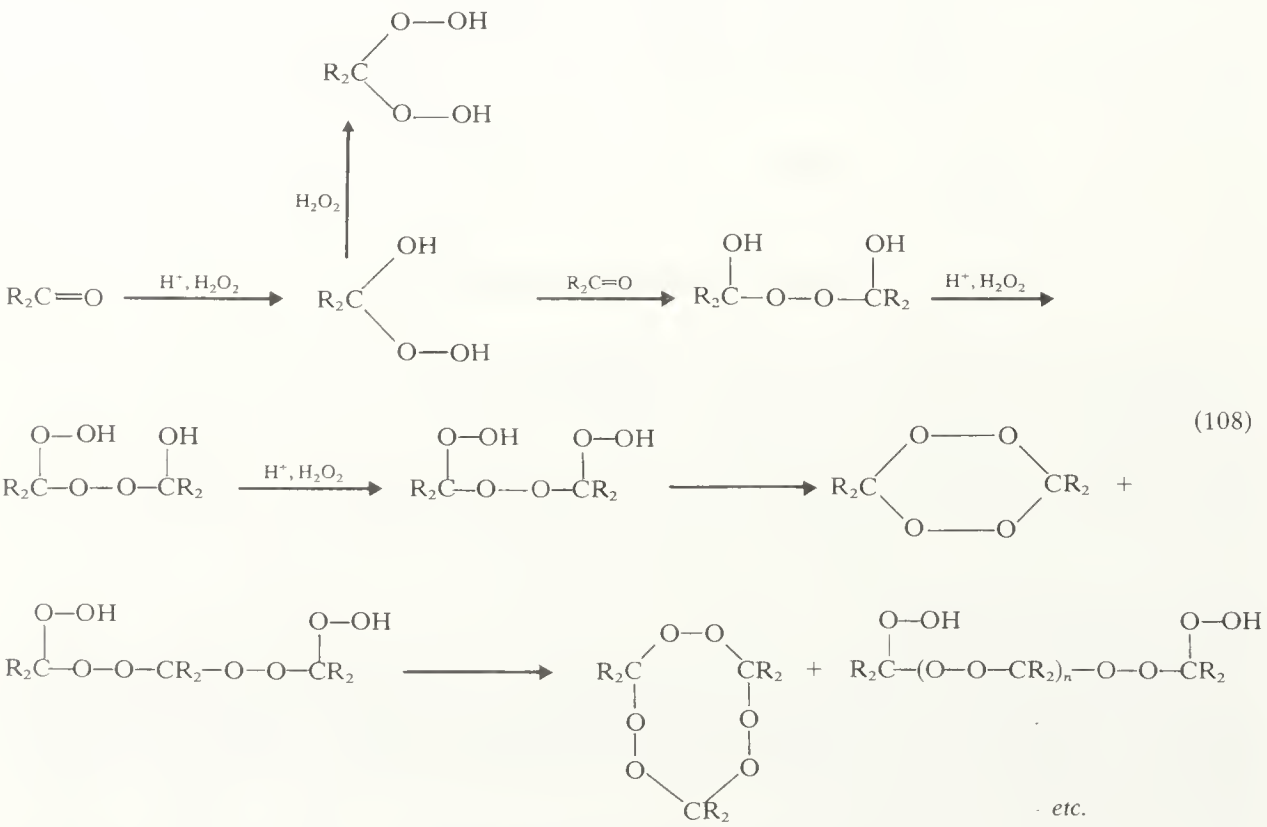
Alkenes that polymerize or copolymerize readily, such as styrene, α-methylstyrene, indene, and others, form polyperoxides by a chain reaction.[73] Homolytic thermal decomposition of the polyperoxides from styrene and oxygen yields benzaldehyde and formaldehyde by β-scission; the decomposition is also a chain process.

Dimethyl-, diethyl-, and diphenyl-keten react with oxygen at −70 °C to form polyperoxides of low stability. Those from diphenylketen decompose at −70 °C to benzophenone and formaldehyde; the others are unstable above about −20 °C.

Polymerizable dienes, such as butadiene and isoprene, behave similarly, giving 1:1 copolymers with oxygen in which 1,2- and 1,4-unsaturated linkages are randomly distributed. Esters of long-chain conjugated fatty acids are autoxidized to form complex mixtures containing both hydroperoxides and polyperoxides.

4.6.3.2 Ketone peroxides

Although not polymeric in the conventional sense, linear and cyclic dimeric, trimeric, and tetrameric peroxides are best discussed here. Reaction of hydrogen peroxide with carbonyl compounds, especially ketones, in the presence of catalytic quantities of strong acids yields complex mixtures of linear and cyclic peroxides in equilibrium. Ketone peroxides are possibly the most hazardous class of organic peroxides and often explode when heated, touched, or ground, although they may have good stability and be safe to handle in dilute solution. Equation (108) illustrates some of the reactions involved in the preparation of ketone peroxides.[1]



(108)

Chromatographic techniques have been used to separate at least seven of the peroxides shown in equation (108).[74] Ketones studied include acetone, methyl ethyl ketone, diethyl ketone, cyclohexanone, cycloheptanone, and other cyclic ketones.

Decomposition of dimeric and trimeric cyclic ketone peroxides in methanol or benzene yields macrocyclic hydrocarbons and lactones by photolytic and thermolytic homolysis.[75] The procedure is probably the best way to obtain hitherto inaccessible macrocycles.

4.6.3.3 Physical and chemical properties

Polymeric peroxides derived from olefinic monomers and oxygen are usually viscous liquids or amorphous white powders containing up to about ten repeat units. They usually explode on heating but thermal or photochemical decomposition in solution yields two carbonyl compounds as the major products, indicating cleavage of —O—O— and —C—C— bonds. Decomposition in the presence of acids or bases gives products similar to those of thermal decomposition (—O—O— cleavage) of primary and secondary dialkyl peroxides. If the initially formed carbonyl compounds are base-sensitive they are converted to other complex products.

Polymeric peroxides are apparently reduced more easily than conventional dialkyl peroxides by hydrogen iodide, zinc, or tin plus acid, hydrogen and catalysts, lithium aluminium hydride, and other reducing agents.

4.6.4 SAFETY AND HEALTH HAZARDS[76,77]

Many organic peroxides decompose violently when ground, heated, ignited, or subjected to mechanical shock. The stored potential energy is low compared with that of conventional explosives but it is high enough to be very destructive. Although all organic peroxides must be considered to be potentially hazardous, the first members of each series are the most dangerous as they contain the highest percentage of peroxide oxygen. However, every new peroxide should be handled with care regardless of its active oxygen content. A maximum of one gram, but preferably less, should be prepared initially with appropriate shielding and handling faculties.

Since peroxide decomposition is accelerated on heating, peroxides should be stored in cool, dark areas. When peroxides are used on a large scale, storage containers should have adequate space between them to dissipate heat if a spontaneous but initially slow autocatalytic decomposition is initiated. The contents of a container of organic peroxide should be utilized completely after the container is opened or, if only a portion is used, the remainder should be disposed of. The introduction of adventitious impurities that catalyse runaway decomposition in a partially used container of peroxide is too risky. Peroxides that decompose slowly but spontaneously with gas evolution should be vented using a device that prevents the entry of impurities.

Except for peroxides that are stable only at low temperatures, excessively low storage temperatures may actually increase the hazard. If cooling a liquid peroxide or solution causes crystallization of a hazardous peroxide or separation into two liquid phases, one of which is almost certain to be more impact-sensitive than the original liquid or solution, the hazard may increase manyfold. In general, low volatility solvents should be used for the storage of solutions of organic peroxides so that unanticipated large increases in peroxide concentration will not occur.

Numerous tests for the thermal, mechanical, ignition, and impact sensitivity of organic peroxides are available.[76]

Many organic peroxides are prepared from concentrated (50–98%) hydrogen peroxide. A useful guideline in designing safe reaction conditions is to avoid the preparation or handling of solutions or mixtures that contain organic matter and a hydrogen peroxide concentration exceeding about 70%, but preferably lower.

Some organic peroxides are powerful eye and skin irritants. Eye and body protection should always be worn when working with organic peroxides; the work should be conducted in an efficient fume cupboard (fume hood). Although the toxicity of many organic peroxides is not extremely high, ingestion should be avoided. Spills on clothing increase fire hazards.

Manufacturers of organic peroxides and hydrogen peroxide distribute literature on safe handling practices and health hazards at no cost. Such material should be carefully studied before any work with peroxides is initiated. The single most important safety factor in working with organic peroxides in the laboratory is to work on the smallest possible scale.

In the plant, peroxides (and hydrogen peroxide) should be stored in separate areas from other organic compounds.

In spite of their hazardous nature, peroxides are widely used in industry on a large scale and the safety record is highly commendable. The price of safety is eternal vigilance!

References

1. R. Hiatt, in 'Organic Peroxides', ed. D. Swern, Wiley-Interscience, New York, 1971, vol. II, chapter 1, and references therein.
2. J. Rouchaud, *Bull. Soc. chim. belges*, 1967, **76,** 171.
3. W. H. Richardson and R. F. Steed, *J. Org. Chem.*, 1967, **32,** 771.
4. C. Walling and S. A. Buckler, *J. Amer. Chem. Soc.*, 1955, **77,** 6032.
5. H. Hock and F. Ernst, *Chem. Ber.*, 1959, **92,** 2716, 2723.
6. G. Wilke and P. Heimbach, *Annalen*, 1962, **652,** 7.
7. A. Baeyer and V. Villiger, *Ber.*, 1901, **34,** 738.
8. H. R. Williams and H. S. Mosher, *J. Amer. Chem. Soc.*, 1954, **76,** 2984, 2987.
9. S. Wawzonek, P. D. Klimstra, and R. E. Kallio, *J. Org. Chem.*, 1960, **25,** 621.
10. S. Dykstra and H. S. Mosher, *J. Amer. Chem. Soc.*, 1957, **79,** 3474.
11. A. G. Davies, R. V. Foster, and A. M. White, *J. Chem. Soc.*, 1953, 1541; 1954, 2200.
12. A. G. Davies and R. Feld, *J. Chem. Soc.*, 1956, 4669.
13. A. G. Davies, *J. Chem. Soc.*, 1962, 4288.
14. A. Rieche, E. Schmitz, and E. Beyer, *Chem. Ber.*, 1958, **92,** 1212.
15. E. Höft and A. Rieche, *Angew. Chem. Internat. Edn.*, 1965, **4,** 524.
16. A. Rieche, *Angew. Chem.*, 1958, **70,** 251.
17. M. S. Kharasch and G. N. Sosnovsky, *J. Org. Chem.*, 1958, **23,** 1322.
18. V. L. Antonovskii and V. A. Terent'ev, *Zhur. fiz. Khim.*, 1966, **40,** 3078.
19. N. A. Milas and A. Golubovic, *J. Amer. Chem. Soc.*, 1959, **81,** 6461.
20. N. A. Milas and A. Golubovic, *J. Amer. Chem. Soc.*, 1959, **81,** 5824.
21. L. S. Silbert, in 'Organic Peroxides', ed. D. Swern, Wiley-Interscience, New York, 1971, vol. II, chapter 7, and references therein.
22. D. Swern, A. H. Clements, and T. M. Luong, *Anal. Chem.*, 1969, **41,** 412.
23. A. R. Burgess, R. D. G. Lane, and D. K. Sen Sharma, *J. Chem. Soc. (B)*, 1969, 341.
24. R. D. Mair and R. T. Hall, in 'Organic Peroxides', ed. D. Swern, Wiley-Interscience, New York, 1971, vol. II, chapter 6, and references therein.
25. L. Dulog, *Z. anal. Chem.*, 1964, **202,** 192.
26. G. Sorge and K. Ueberreiter, *Angew. Chem.*, 1956, **68,** 486.
27. F. W. Heaton and N. Uri, *J. Sci. Food Agric.*, 1958, **9,** 781.
28. D. K. Banerjee and C. C. Budke, *Anal. Chem.*, 1964, **36,** 792.
29. J. O. Edwards and R. G. Pearson, *J. Amer. Chem. Soc.*, 1963, **84,** 16.
30. V. L. Antonovskii and V. A. Terent'ev, *Zhur. org. Khim.*, 1967, **3,** 1011.
31. A. G. Davies, R. V. Foster, and R. Nery, *J. Chem. Soc.*, 1954, 2204.
32. G. Burtzlaff, U. Felber, H. Hubner, W. Pritzkow, and W. Rolle, *J. prakt. Chem.*, 1965, **28,** 305.
33. G. H. Anderson and J. G. Smith, *Canad. J. Chem.*, 1968, **46,** 1553.
34. J. O. Turner, *Tetrahedron Letters*, 1971, 887.
35. H. E. De La Mare and G. M. Coppinger, *J. Org. Chem.*, 1963, **28,** 1068.
36 N. Kornblum and H. E. De La Mare, *J. Amer. Chem. Soc.*, 1951, **73,** 880.
37. E. S. Gould, R. Hiatt, and K. C. Irwin, *J. Amer. Chem. Soc.*, 1968, **90,** 4573.
38. M. N. Sheng and J. G. Zajacek, *J. Org. Chem.*, 1968, **33,** 588.
39. L. Kuhnen, *Angew. Chem. Internat. Edn.*, 1966, **5,** 893.
40. A. Factor, C. A. Russell, and T. G. Traylor, *J. Amer. Chem. Soc.*, 1965, **87,** 3692.
41. T. G. Traylor and P. D. Bartlett, *Tetrahedron Letters*, 1960, [24], 30.
42. R. Hiatt, T. Mill, K. C. Irwin, and J. K. Castleman, *J. Org. Chem.*, 1968, **33,** 1428.
43. G. A. Russell, *J. Amer. Chem. Soc.*, 1957, **79,** 3871.
44. C. F. Cullis, A. Fish, A. Saeed, and D. L. Trimm, *Proc. Roy. Soc.*, 1966, **A289,** 402.
45. A. Fish, in 'Organic Peroxides', ed. D. Swern, Wiley-Interscience, New York, 1970, vol. I, chapter 3, and references therein.
46. R. Hiatt, T. Mill, and F. R. Mayo, *J. Org. Chem.*, 1968, **33,** 1416.
47. R. Hiatt, K. C. Irwin, and C. W. Gould, *J. Org. Chem.*, 1968, **33,** 1430.
48. A. Rieche, C. Bischoff, and D. Prescher, *Chem. Ber.*, 1964, **97,** 3071.
49. R. H. Hall, in 'Basic Organic Chemistry. Industrial Products', ed. J. M. Tedder, A. Nechvatal, and A. H. Jubb, Wiley, London, 1975, chapter 5.
50. R. Hiatt, in 'Organic Peroxides', ed. D. Swern, Wiley-Interscience, New York, 1972, vol. III, chapter 1, and references therein.

50a. M. F. Salomon, R. G. Salomon, and R. D. Glein, *J. Org. Chem.*, 1976, **41,** 3983.

51. H. Hock and H. Kropf, *Chem. Ber.*, 1955, **88,** 1544.

52. H. Kropf, C.-R Bernert, and L. Dahlenburg, *Tetrahedron*, 1970, **26,** 3279.
53. J. K. Kochi, *J. Amer. Chem. Soc.*, 1962, **84,** 2785.
54. M. Schulz and K. Kirschke, in 'Organic Peroxides', ed. D. Swern, Wiley-Interscience, New York, 1972, vol. III, chapter 2, and references therein.
55. O. L. Magelli and C. S. Sheppard, in 'Organic Peroxides', ed. D. Swern, Wiley-Interscience, New York, 1970, vol. I, chapter 1, and references therein.
56. P. D. Bartlett and A. P. Schaap, *J. Amer. Chem. Soc.*, 1970, **92,** 3223.
57. G. Sosnovsky and J. H. Brown, *Chem. Rev.*, 1966, **66,** 529.
58. H. L. Roberts, *J. Chem. Soc.*, 1964, 4538.
59. R. L. Talbott, *J. Org. Chem.*, 1968, **33,** 2095.
60. D. H. Ballard, A. J. Bloodworth, and R. J. Bunce, *Chem. Comm.*, 1969, 815.
61. W. Lobunez, J. R. Rittenhouse, and J. G. Miller, *J. Amer. Chem. Soc.*, 1958, **80,** 3505.
62. S. W. Bukata, L. L. Zabrocki, and M. F. McLaughlin, *Anal. Chem.*, 1963, **35,** 885.
63. W. Eggersglüs, 'Organische Peroxyde', Verlag Chemie, Weinheim, 1951.
64. R. D. Mair and A. J. Graupner, *Anal. Chem.*, 1964, **36,** 194.
65. L. Horner and W. Jurgeleit, *Annalen*, 1955, **591,** 138.
66. L. Dulog and K. H. Burg, *Z. anal. Chem.*, 1964, **203,** 184.
67. S. Herbstman, *Diss. Abs.*, 1964, **24,** 3096.
68. C. Walling, 'Free Radicals in Solution,' Wiley, New York, 1957.
69. K. H. Maheshwari, P. de Mayo, and D. Wiegand, *Canad. J. Chem.*, 1970, **48,** 3265.
70. L. Batt and S. W. Benson, *J. Chem. Phys.*, 1962, **36,** 895.
71. L. J. Durham and H. S. Mosher, *J. Amer. Chem. Soc.*, 1962, **82,** 4537; 1964, **84,** 2811.
72. R. Hiatt and S. Szilagyi, *Canad. J. Chem.*, 1970, **48,** 615.
73. F. R. Mayo, *J. Amer. Chem. Soc.*, 1958, **80,** 2465.
74. N. A. Milas and A. Golubovic, *J. Amer. Chem. Soc.*, 1959, **81,** 5824.
75. P. R. Story, D. D. Denson, C. E. Bishop, B. C. Clark, and J. C. Farine, *J. Amer. Chem. Soc.*, 1968, **90,** 817; *Chem. Eng. News*, 1968, **46,** 20.
76. E. S. Shanley, in 'Organic Peroxides', ed. D. Swern, Wiley-Interscience, New York, 1972, vol. III, chapter 5, and references therein.
77. E. P. Floyd and H. E. Stokinger, *J. Amer. Ind. Hygiene Assoc.*, 1958, **19,** 205.

PART 5

ALDEHYDES AND KETONES

5.1
Aldehydes

R. BRETTLE
University of Sheffield

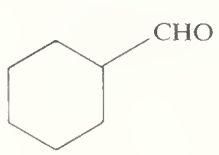
5.1.1 INTRODUCTION 944
5.1.1.1 Nomenclature 944
5.1.1.2 Structure and bonding 944
5.1.1.3 Conformations 946
5.1.1.4 Naturally occurring aldehydes 946
5.1.2 PREPARATION OF NON-CONJUGATED ALDEHYDES 947
5.1.2.1 From alcohols and their derivatives 947
5.1.2.2 From nitroalkanes 947
5.1.2.3 From oxirans 947
5.1.2.4 From carboxylic acids and their derivatives 948
5.1.2.5 From alkynes 948
5.1.2.6 From organoboranes 948
5.1.2.7 By hydroformylation and related reactions 948
5.1.2.8 From Grignard reagents 949
5.1.2.9 Through dihydro-oxazines and related heterocyclic systems 950
5.1.2.10 From 1,3-dithians and other sulphur-containing formyl carbanion equivalents 950
5.1.2.11 By the Wittig and related reactions 950
5.1.2.12 By the α-alkylation of aldehydes 950
5.1.2.13 From α,β-olefinic aldehydes 953
5.1.2.14 By oxidative degradation 953
5.1.2.15 Some industrial aldehyde syntheses 954
5.1.3 PHYSICAL AND SPECTROSCOPIC PROPERTIES OF ALDEHYDES 954
5.1.3.1 Physical properties 954
5.1.3.2 Infrared spectra 954
5.1.3.3 Ultraviolet spectra 955
5.1.3.4 Nuclear magnetic resonance spectra 955
5.1.3.5 Mass spectra 956
5.1.4 OXIDATION, REDUCTION, AND DECARBONYLATION OF ALDEHYDES 956
5.1.4.1 Oxidation 956
5.1.4.2 Reduction 958
5.1.4.3 Decarbonylation 959
5.1.5 ADDITIONS OF ALDEHYDES 960
5.1.5.1 Oxygen and sulphur nucleophiles 961
5.1.5.2 Carbon nucleophiles 963
5.1.5.3 Nitrogen nucleophiles 973
5.1.5.4 Other reactions 974
5.1.6 OLEFINIC ALDEHYDES 979
5.1.6.1 Preparation 979
5.1.6.2 Reduction of conjugated olefinic aldehydes 992
5.1.6.3 Cycloadditions of conjugated aldehydes 993
5.1.6.4 Other additions of conjugated aldehydes 995

5.1.7 SOME HALOGENATED COMPOUNDS 1000
5.1.7.1 α-Monohalogen-substituted aldehydes 1000
5.1.7.2 β-Haloalk-2-enals 1002
5.1.7.3 1-Alkoxy-1-chloroalkanes 1002
5.1.8 HYDROXYALDEHYDES 1002
5.1.8.1 α-Hydroxyaldehydes 1002
5.1.8.2 β-Hydroxyaldehydes 1004
5.1.8.3 γ- and δ-hydroxyaldehydes 1004
5.1.8.4 Polyhydroxyaldehydes 1005
5.1.9 DIALDEHYDES 1007
5.1.9.1 Glyoxal 1007
5.1.9.2 Malondialdehydes 1007
5.1.9.3 1,4-Dialdehydes 1008
5.1.9.4 Other dialdehydes 1009
5.1.9.5 General reactions of dialdehydes 1010

5.1.1 INTRODUCTION

5.1.1.1 Nomenclature

Simple aliphatic aldehydes are named according to the IUPAC rules by adding the suffix '-al' to the name of the hydrocarbon containing the same number of carbon atoms, with the elision of the final 'e'. However, many aldehydes continue to be named using an older system which emphasizes the relationship between an aldehyde and its oxidation product, a carboxylic acid. In this system the semi-trivial name for the related acid is taken and the ending '-ic acid' is replaced by 'aldehyde'. For example, ethanal is still frequently called acetaldehyde. An alternative system of nomenclature, and the one normally adopted for simple alicyclic aldehydes, adds the suffix 'carbaldehyde' to the name of the hydrocarbon containing one less carbon atom than the aldehyde; thus (**1**) is cyclohexanecarbaldehyde. In the naming of polyfunctional compounds, in which the aldehyde function is not considered to be the principal one, the group —CHO, the formyl group, is denoted by the prefix 'formyl'. Several well-known aldehydes have trivial names, *e.g.* chloral (**2**) and acrolein (**3**), or systematic names, *e.g.* retinal, *i.e.* vitamin A aldehyde (**4**), which give no indication of their structures.



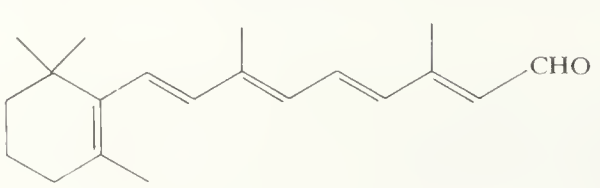
(**1**)

CCl_3CHO

(**2**)

$CH_2{=}CH{-}CHO$

(**3**)



(**4**)

5.1.1.2 Structure and bonding

In an aldehyde the three atoms attached to the central trigonal atom (*viz.* the oxygen atom, the hydrogen atom, and a carbon atom) together with the trigonal carbon atom all

lie in one plane. The bond angles relating the atoms attached to the trigonal atom are all close to 120°. The bond lengths and bond angles for the zero-point average structure of ethanal[1] are shown in Figure 1. The C—C bond length is less than that for a single bond in a saturated system but more than that for the central bond in a conjugated system. Figure 2 illustrates the situation[2] for the α,β-olefinic aldehyde propenal, in which all the atoms are essentially coplanar.

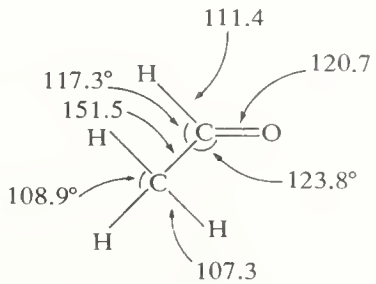


Figure 1 Bond angles and bond lengths (pm) in ethanal

In the carbonyl group there is a very large difference in electronegativity between the carbon and oxygen atoms. This is reflected in the large dipole moments of simple aldehydes, *e.g.* for methanal (formaldehyde) in the gas phase it is 7.7×10^{-30} C m. The electrons involved in the >C=O bond are very unequally shared, and aldehydes are highly polar molecules. The bonding in the carbonyl group is usually described qualitatively in terms of a double bond having both a σ- and a π-component, with two pairs of non-bonding (n) electrons on the oxygen atom; the trigonal carbon atom is considered to be hybridized in the sp^2 state, and forms σ-bonds to a hydrogen and another carbon atom. The unequal distribution of the electrons in the carbonyl group can be depicted in terms of simple resonance theory by means of the two canonical structures shown in

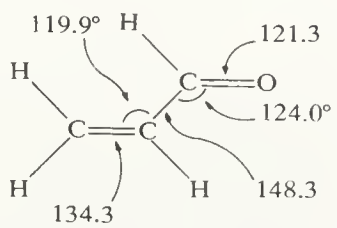


Figure 2 Bond angles and bond lengths (pm) in propenal

Figure 3. In the qualitative molecular orbital picture the overlap of the p-orbitals on the carbon and oxygen atoms to produce the π-bond leads to (i) a bonding (π) molecular orbital which is nearer in energy to that of the oxygen atomic orbital and in which the charge distribution between the two atoms is unsymmetrically distributed in favour of the oxygen atom, and (ii) an antibonding (π^*) molecular orbital of higher energy which is closer in energy to that of the carbon atomic orbital. Theoretical treatments of the simple carbonyl group abound, and the σ,π-model of the carbon–oxygen double bond is not the only valid approach.

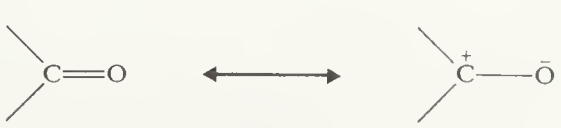
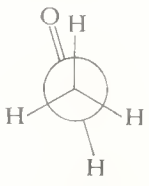


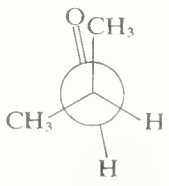
Figure 3 The resonance picture of the carbonyl group

5.1.1.3 Conformations

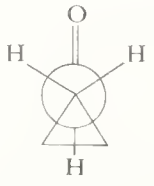
Although all the atoms in methanal are coplanar, this is not the case in its higher homologues. In these aldehydes, different conformations are possible as a result of torsion about the C-1—C-2 bond.[3] The preferred conformation for ethanal in the gas phase is the eclipsed conformation (**5**); the three-fold energy barrier for torsion about the C-1—C-2 bond has a value of 4.6 kJ mol^{-1}. For propanal and 2-methylpropanal the preferred conformation in each case is one in which the carbon–oxygen double bond is eclipsed by a methyl group. The conformation (**6**) of 2-methylpropanal is populated to the extent of ~90% and the other populated conformer is the one in which the >C=O group is eclipsed by a hydrogen atom. However, in 3,3-dimethylbutanal the t-butyl group prefers to be anticlinal to the carbonyl group, which is eclipsed by a hydrogen atom. The two conformers (**7**) and (**8**) of cyclopropanecarbaldehyde are almost equally populated and there is a two-fold and not a three-fold torsional barrier. α,β-Olefinic aldehydes usually exist mainly in the *s-trans*-conformation (**9**).



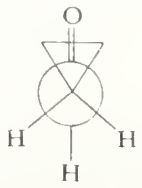
(5)



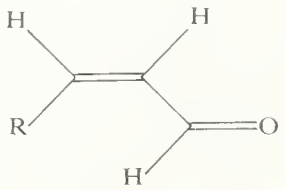
(6)



(7)



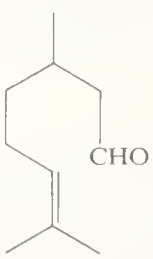
(8)



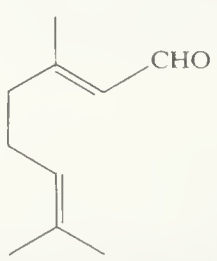
(9)

5.1.1.4 Naturally occurring aldehydes

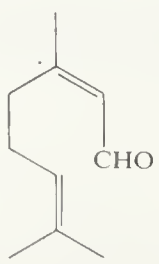
Several aldehydes are important in perfumery. In recent years these have come from technical syntheses as well as from the traditional essential oils, such as Citronella and Lemongrass oils. Citronellal is the monoterpene (**10**); both the (*R*)-(+)- and (*S*)-(−)-forms occur naturally. Citral exists as (*E*)- and (*Z*)-forms known as citral a (**11**) and citral b (**12**), respectively. The mixture is used in perfumery and in flavourings and is an important intermediate in the manufacture of α-ionone, another perfumery material, and of β-ionone, which is the starting point for the manufacture of vitamin A and the related food-colouring matter and provitamin A (ε-apo-8′-carotenal, **13**). The characteristic flavours of many common fruits, for example soft fruits, are due to the presence of small quantities of saturated and unsaturated aldehydes, together with other components such as alcohols and ketones.[4] For example, one of three compounds responsible for the aroma of the bilberry is (*E*)-hex-2-enal, which is present at a level of 0.3 p.p.m. in the unprocessed juice.



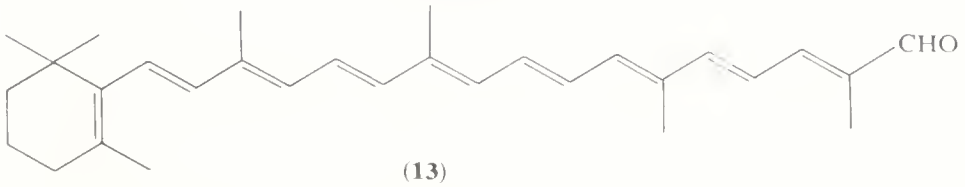
(10)



(11)



(12)



(13)

The sex-attractant pheromones of several species of Lepidoptera are straight chain non-conjugated olefinic aldehydes.[5]

5.1.2 PREPARATION OF NON-CONJUGATED ALDEHYDES

Review articles[6] covering aldehyde syntheses appeared in 1954 and 1966.

5.1.2.1 From alcohols and their derivatives

Aldehydes (from *al*cohol *dehyd*rogenatum), although themselves oxidizable to carboxylic acids, can be prepared by the oxidation of primary alcohols. In recent years several excellent selective reagents based on chromium(VI) have been developed. The oxidation can also be effected by systems based on combinations of dimethyl sulphoxide and a carbodi-imide. Details are given in Section 4.1.1.

Primary alcohol derivatives, *e.g.* toluene-*p*-sulphonates and chloroformates, can also be oxidized to aldehydes by DMSO[7] and primary bromides are oxidized to aldehydes at room temperature by DMSO with silver ion catalysis.[8]

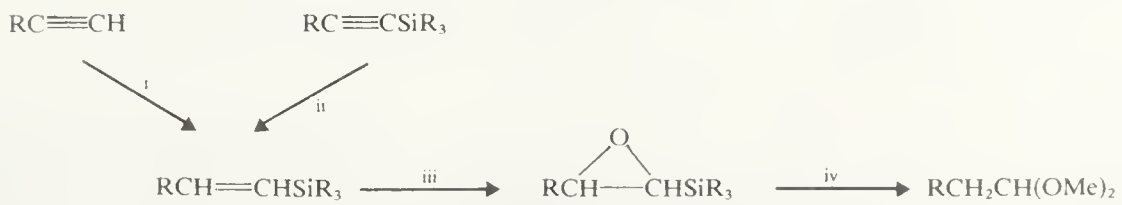
5.1.2.2 From nitroalkanes

Primary nitroalkanes are converted by the Nef reaction[9] into aldehydes on treatment of their alkali metal salts with concentrated mineral acids. The reduction of primary nitroalkanes or their anions with aqueous titanium(III) chloride gives the aldehyde[10] and may succeed where the Nef reaction fails.[11] Ozonolysis of the alkali metal salt of a primary nitroalkane also gives the aldehyde.[12]

5.1.2.3 From oxirans

2-Alkyl- or 2,2-dialkyl-oxirans, available for example from olefins or ketones, rearrange under the influence of Lewis acids to give aldehydes. The decarboxylative rearrangement of glycidic acids (α,β-epoxy acids) having no α-alkyl substituent leads to aldehydes. The acids can be obtained by careful hydrolysis of the corresponding glycidic esters, available through the Darzens condensation;[13] the use of the t-butyl chloroester in the Darzens condensation permits direct pyrolysis of the product to give the aldehyde.

Trialkylsilyl-substituted oxirans, prepared by the epoxidation of vinylsilanes, rearrange under acid conditions to give aldehydes, isolable as derivatives.[14] An example is shown in Scheme 1.



i, R_3SiH; ii, H_2, Lindlar's catalyst; iii, *m*-$ClC_6H_4CO_3H$; iv, MeOH, H^+.

SCHEME 1

5.1.2.4 From carboxylic acids and their derivatives

The synthesis of aldehydes by the partial reduction of carboxylic acid derivatives with complex aluminium hydrides has recently been reviewed.[15]

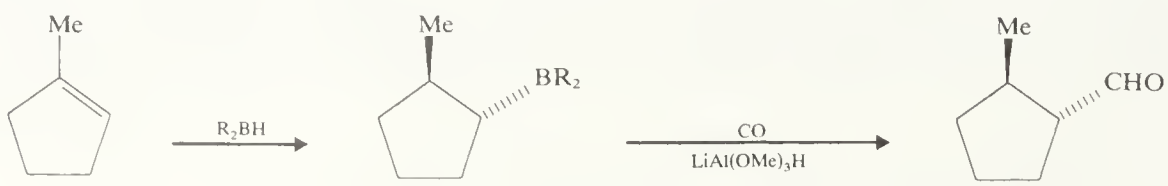
Carboxylic acids themselves can be reduced to aldehydes by diaminoaluminium hydrides,[16] *e.g.* bis-(4-methyl-1-piperazinyl)aluminium hydride, but more commonly acid derivatives have been reduced. Methyl esters are reduced to aldehydes by diaminoaluminium hydrides[17] and sodium bis-(methoxyethoxy)aluminium hydride,[15] and phenyl esters by lithium tri(t-butoxy)aluminium hydride.[15] Mixed carboxylic ethylcarbonic anhydrides are reduced to aldehydes by disodium tetracarbonylferrate,[18] and acylmalonic esters can be reduced by sodium borohydride under conditions such that *retro*-aldol fission of the product leads directly to the aldehyde.[19] Acyl chlorides can be reduced to aldehydes by lithium tri(t-butoxy)aluminium hydride[15] or by catalytic hydrogenolysis (the Rosenmund reduction).[20] Thiol esters, RCOSR, are reduced to aldehydes by treatment with Raney nickel.[21] Quite a variety of tertiary amides has been reduced to aldehydes with lithium aluminium hydride,[15] but more recently the simple *N,N*-dimethylamides have been used with lithium bis(ethoxy)aluminium hydride or another alkoxyaluminium hydride as the reductant.[15] A nitrile can be transformed into an aldehyde directly by reduction with a lithium tri(alkoxy)aluminium hydride,[15] and indirectly by conversion into an *N*-alkylnitrilium salt which is reduced by triethylsilane to the *N*-alkylaldimine and subsequently hydrolysed.[22]

5.1.2.5 From alkynes

The hydroboration of an alk-1-yne with a hindered borane, followed by oxidative rearrangement of the resultant vinylborane with alkaline hydrogen peroxide, leads to an aldehyde by anti-Markownikov hydration of the triple bond.[22]

5.1.2.6 From organoboranes

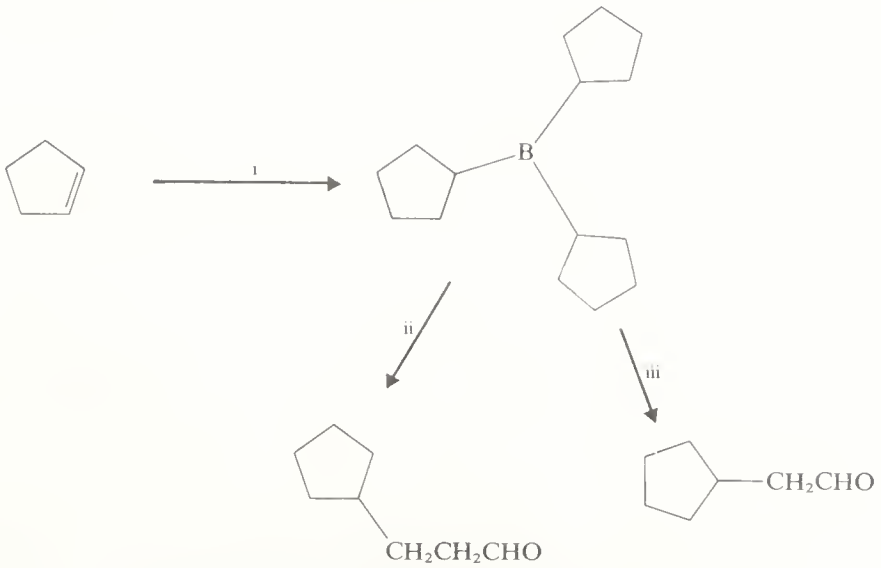
Trialkylboranes are available from the hydroboration of olefins and can be converted into aldehydes by several routes.[22] A single carbon atom can be introduced by the reaction of the trialkylborane with carbon monoxide under pressure in the presence of lithium trimethoxyaluminium hydride. Only one of the alkyl groups appears in the aldehyde; if the initial hydroboration of the olefin is performed with 9-borabicyclo[3,3,1]nonane it is the 9-alkyl group, derived from the olefin, which appears. The reaction proceeds with retention of configuration (equation 1). Reaction with diazoacetaldehyde introduces two carbon atoms, and reaction with acrolein and methylacrolein results in the transfer of one alkyl group to the β-position (see Scheme 2). The last reaction also works with crotonaldehyde in the presence of oxygen or diacetyl peroxide as radical catalysts.



(1)

5.1.2.7 By hydroformylation and related reactions

Olefins give aldehydes on treatment with carbon monoxide and hydrogen under pressure at elevated temperatures in the presence of octacarbonyldicobalt[23] (see equation 2). Hydroformylation can also be effected with platinum and rhodium catalysts.



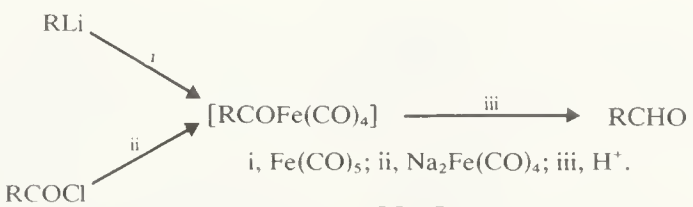
i, B_2H_6; ii, CH_2=CHCHO, H_2O: iii, N_2CHCHO.

SCHEME 2

Using hydridotrichlorostannatocarbonylbis(triphenylphosphine)platinum(II), pent-1-ene gives >95% of the straight-chain aldehyde, hexanal.[24] Hydroformylation with a rhodium-based catalyst involves the *syn* addition of H and CHO to the carbon–carbon double bond.[25]

$$RCH{=}CH_2 + CO + H_2 \xrightarrow{Co_2(CO)_8} RCH_2CH_2CHO + \text{some } RCHMeCHO \qquad (2)$$

Similar results can be achieved under much milder conditions through the alkylzirconium complexes formed by the hydrozirconation of olefins with dicyclopentadienylzirconium hydridochloride; these react with carbon monoxide to give acyl complexes which are cleaved quantitatively by dilute hydrochloric acid to give aldehydes.[26] Acyl iron complexes, which are cleaved by acid to give aldehydes, can be prepared from acyl chlorides by the action of disodium tetracarbonylferrate, and from alkyl-lithiums by the action of pentacarbonyliron[27] (see Scheme 3).



i, $Fe(CO)_5$; ii, $Na_2Fe(CO)_4$; iii, H^+.

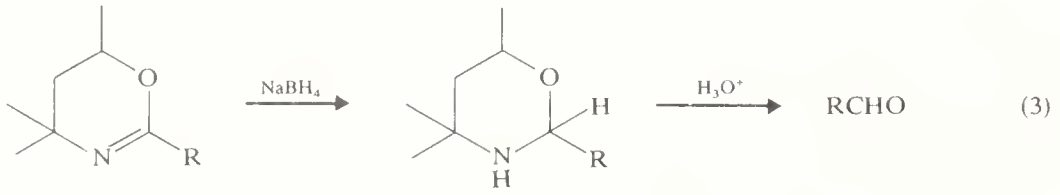
SCHEME 3

5.1.2.8 From Grignard reagents

Grignard reagents have been formylated by reaction with, for example, trialkyl orthoformates, to give the acetal, and *N*,*N*-dialkylformamides.[6] A newer route[28] to aldehydes involves the reaction of a Grignard reagent with 1,1,3,3-tetramethylbutyl isocyanide and hydrolysis of the resultant metallated aldimine.

5.1.2.9 Through dihydro-oxazines and related heterocyclic systems

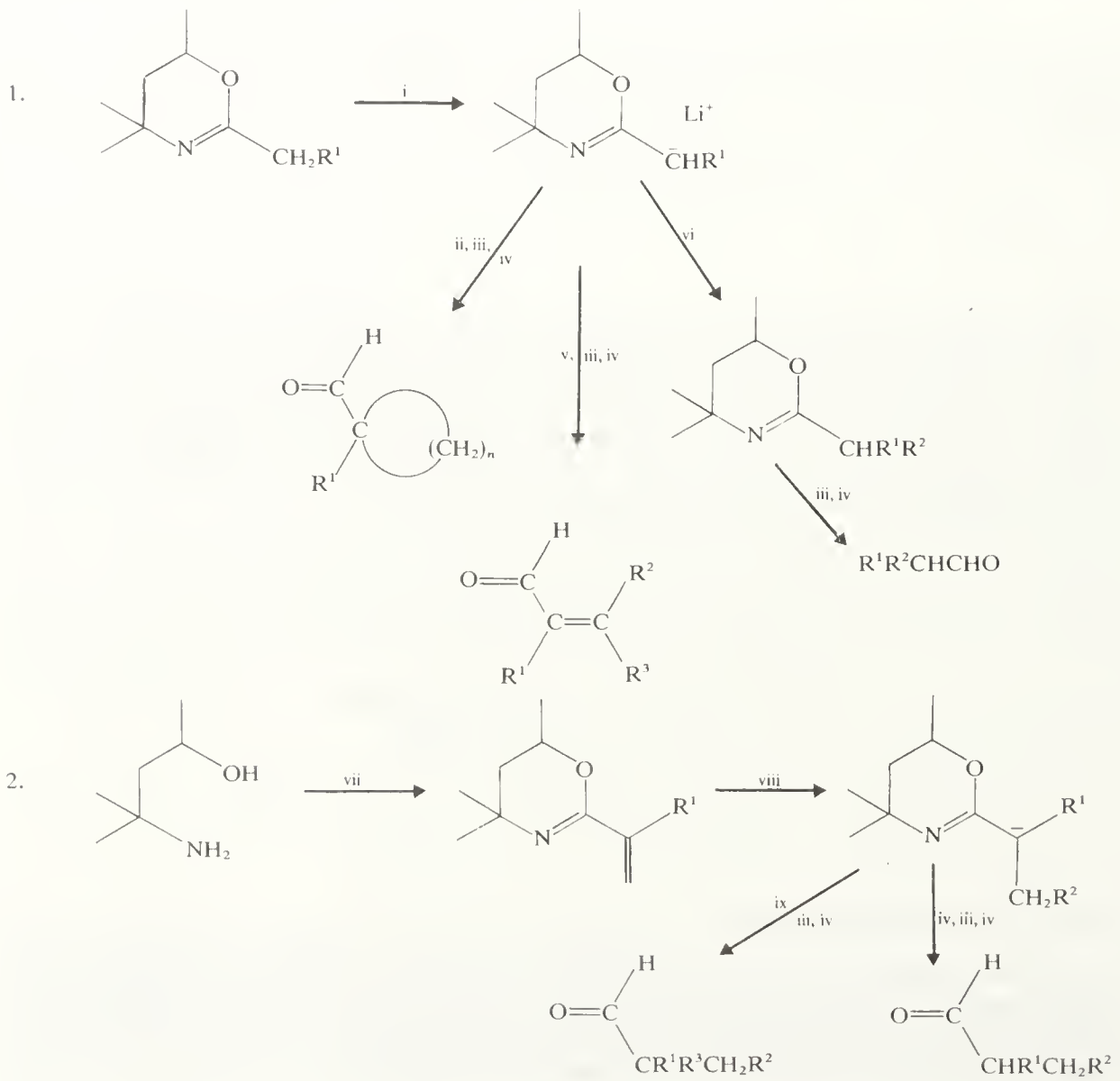
A. I. Meyers has developed a range of versatile aldehyde syntheses based on the production and subsequent hydrolysis of tetrahydro-oxazines. In the first of these[29] (see equation 3) a dihydro-4*H*-1,3-oxazine is prepared from a nitrile and 2-methylpentane-2,4-diol, and reduced to the tetrahydro derivative, which is then hydrolysed to the aldehyde.

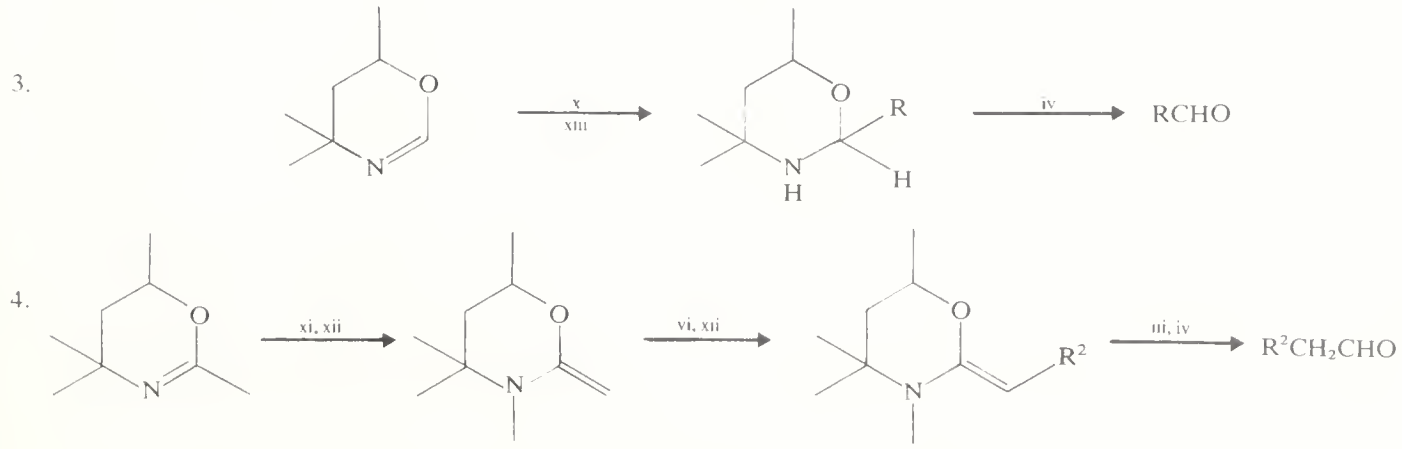


(3)

This method has been much extended. The procedures now available are shown in Scheme 4. The first three have been summarized[30] and the last[31] provides a one-pot method for converting a halide into the aldehyde containing two more carbon atoms.

Related methods, but based on the five-membered thiazole,[32] thiazoline,[33] oxazoline,[34] and triazole[35] systems have also received some attention.



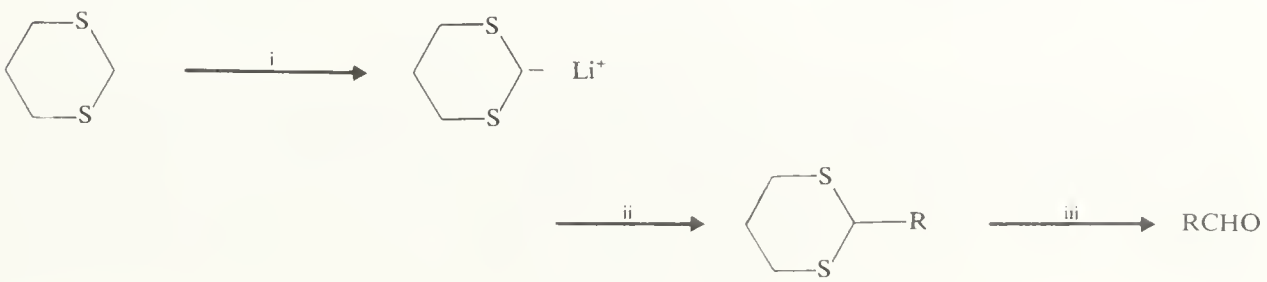


i, BuLi; ii, $X(CH_2)_nX$; iii, $NaBH_4$; iv, H_3O^+; v, $R^2R^3C{=}O$; vi, R^2X; vii, $CH_2{=}CR^1CN$; viii, R_2M; ix, R^3X; x, RLi; xi, MeI; xii, NaH; H_2O

SCHEME 4

5.1.2.10 From 1,3-dithians and other sulphur-containing formyl carbanion equivalents

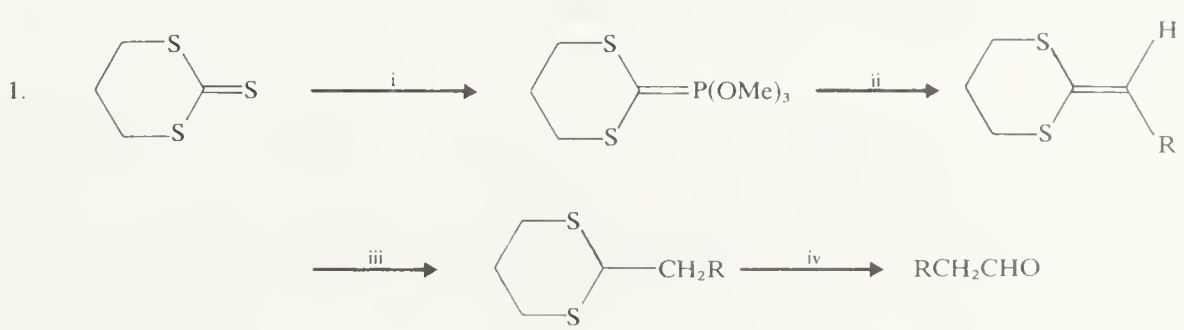
The 'umpolung' principle of reversed polarities was first demonstrated by Corey and Seebach in their use of dithian as a formyl carbanion equivalent. Alkylation of the lithium derivative permits the preparation of the homologous aldehydes through their thioacetals,[36] as shown in Scheme 5.



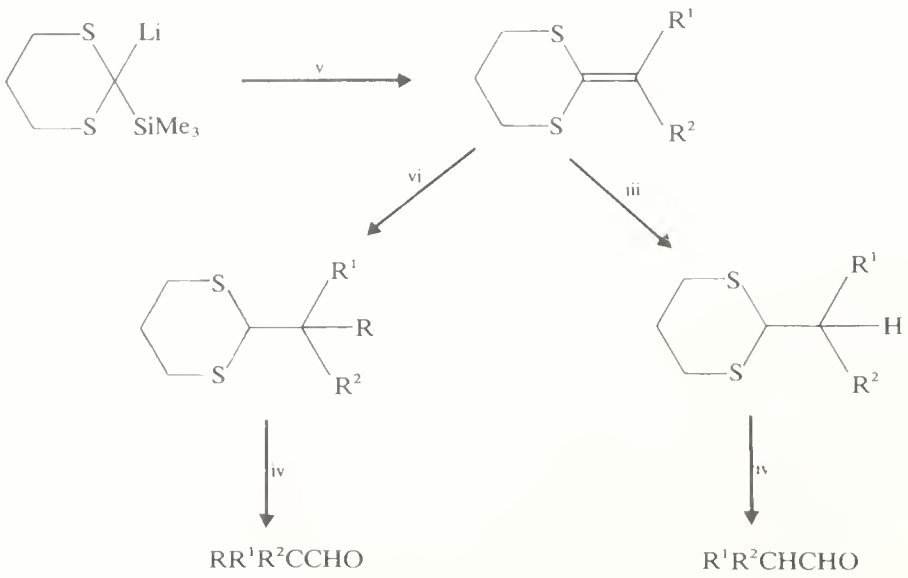
i, BuLi; ii, RX; iii, HgO, BF_3, H_2O.

SCHEME 5

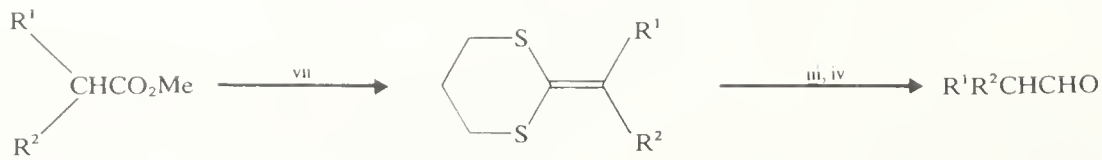
Aldehyde thioacetals can often conveniently be prepared through keten thioacetals. Methods for the homologation of aldehydes,[37] the conversion of ketones into the next higher aldehyde,[38] and the indirect reduction of esters to aldehydes[39] are illustrated in Scheme 6.



2.



3.



i, $P(OMe)_3$; ii, RCHO; iii, CF_3CO_2H, Et_3SiH; iv, HgO; v, R^1R^2CO; vi, RLi; vii, $Me_2AlS(CH_2)_3SAlMe_2$.

SCHEME 6

The best of the other sulphur-containing formyl carbanion equivalents seems to be the anion from ethyl ethylthiomethyl sulphoxide (**14**; R=Et), developed by Schlesinger.[40] Others which have been used in aldehyde synthesis include the corresponding methyl compound (**14**; R=Me),[41] the dithiocarbamate (**15**),[42] and the bis(dithiocarbamate) (**16**).[43]

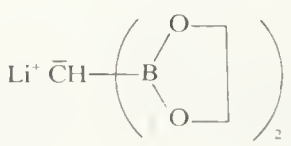
$RSCH_2SOR$ $MeSCH_2SCSNMe_2$ $Me_2NCSSCH_2SCSNMe_2$

(**14**) (**15**) (**16**)

5.1.2.11 By the Wittig and related reactions

The use of an alkoxymethylenetriphenylphosphorane with a carbonyl compound in the Wittig reaction leads to an enol ether which can be hydrolysed to the aldehyde with one more carbon atom[44] (see equation 4). The same result is achieved by condensing the carbonyl compound with lithium bis(ethylenedioxyboryl)methide (**17**) to give an alkeneborinic ester which on oxidative rearrangement and hydrolysis gives the aldehyde.[45]

$$R^1CHO + R^2O\bar{C}H\overset{+}{P}Ph_3 \longrightarrow R^1CH{=}CHOR^2 \longrightarrow R^1CH_2CHO \qquad (4)$$



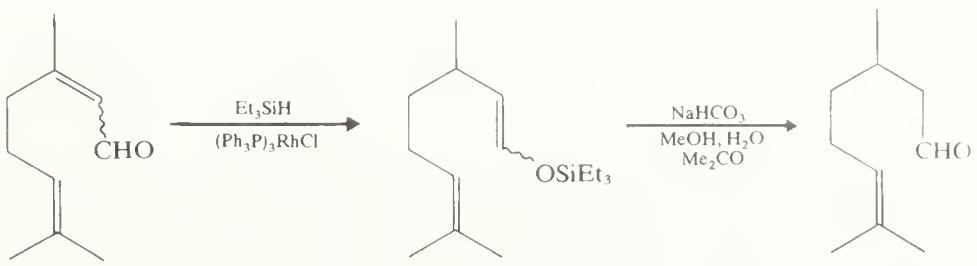
(**17**)

5.1.2.12 By the α-alkylation of aldehydes

Procedures for the α-alkylation of aldehydes involving intermediate tin compounds,[46] enol trimethylsilyl ethers,[47] and *N*-alkylimides[48] have been worked out in recent years, but they are restricted in their applicabilities.

5.1.2.13 From α,β-olefinic aldehydes

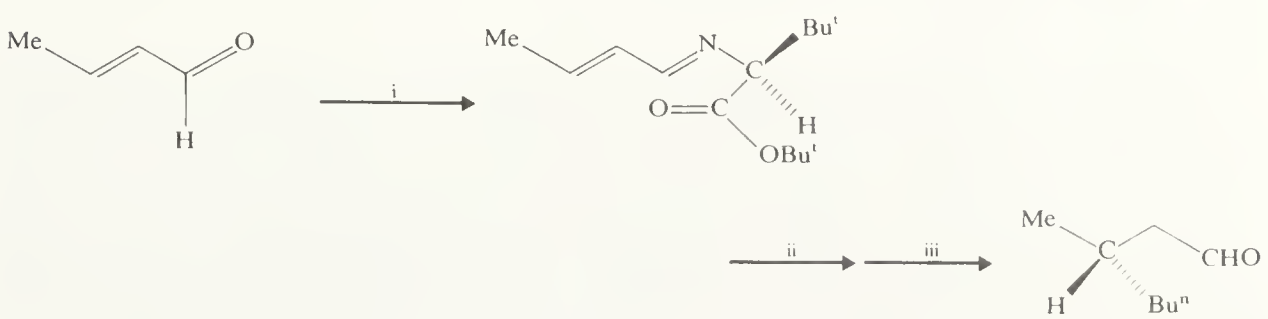
Hydrosilylation of an α,β-olefinic aldehyde gives the enol silyl ether of the corresponding saturated aldehyde, which can be obtained by hydrolysis of the ether.[49] Isolated double bonds are not affected. The conversion of citral into citronellal (**10**) is shown in equation 5.



(5)

(**10**)

Selective reduction of the carbon-carbon double bond in an α,β-olefinic aldehyde has also been achieved using an iron hydride reagent based on pentacarbonyliron,[50] by the use of the 'ate' complex from copper(I) hydride and lithiopent-1-yne,[51] and by the use of metal–liquid ammonia systems.[52] Reductive alkylation of an α,β-olefinic aldehyde can be achieved through the corresponding aldimine provided that a bulky amine is used to ensure that exclusive 1,4-addition to the conjugated system occurs. An example[53] of a completely stereospecific alkylation based on the use of a chiral amine is shown in Scheme 7.



i, L-$Bu^tCH(NH_2)CO_2Bu^t$; ii, Bu^nMgBr; iii, 2M HCl.

SCHEME 7

5.1.2.14 By oxidative degradation

Aldehydes are produced,[6] where the substitution pattern is appropriate, by the ozonolysis of olefins and by the cleavage of vicinal diols with sodium metaperiodate, periodic acid, or lead tetra-acetate. Oxidative hydrolysis of an epoxide with ethereal periodic acid monohydrate is a very mild way of preparing aldehydes. The method has been applied to the preparation of the acid-sensitive 4-bromobutanal from 3-bromopropyloxiran.[54]

5.1.2.15 Some industrial aldehyde syntheses[55]

The major industrial route to ethanal is now by the Wacker process involving the oxidation of ethylene derived by the cracking of hydrocarbons. This is much more important than the oxidation or catalytic dehydrogenation of ethanol, or the hydration of acetylene. In the Wacker process, ethylene is oxidized in an aqueous solution containing copper(II) and palladium(II) chlorides. In the one-stage process the catalyst is regenerated by oxygen in a continuous process; in the two-stage process the catalyst is regenerated with air in a separate reactor. The reaction is catalytic in palladium (see equations 6, 7, and 8).

$$CH_2{=}CH_2 + PdCl_2 + H_2O \longrightarrow CH_3CHO + Pd + 2HCl \quad (6)$$

$$Pd + 2CuCl_2 \longrightarrow PdCl_2 + 2CuCl \quad (7)$$

$$2CuCl + \tfrac{1}{2}O_2 + 2HCl \longrightarrow 2CuCl_2 + H_2O \quad (8)$$

Butanal is produced commercially by the catalytic hydrogenation of crotonaldehyde (but-2-enal).[56] This is a continuous hydrogenation process in the liquid phase with a Raney nickel catalyst at a slightly elevated temperature. It is conducted in such a way that there is always a large excess of butanal in the reactor; the solvent is butan-1-ol.

The hydroformylation of olefins (see Section 5.1.2.7) is a major industrial source of aldehydes.

Heptanal is produced by the *in vacuo* pyrolysis of castor oil, which contains ~80% of triricinolein (the triglyceride of 12-hydroxyoctadec-9-enoic acid); the other product is undec-10-enoic acid.[57]

5.1.3 PHYSICAL AND SPECTROSCOPIC PROPERTIES OF ALDEHYDES

5.1.3.1 Physical properties

Formaldehyde (methanal) is a gas and acetaldehyde (ethanal), the other lower alkanals, and cycloalkanecarbaldehydes are liquids. Their physical properties are in accord with the polar nature of the carbon–oxygen double bond. Thus their boiling points are greater than those of the corresponding saturated hydrocarbon having the same number of carbon atoms. They are usually less soluble in water than the corresponding alcohols, and freely soluble in organic solvents. Many aldehydes have characteristic odours, those of the simple α,β-olefinic aldehydes being particularly pungent. In view of their highly toxic and flammable natures, low molecular mass aldehydes must be regarded as hazardous chemicals.[58]

5.1.3.2 Infrared spectra

Aldehydes show a very characteristic absorption near 2720 cm^{-1} due to the stretching mode of the C—H bond of the formyl group. There are usually two bands in the 2900–2700 cm^{-1} region. Saturated aldehydes show absorption due to the carbonyl stretching mode in the region 1740–1720 cm^{-1} when the spectrum is measured as the liquid film; α,β-olefinic aldehydes absorb at 1705–1685 cm^{-1} and in more highly conjugated systems the absorption occurs in the region 1677–1664 cm^{-1}. There is also in α,β-olefinic aldehydes a much weaker band at 1640–1590 cm^{-1} associated with the C=C stretching mode.

5.1.3.3 Ultraviolet spectra

The ultraviolet spectra of aldehydes, especially conjugated aldehydes, is dealt with in some detail in 'Electronic Absorption Spectroscopy in Organic Chemistry'.[59]

In presenting u.v. spectroscopic data it is customary to quote the wavelengths of any absorption maxima (λ_{max}) and the value of the molar absorptivity at those wavelengths (ε_{max}) as an indication of the intensity of the absorption. The solvent is also stated.

Saturated and other non-conjugated aldehydes show a low intensity absorption near 290 nm, with ε_{max} 15–20. This is due to an $n-\pi^*$ transition, *i.e.* the electron excited by the light quantum is in one of the non-bonding orbitals on oxygen and is promoted to the empty anti-bonding π-orbital associated with the carbon–oxygen double bond. In α,β-olefinic aldehydes this $n-\pi^*$ transition is moved to longer wavelengths, *e.g.* propenal has λ_{max} 345 nm (in cyclohexane) with ε_{max} 20. However, conjugated aldehydes show a much more intense absorption in the wavelength range 203–240 nm, with ε_{max} 11 000–17 500. This is due to a $\pi-\pi^*$ transition in which the excitation is of one of the bonding π-electrons associated with the conjugated system. On average there is a shift of 12 nm to longer wavelength in the position of the $\pi-\pi^*$ absorption maximum each time one of the three olefinic hydrogen atoms in propenal is replaced by an alkyl group, *e.g.* $CH_2{=}CH{-}CHO$, λ_{max} 203 nm; $Me_2C{=}CMe{-}CHO$, λ_{max} 240 nm.

In more extended conjugated systems the position of the $\pi-\pi^*$ absorption shifts progressively to longer wavelengths until in highly unsaturated aldehydes, for example in the carotenoid field, the absorption curve may occur at a wavelength greater than 400 nm, corresponding to absorption in the blue end of the visible spectrum, so giving rise to compounds coloured red, yellow, or orange. In well-studied areas where the spectra of many related compounds have been recorded, u.v.–visible spectroscopy can be of considerable use for characterization.

5.1.3.4 Nuclear magnetic resonance spectra

In the ^1H n.m.r. spectrum of an aldehyde the formyl proton is highly characteristic, usually resonating at extremely low field in the region 9.3–10.0 p.p.m. The magnetic anisotropy of the carbonyl group acts to cause deshielding of this proton, which lies in the cone extending from the carbonyl oxygen atom, as shown in Figure 4.

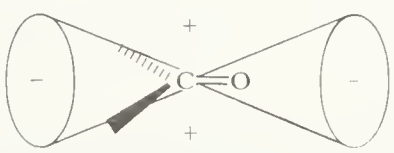


Figure 4 The magnetic anisotropy of the carbonyl group

In α,β-olefinic aldehydes the chemical shift of an α-hydrogen occurs in the range δ 5.8–6.7 and that of a β-hydrogen in the range δ 6.5–8.0. In the 2-methylalk-2-enals[60] there is very little difference in the chemical shifts of the 2-methyl or 3-vinyl protons between the two diastereoisomers, but, in the (*E*)-form, the formyl proton resonates at a higher field than the one in the (*Z*)-form, and the absorption due to the C-4 methylene protons is at lower field in the (*Z*)-form when the methylene group is in a *cis* relationship with the formyl group. In 3-methylalk-2-enals[61] it is observed that both the C-4 methylene protons and the C-3 methyl protons resonate at lower field in the diastereoisomer in which those protons are in a *cis* relationship with the formyl group.

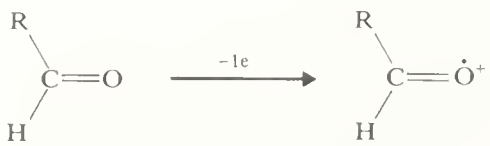
The chemical shifts quoted above for ^1H n.m.r. spectra refer to measurements in the normal halogenated solvents, $CDCl_3$ or CCl_4. Differences in the chemical shifts (aromatic solvent induced shifts) are observed when the spectra are measured in aromatic solvents, C_6D_6 or C_5D_5N.[61]

In the ^{13}C n.m.r. spectrum of an aldehyde the trigonal formyl carbon atom resonates at *ca.* 218–185 p.p.m. relative to tetramethylsilane.

In the ^{17}O n.m.r. spectrum of an aldehyde the oxygen atom resonates some 540–600 p.p.m. downfield from $H_2{}^{17}O$, whereas most other oxygen atoms (except those in ketones) resonate at much higher fields; the ^{17}O chemical shifts are markedly concentration dependent.[62]

5.1.3.5 Mass spectra

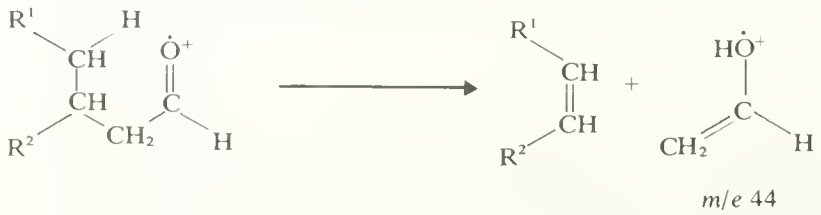
In the ionization of a saturated aldehyde in a mass spectrometer the lowest-energy ionization process corresponds to the removal of one of the lone-pair electrons of the oxygen atom, although energy sufficient to cause higher-energy ionization processes to occur simultaneously is usually available. Nevertheless, it is convenient to represent the molecular ion, a radical cation formed by electron impact, as (**18**) (see equation 9).



(9)

(**18**)

A peak corresponding to the molecular ion is not the most abundant peak (the base peak) in the mass spectra of saturated aldehydes, as fragmentation to give other positive ions of lower mass takes place in the spectrometer. Methanal, ethanal, and propanal give peaks at *m/e* 29 and $M-1$ due to α-cleavage of the molecular ion, but in aldehydes with more carbon atoms and at least one γ-hydrogen atom the base peak is at *m/e* 44, or for α-methyl-substituted aldehydes at *m/e* 58, due to β-cleavage with transfer of the γ-hydrogen atom (the so-called McLafferty rearrangement) as shown in equation 10. Only



(10)

m/e 44

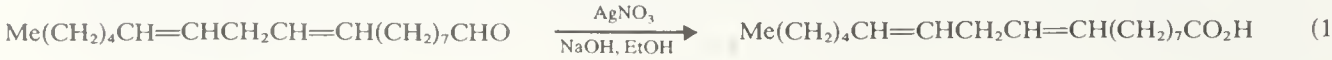
the charged fragment is registered by the spectrometer. This fragmentation makes the recognition of α-branching easy. Other abundant peaks in the mass spectra of simple aldehydes include those at *m/e* $M-44$, $M-43$, $M-28$, and $M-18$.

5.1.4 OXIDATION, REDUCTION, AND DECARBONYLATION OF ALDEHYDES

5.1.4.1 Oxidation

Aldehydes can be converted into carboxylic acids by the following methods.

(i) By oxidation with silver(I) oxide[63] (see equation 11). Variations on this method form the basis of the 'silver mirror' test for aldehydes, in which the formation of Ag^0 is



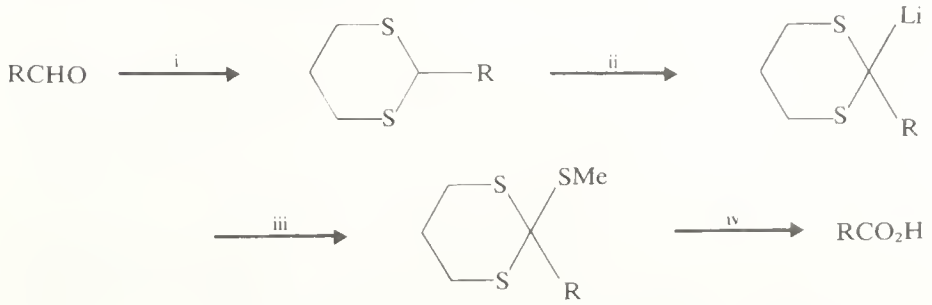
(11)

detected. The reagent may be diamminesilver(I) hydroxide or the same reagent containing, in addition, sodium hydroxide, *i.e.* Tollen's reagent. Tollen's reagent is useful for the oxidation of α,β-olefinic aldehydes to α,β-olefinic acids.[64]

(ii) By silver(II) oxide.[65] The oxidation is carried out either in the presence of cyanide ion in anhydrous methanol, or in aqueous THF.

(iii) By potassium manganate(VII) (potassium permanganate) in dilute sulphuric acid at room temperature;[66] the inorganic product is manganese(IV) oxide.

(iv) Through the thioacetal, which is then converted into an orthothioester, from which the acid is regenerated[67] (see Scheme 8).



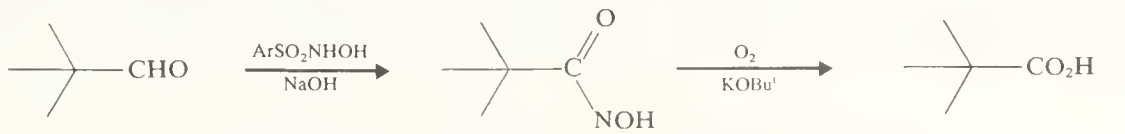
i, $HS(CH_2)_3SH$, H^+; ii, BuLi; iii, MeSSMe; iv, Hg^{2+}, H_2O, Me_2CO.

SCHEME 8

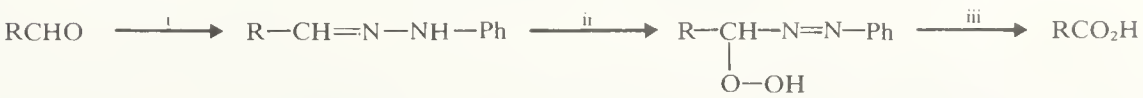
(v) Through the acetal, which can be oxidized by ozone to the ester, which is then hydrolysed.[68]

(vi) Through the hydroxamic acid (*N*-acylhydroxylamine), which can be prepared by the action of benzenesulphonhydroxamic acid on the aldehyde and then oxidized to the carboxylic acid by a variety of reagents. An example[69] is given in equation 12.

(vii) Through the phenylhydrazone,[69] as shown in Scheme 9.



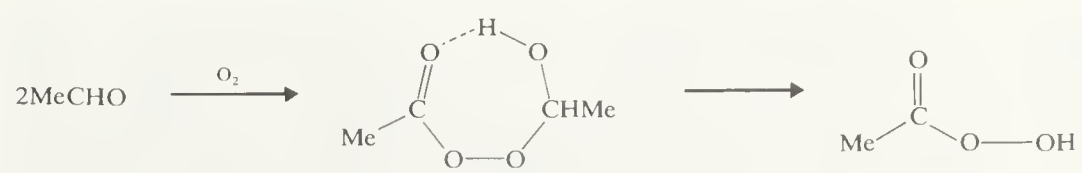
(12)



i, $PhNHNH_2$; ii, O_2; iii, H_2CrO_4, H_2SO_4, H_2O.

SCHEME 9

Industrially, acetaldehyde is oxidized to acetic acid and peracetic acid by air.[70] For the production of acetic acid the oxidation is usually carried out in the vapour phase at temperatures above the ambient temperature. For the production of peracetic acid (see Chapter 9.6), the reaction is conducted at or below 0 °C in a solvent; 1-hydroxyethyl peracetate is formed as an intermediate and decomposes to give peracetic acid and acetaldehyde, which can be recycled (see equation 13).



(13)

5.1.4.2 Reduction

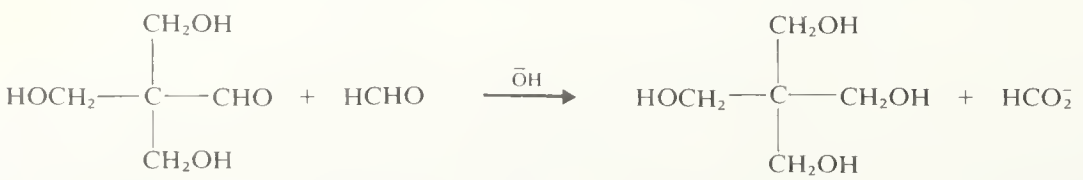
Aldehydes can be reduced to primary alcohols (equation 14) in several ways. Aldehydes are reduced to primary alcohols by sodium borohydride in methanol or water at room temperature, or by lithium borohydride in THF. With borohydrides, selective reduction of

$$RCHO \longrightarrow RCH_2OH \qquad (14)$$

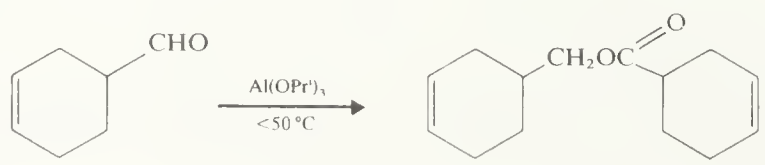
an aldehyde in the presence of most other reducible functions, including esters, lactones, epoxides, carboxylic acids, tertiary amides, nitriles, nitro groups, and isolated carbon–carbon double bonds, is possible. Aldehydes can also be reduced to primary alcohols by a wide variety of other more powerful hydride reducing agents based on boron[22] and aluminium.[15] Some interest attaches to the selective reduction of an aldehyde in the presence of a ketone and this can be achieved in several ways. Tetrabutylammonium cyanoborohydride in the presence of 0.1 M sulphuric acid in hexamethylphosphoric triamide permits this.[71] Under these conditions an aldehyde can also be reduced in the presence of a primary iodide, but, in the absence of the acid, the selectivity is reversed and the iodide is reduced but not the aldehyde.[71] An aldehyde can also be reduced selectively in the presence of a ketone by propan-2-ol on dehydrated alumina[72] and by the lithium 'ate' complex from di-n-butyl-9-borabicyclo[3,3,1]nonane in methanol.[73]

These modern hydride reagents have superseded older methods, such as dissolving metal reductions, although the Meerwein–Ponndorff–Verley reduction[74] with aluminium alkoxides as hydride donors can still be useful for aldehydes such as chloral bearing other reducible groups. Most aldehydes undergo the aldol condensation (see Section 5.1.5.2) with aqueous alkali, but those lacking α-hydrogen atoms undergo the Cannizzaro reaction.[75] Equation 15 illustrates an example of this oxidation–reduction reaction. Crossed Cannizzaro reactions can be useful synthetically, the usual hydride donor being formaldehyde as in the last step of the synthesis of pentaerythritol by the base-catalysed condensation of acetaldehyde with excess of formaldehyde (see equation 16). Aldehydes bearing an α-hydrogen atom undergo the related Tischenko reaction[76] on treatment with aluminium alkoxides (see equation 17) and crossed Tischenko reactions can be performed.[77]

$$Me_3CCHO \xrightarrow[EtOH]{50\%\ KOH} Me_3CCH_2OH + Me_3CCO_2K^+ \qquad (15)$$



(16)



(17)

Saturated aldehydes can also be converted into primary alcohols by catalytic hydrogenation.[78] This is most conveniently accomplished using a ruthenium or carbon catalyst in aqueous ethanol at room temperature. Platinum can also be used as the catalyst provided that a promoter, *e.g.* tin(II) chloride, is present. Even so, the reduction of aldehydes is not an easy process, and elevated temperatures and pressures are often needed. Palladium catalysts tend to be ineffectual, so that selective reduction of other groups susceptible to hydrogenation may be possible. Both palladium and tris(triphenylphosphine)rhodium

chloride tend to promote the decarbonylation of aldehydes.[79] However, homogeneous catalytic reduction of hexanal has been reported[80] in benzene using carbonyltris(triphenylphosphine)rhodium chloride at 140 °C under 100 atm of hydrogen.

Some vicinal diols (pinacols) can be prepared by the bimolecular reduction of aldehydes. The best method seems to be the electrochemical one[81] shown in equation 18, although this method when applied to acetaldehyde gives only ethanol. The reduction of an aldehyde with active titanium metal powder[82] also goes *via* the pinacol, but further reduction with the formation of titanium dioxide leads to an olefin, as shown in equation 19.

$$\mathrm{EtCHO} \xrightarrow[\text{pH 9, 5–10 °C}]{\text{Sn cathode}} \mathrm{EtCH(OH)CH(OH)Et} \qquad (18)$$

$$\mathrm{Bu^nCHO} \xrightarrow{\text{Ti(0)}} \mathrm{Bu^nCH{=}CHBu^n} \qquad (19)$$

The monomolecular deoxygenation of aldehydes in which the formyl group is replaced by a methyl group is also possible. The standard procedures, for example the Clemmensen[83] and Wolff–Kishner[84] reductions, and the desulphurization of thioacetals, have occasionally been used, as have indirect routes such as reduction to the alcohol, conversion into the methanesulphonate and then either reduction with lithium aluminium hydride or displacement by a thiolate anion followed by desulphurization with Raney nickel. A recent mild method is the reduction of the tosylhydrazone with sodium cyanoborohydride.[85] The aldehyde tosylhydrazones can also be converted into alkenes by the Bamford–Stevens reaction or by treatment with alkyl-lithiums.[86]

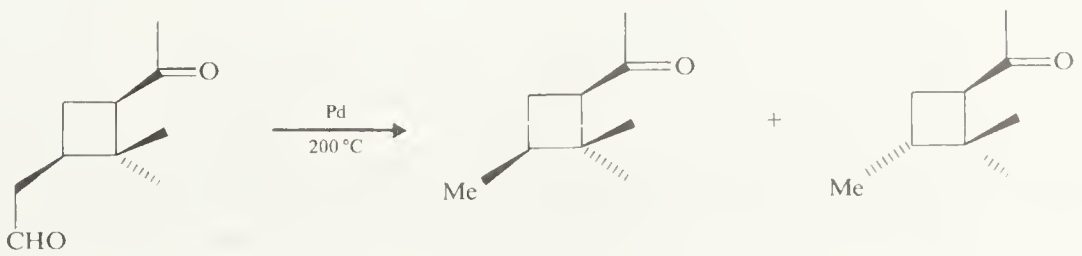
Aldehydes can be reductively aminated, for example see equation 20, by preparing the imines *in situ* and reducing them with sodium cyanoborohydride, the imines being reduced much faster than the aldehydes.[87]

$$\mathrm{Pr^iCHO} + \mathrm{PhNH_2} \xrightarrow[\text{pH 6}]{\mathrm{NaBH_3(CN)}} \mathrm{Pr^iCH_2NHPh} \qquad (20)$$

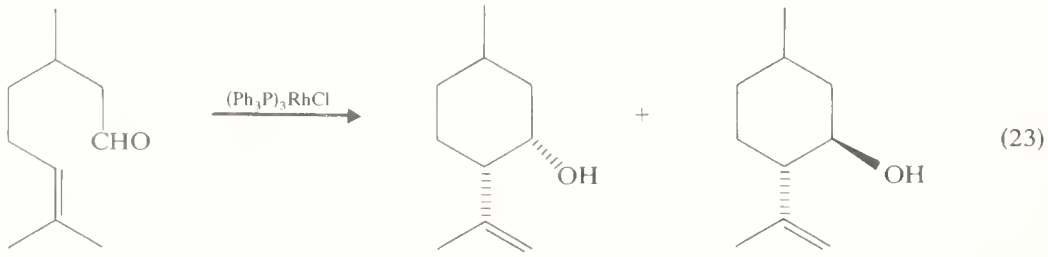
5.1.4.3 Decarbonylation

Aldehydes are decarbonylated by heating them with tris(triphenylphosphine)rhodium chloride[88] (see equation 21). The reaction takes place in homogeneous solution. Hindered aldehydes are decarbonylated in benzonitrile at 160 °C. The reaction proceeds with retention of configuration.[89] Palladium at 200 °C also decarbonylates aldehydes,[90] but without any marked stereoselectivity (see equation 22). Tris(triphenylphosphine)rhodium chloride catalyses the cyclization of certain non-conjugated olefinic aldehydes without deoxygenation.[91] Equation 23 illustrates this.

$$(\mathrm{Ph_3P})_3\mathrm{RhCl} + \mathrm{RCHO} \longrightarrow \mathrm{RH} + (\mathrm{Ph_3P})_2\mathrm{RhCOCl} + \mathrm{Ph_3P} \qquad (21)$$



(22)



(23)

5.1.5 ADDITIONS OF ALDEHYDES

In all aldehydes except formaldehyde the two faces of the carbonyl group are prochiral (see Section 1.5). For example, in acetaldehyde the two faces and their designations are as shown in Figure 5. Alternatively, the two sites above and below the plane of the carbonyl

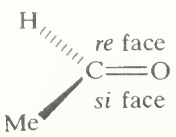
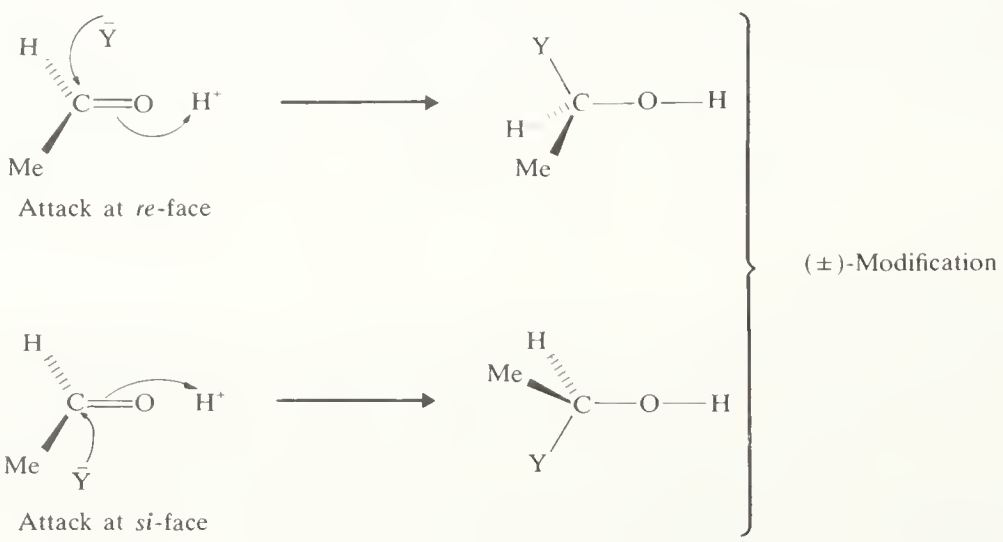


Figure 5 The prochiral faces of acetaldehyde

group in acetaldehyde can be described as enantiotopic, provided that the methyl group is regarded as having an average symmetry. Addition of an achiral molecule HY to acetaldehyde gives equal amounts of two enantiomeric products; these are formed by attack on one or other of the two prochiral (enantiotopic) faces, as shown in Scheme 10. If



SCHEME 10

the aldehyde is itself chiral, then the two faces of the carbonyl group will be diastereotopic, and the addition of an achiral reagent, generating an additional chiral centre, will produce two diastereoisomeric forms of the product. With an achiral aldehyde, attack by a chiral reagent HY* will similarly give diastereoisomeric products. In each of these situations, attack at the two carbonyl faces will not be equally probable and the two diastereoisomers will not be formed in equal amounts. These points are discussed in greater detail in the reviews of Mislow and Raban[92] and of Morrison and Mosher.[93]

When a nucleophile attacks the carbonyl group in an aldehyde, the incoming group Y approaches the plane of the carbonyl group at an angle of ~107°. The Y—C to C—O angle is maintained at that value during the reaction and becomes the Y—C to C—O

angle in the tetrahedral intermediate (see Scheme 11). This general conclusion[94] is based on mapping the pathway for addition of a nitrogen nucleophile to a carbonyl group by means of crystal structure data[95] and on quantum mechanical calculations.[96]

$\alpha \approx 107°$

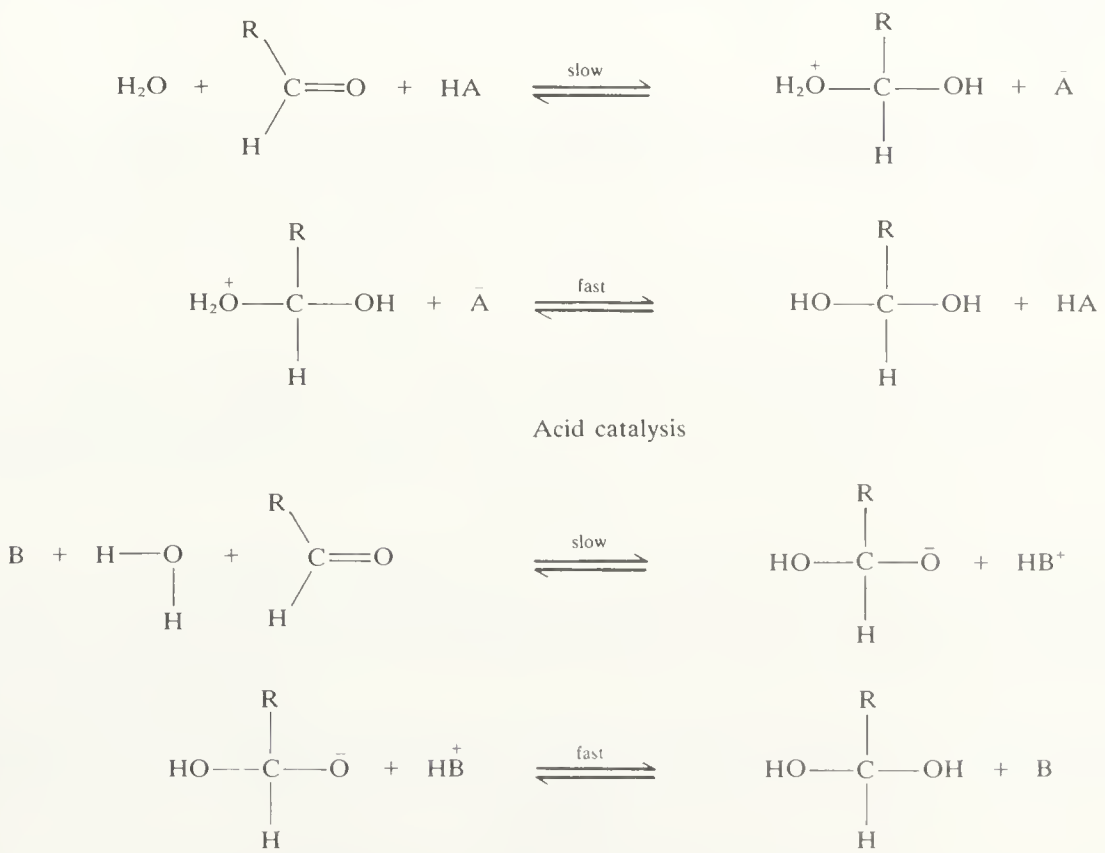
SCHEME 11

5.1.5.1 Oxygen and sulphur nucleophiles

The addition of an oxygen or sulphur nucleophile to an aldehyde is mostly governed by a reversible equilibrium. In aqueous solution the equilibrium between the aldehyde and the 1,1-dihydroxy compound (see equation 24) is very rapidly established. This process complicates many kinetic studies of reactions of aldehydes with other nucleophiles in aqueous media. The equilibrium often favours the 1,1-dihydroxy compound; formaldehyde is almost completely present as 1,1-dihydroxymethane in water.

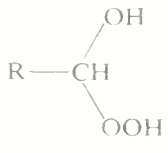
$$RCHO + H_2O \rightleftharpoons RCH(OH)_2 \qquad (24)$$

The hydration of aldehydes, like many other addition reactions of the aldehyde carbonyl group, is subject to both general acid and general base catalysis.[97] The acid- and base-catalysed addition processes are set out in Scheme 12.

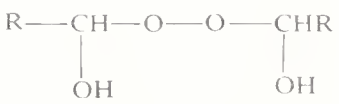


SCHEME 12

Hydrogen peroxide reacts with aldehydes to give 1-hydroxyalkyl hydroperoxides (**19**) and bis-(1-hydroxyalkyl)peroxides (**20**),[98] and peroxycarboxylic acids react to give 1-hydroxyalkyl esters (*cf.* equation 13).

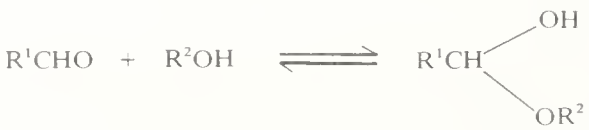


(**19**)



(**20**)

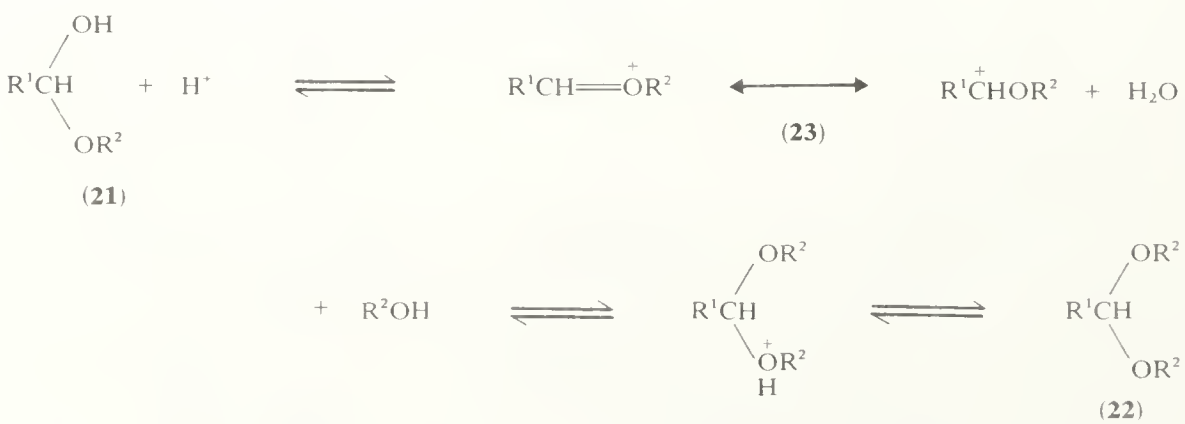
Aldehydes react with alcohols to give hemiacetals (**21**), as shown in equation 25. Hemiacetals are generally too unstable to be isolated, but a solution of an aldehyde in an alcohol contains an equilibrium amount of the hemiacetal. Formaldehyde has been



(25)

(**21**)

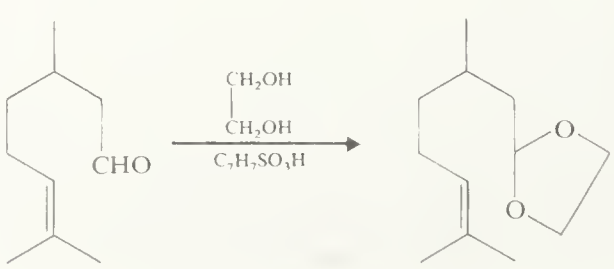
purified commercially through conversion into the hemiacetal of a high-boiling alcohol or diol which, on thermal decomposition, gives formaldehyde free of water and formic acid. In the presence of strong mineral acids, or an ion-exchange resin in the H^+ form, further reaction leading to the acetal (**22**) occurs. Acetals are stable compounds, and can be isolated after neutralization of the reaction mixture. The steps leading from the hemiacetal (**21**) to the acetal (**22**) are shown in Scheme 13. An oxygen-stabilized cation (**23**), formed by the loss of water from the protonated form of the hemiacetal, is a key intermediate.



(**21**) (**23**) (**22**)

SCHEME 13

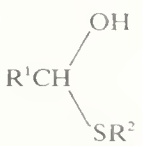
Aldehydes also form cyclic acetals (1,3-dioxolans) with ethane-1,2-diol (see equation 26). Acetals are inert to many of the reagents which react with aldehydes, *e.g.*



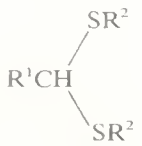
(26)

metal hydrides and organometallic reagents. The parent aldehyde can readily be regenerated by the action of dilute aqueous acid.[99] Acetals can also be prepared by the action of an ester of orthoformic acid on an aldehyde in the presence of a mineral acid catalyst.[100] Aldehydes react with alcohols in the presence of an excess of hydrogen chloride to give α-chloroethers (see Section 5.1.7).

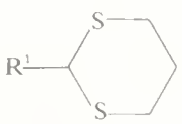
Aldehydes react with thiols to give hemithioacetals (**24**) and, in the presence of an acid, thioacetals (**25**). The chemistry of aldehyde hydrates, hemiacetals, and hemithioacetals has been extensively reviewed.[101] Much work[36] has been done in recent years on the preparation of cyclic thioacetals, *e.g.* 1,3-dithians (**26**) (see Section 5.1.2.10). In these



(**24**)

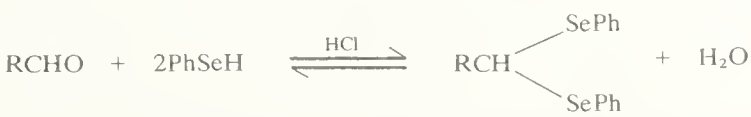


(**25**)



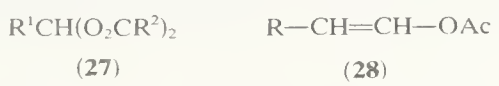
(**26**)

derivatives the polarity of the carbon atom of the original carbonyl group is reversed, so that it can, for example, be alkylated through the lithium derivative, thus providing a route for the conversion of aldehydes into ketones, as the carbonyl compounds can be readily regenerated from their cyclic thioacetals (see Section 11.4.1). Aldehydes react with hydrogen sulphide to give a variety of products, all formed as secondary products from the initial adduct the 1-hydroxyalkanethiol. Aldehydes react with selenols to give 1,1-diselenides (see equation 27) which have some synthetic uses as lithium–phenylselenyl exchange can be achieved.[102]



(27)

When an aldehyde is heated with an acid anhydride a 1,1-diacyloxyalkane (**27**) is formed.[103] Aldehydes can be converted into their enol acetates (**28**) either by the action of isopropenyl acetate[104] with sulphuric acid as catalyst, or by the action of acetyl chloride in the presence of pyridine.[105]



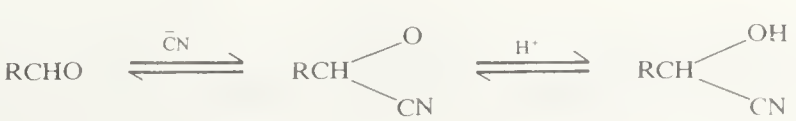
(**27**) (**28**)

Aldehydes react with sodium bisulphite to give 'bisulphite compounds', the sodium salts of α-hydroxyalkanesulphonic acids. The equilibrium lies very far in favour of the products (see equation 28) and the salts can be isolated as crystalline solids.

(28)

5.1.5.2 Carbon nucleophiles

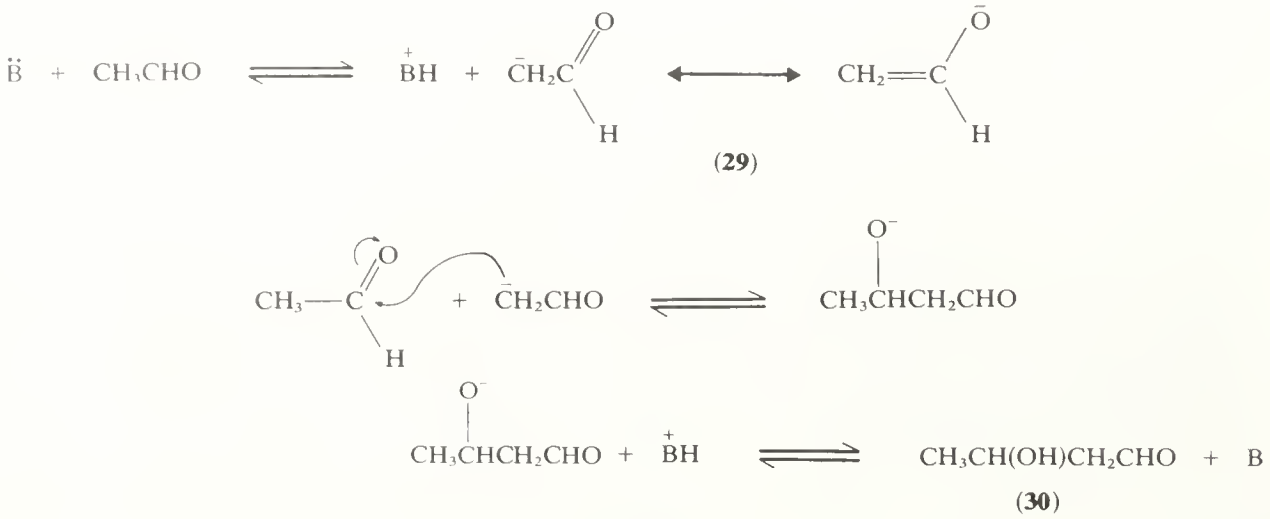
Aldehydes react with hydrogen cyanide in the presence of acids or bases to give 'cyanohydrins' or α-hydroxynitriles (see equation 29). The reactions are reversible, but



(29)

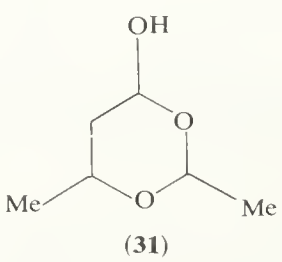
the reaction goes virtually to completion with the lower aldehydes. The reaction is first order in aldehyde and first order in cyanide ion, and the catalysis is of the same general acid or general base catalysed type as is found for other reversible additions to the carbonyl group. Hydrolysis of the cyanohydrin to give the corresponding α-hydroxycarboxylic acid is an important synthetic method.

Aldehydes possessing an α-hydrogen atom undergo the aldol condensation in the presence of base.[106] The self-condensation of acetaldehyde is illustrated in Scheme 14. In the reaction, an enolate ion (*e.g.* **29**) which can be generated by the action of base on the aldehyde (since the resultant ion is stabilized by electron delocalization) attacks the carbonyl group of the aldehyde as a carbon nucleophile. Protonation then gives a β-hydroxyaldehyde, *e.g.* (**30**). In the self-condensation of simple aliphatic aldehydes a



SCHEME 14

catalyst, such as aqueous potassium carbonate, aqueous potassium cyanide, dilute aqueous sodium hydroxide, or a basic ion-exchange resin, can be employed. Concentrated aqueous sodium hydroxide causes further condensation, leading to resinification, with simple aliphatic aldehydes such as acetaldehyde. Those β-hydroxyaldehydes which possess an α-hydrogen atom are readily dehydrated to the α,β-olefinic aldehyde (see Section 5.1.6) and care is needed if the 'aldol' itself is to be isolated. The initial product may be the 'aldoxan', *e.g.* (**31**), but these decompose thermally to give the 'aldol' and the aldehyde. In



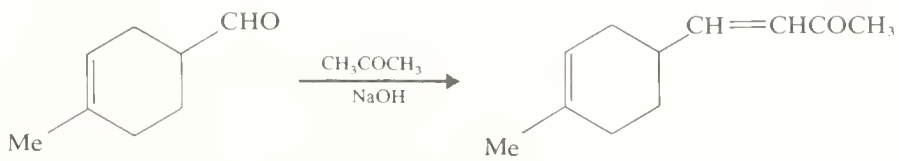
synthesis it is normally the α,β-olefinic aldehyde which is required. Preparatively useful aldol condensations of this type (see equation 30) are successful because the dehydration

(30)

reaction displaces the equilibrium for the formation of the carbon–carbon bond in favour of the addition product. The dehydration occurs in basic conditions, probably by loss of

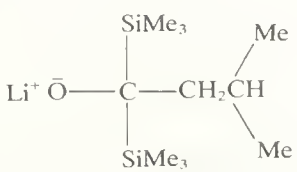
hydroxide ion from the enolate ion derived from the 'aldol' (see equation 31). Crossed aldol condensations, especially with formaldehyde, are useful synthetically, although a crossed Cannizzaro reaction usually follows (see Section 5.1.4.2). Condensations between aliphatic aldehydes and ketones are not usually satisfactory, except with acetone (see equation 32) and some of the other lower homologues.

$$R{-}CH(OH){-}CHCHO \longrightarrow R{-}CH{=}CH{-}CHO \qquad (31)$$



(32)

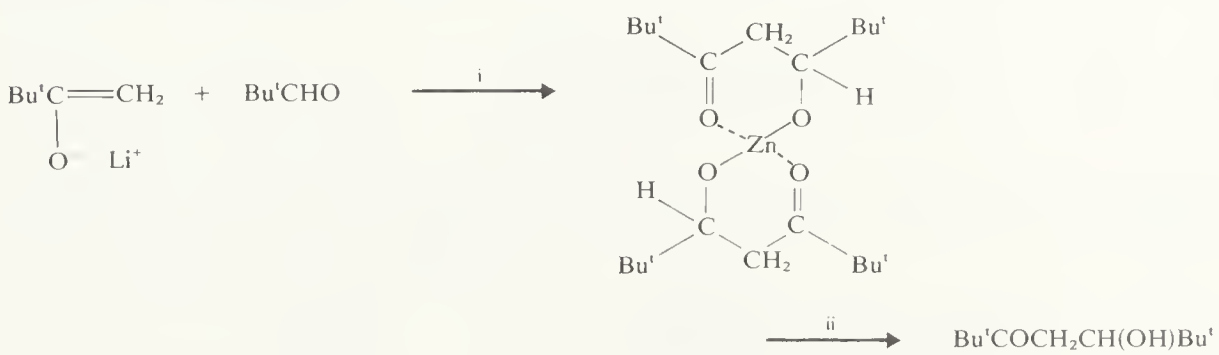
However, by the use of a hindered base, *e.g.* (**32**), the anion from a methyl alkyl ketone can be formed specifically in the presence of an aldehyde, and the reaction (see equation 33) then occurs efficiently.[107] In this case the reaction is kinetically controlled,



(**32**)

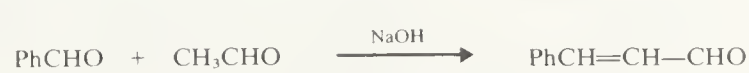
$$C_5H_{11}CHO + CH_3COCH_2CHMe_2 \longrightarrow C_5H_{11}CH(OH)CH_2COCH_2CHMe_2 \qquad (33)$$

and the condensation is faster than proton exchange leading to equilibrium amongst the possible enolates. Alternatively,[108] the preformed lithium enolate of the ketone can be used in the presence of zinc chloride in ether to promote chelation in the aldol alkoxide (see Scheme 15). The base-catalysed condensation of an aliphatic aldehyde with an aromatic aldehyde is a synthetically useful method, illustrated by equation 34.



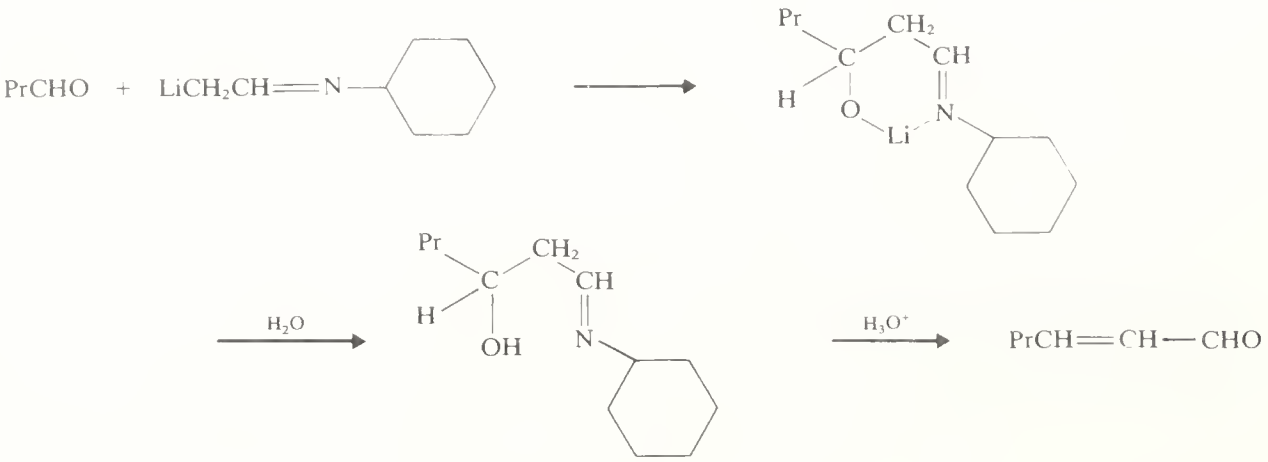
i, $ZnCl_2$; ii, NH_4Cl.

SCHEME 15



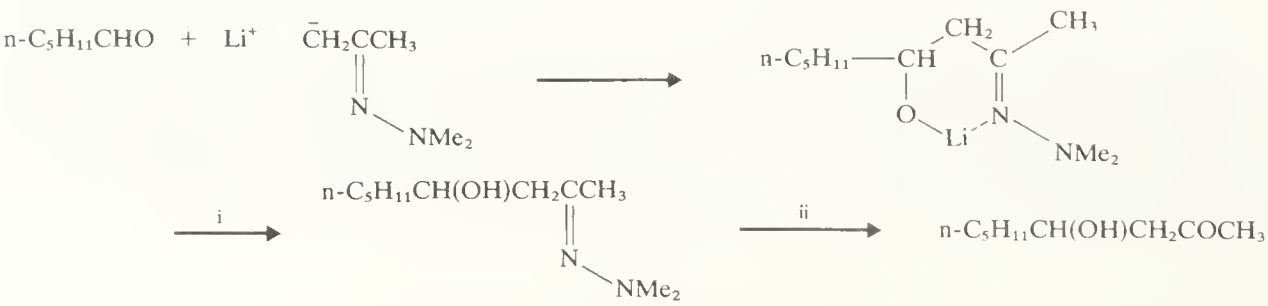
$$PhCHO + CH_3CHO \xrightarrow{NaOH} PhCH{=}CH{-}CHO \qquad (34)$$

In recent years a number of 'directed aldol' reactions have been developed. For example, Wittig showed that the condensation of an aldehyde with the lithium derivative of an aldimine prepared from a second aldehyde could lead to one specific α,β-olefinic aldehyde. The procedure[109] is shown in Scheme 16. The product is one of those which would be formed in the base-catalysed mixed aldol condensation of the two aldehydes, but it is not accompanied by the other products which would also be formed using the conventional conditions. The Wittig 'directed aldol' reaction does not work at all well with aldimines having two α-substituents.



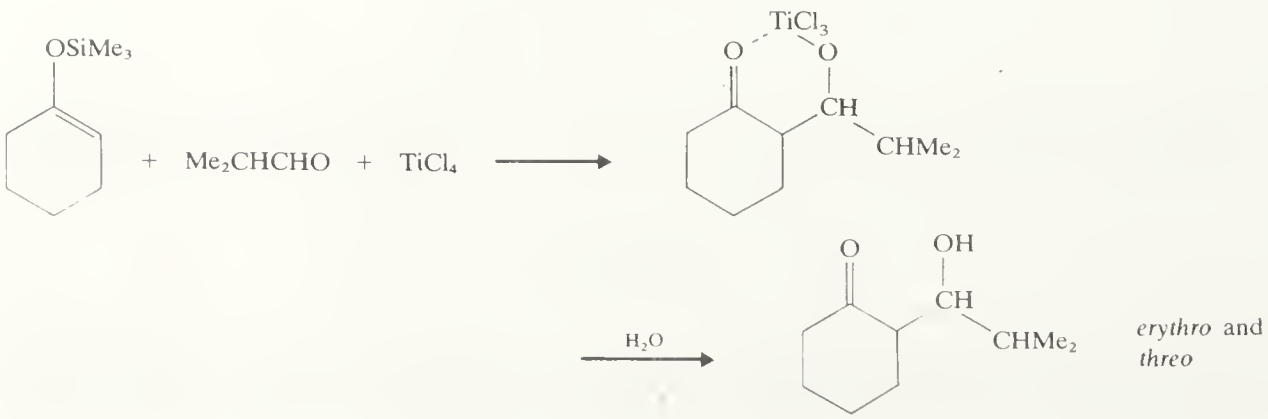
SCHEME 16

An alternative is to condense an aldehyde with an α-lithiated ketone *N,N*-dimethylhydrazone, as shown in Scheme 17. By this means[110] it is possible to obtain the 'aldol' by an oxidative hydrolysis of the corresponding *N,N*-dimethylhydrazone without the occurrence of dehydration. The 'aldol' product can also be obtained[111] by condensing an aldehyde with the trimethylsilyl enol ether of a ketone in the presence of titanium(IV) chloride, as shown in Scheme 18.



i, CH_3CO_2H; ii, $NaIO_4$, MeOH.

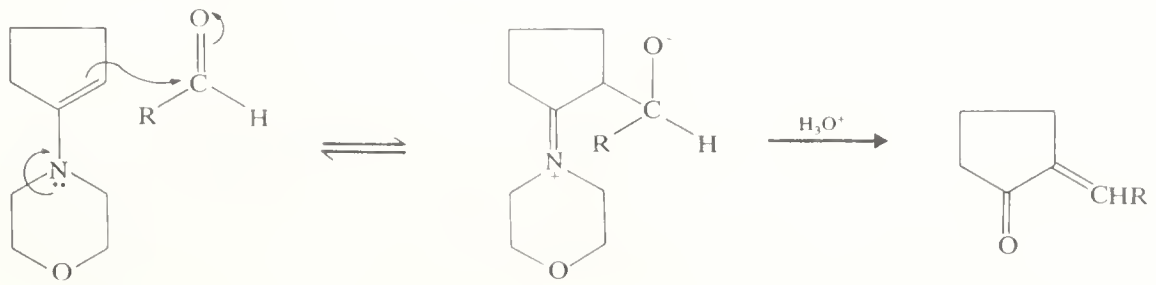
SCHEME 17



SCHEME 18

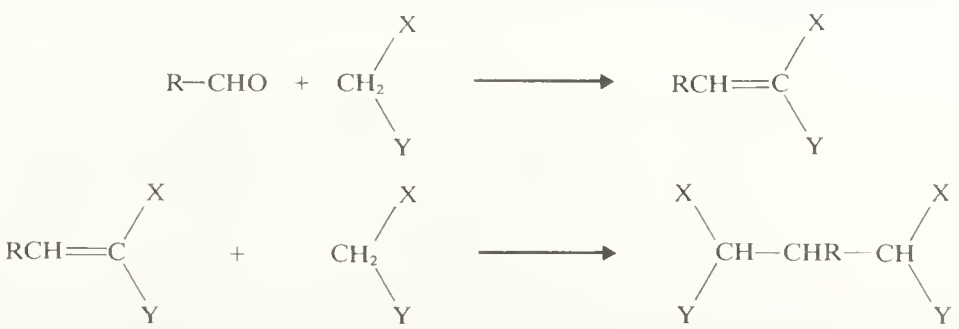
The preparation of α,β-olefinic aldehydes by the aldol and directed aldol reactions is discussed further in Section 5.1.6.1. Aliphatic aldehydes lacking an α-hydrogen atom cannot form an enolate ion in aqueous alkali (*cf.* Scheme 14) and so do not undergo the aldol self-condensation, but may undergo the Cannizzaro reaction[75] (see Section 5.1.4.2), which is initiated by nucleophilic addition of hydroxyl ion to the carbonyl group.

Aliphatic aldehydes react with enamines, *e.g.* (**33**), to give β-hydroxyimmonium salts, which, on treatment with aqueous acid, give α,β-olefinic carbonyl compounds,[112] as shown in equation 35.



(**33**) (35)

Aldehydes react with 'active methylene' compounds, *e.g.* derivatives of malonic acid, β-keto-esters, *etc.*, in the presence of an organic base or ammonia, or their salts. This is the Knoevenagel reaction.[113] The products are either α,β-olefinic carbonyl compounds, *etc.*, or bis-adducts formed by Michael addition of the active methylene component to the initial product. The generalized reaction is shown in Scheme 19. The most widely used

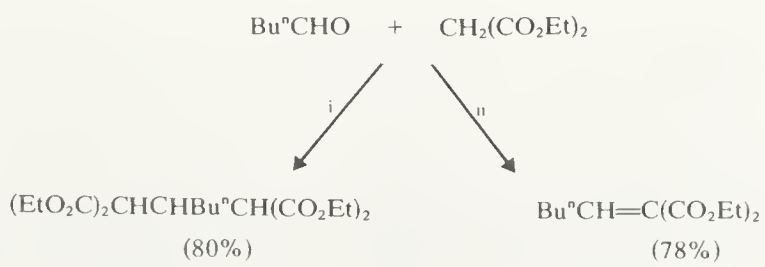


where X and Y = NO_2, CN, COR, COAr, CO_2R, CO_2H, CONHR, CONHAr, *etc.*

SCHEME 19

catalyst has been pyridine, with or without added piperidine, but ammonium salts such as ammonium or piperidinium acetates have also frequently been employed. Several reaction mechanisms may operate. In some cases there is probably a reaction between the aldehyde and the amine catalyst to give an imine or an iminium salt which then, rather than the free aldehyde, reacts with the anion from the active methylene compound formed by amine deprotonation of the active methylene compound. Subsequent loss of water, or amine, generates the conjugated olefinic system.

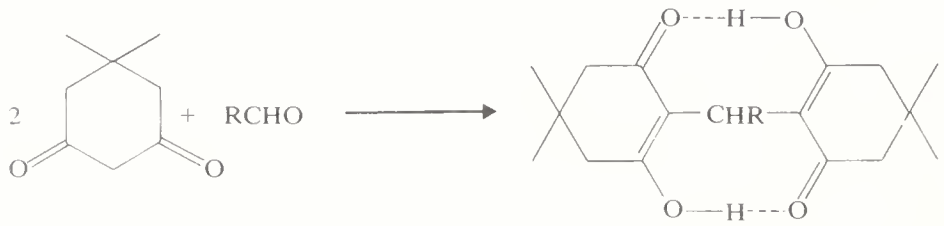
Experimental conditions have often been found which enable both the mono- and the bis-condensation products to be formed. The case of the reaction of pentanal with diethyl malonate is illustrated in Scheme 20.



i, piperidine, room temperature; ii, pyridine, piperidine, 100 °C.

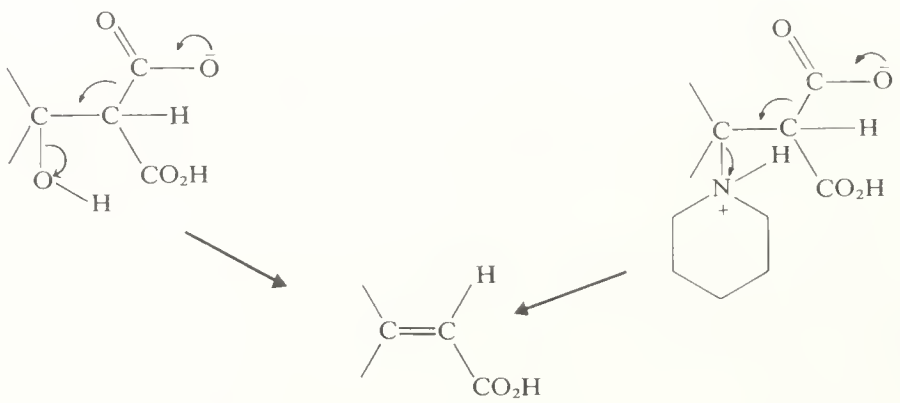
SCHEME 20

The condensation of the β-diketone 'dimedone' or 'methone' (5,5-dimethylcyclohexane-1,3-dione) with aldehydes has been used for the characterization of aldehydes (see equation 36). Under standard conditions ketones do not react.



(36)

An important example of the Knoevenagel reaction is the Doebner condensation,[113,114] in which an aldehyde is condensed with malonic acid. Under the conditions employed, decarboxylation occurs and the product is an olefinic monocarboxylic acid. This ready decarboxylation, which takes place for example at 100 °C in pyridine, is believed to be concerted with the loss of —OH or —$\overset{+}{\text{N}}\!\!<$ from the initial product (*cf.* Scheme 21). For



SCHEME 21

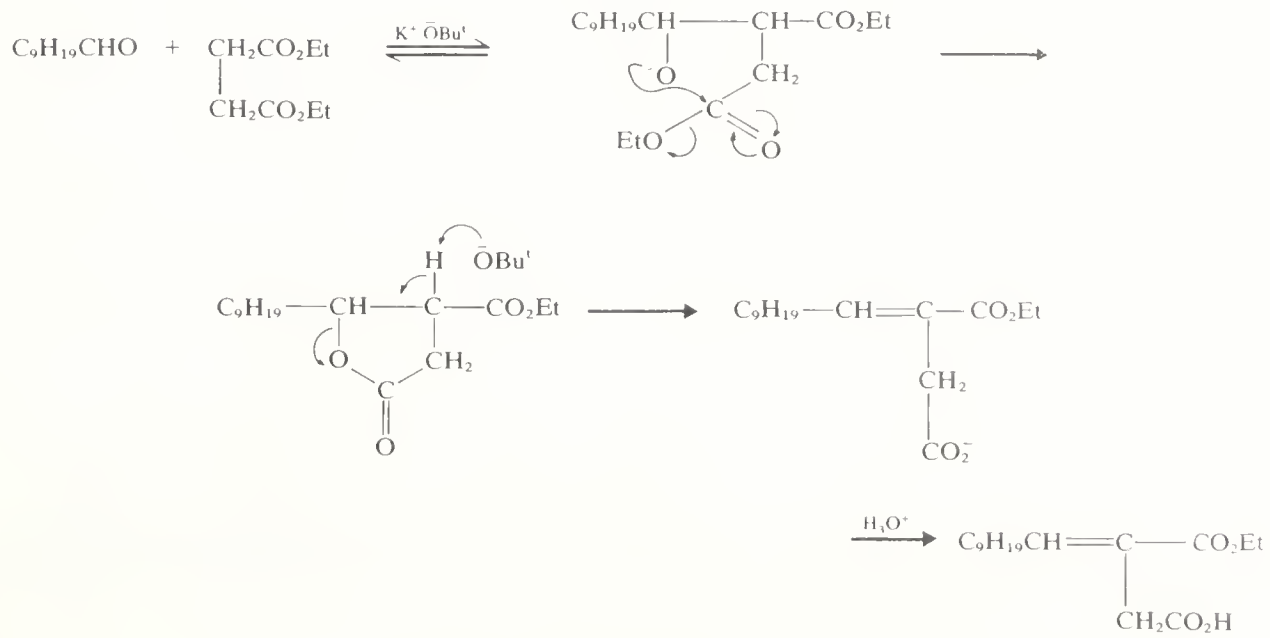
simple aliphatic aldehydes in pyridine the Doebner condensation leads to the (*E*)-form of the α,β-olefinic acid, but with triethanolamine as the catalyst the product may contain substantial amounts of the β,γ-olefinic acid. With cyanoacetic acid in place of malonic acid it is possible to obtain either the alkylidene cyanoacetic acid or the α,β-olefinic nitrile.

The activation of the single nitro group in a nitroalkane is sufficient to permit the formation of an anion in an aqueous medium, and condensation of a nitroalkane with an aldehyde can be achieved. The product is normally a β-hydroxynitroalkane; an example is shown in equation 37. Formaldehyde tends to react further with the initial condensation product if an α-hydrogen is still available.

$$\text{Pr}^{\text{n}}\text{CHO} + \text{CH}_3\text{NO}_2 \xrightarrow{\bar{\text{O}}\text{H}} \text{Pr}^{\text{n}}\text{CH(OH)CH}_2\text{NO}_2 \qquad (37)$$

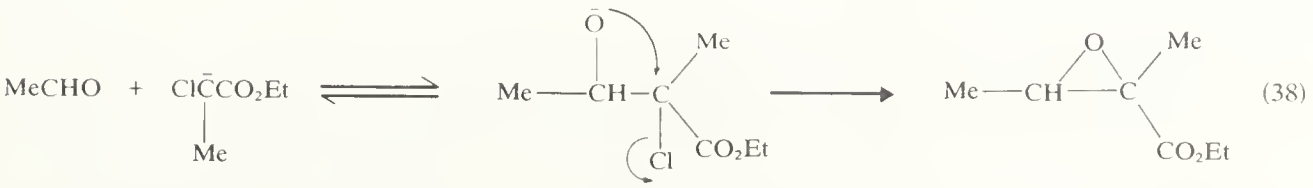
Another carbanion reaction of the aldol condensation type is the Stobbe condensation[115] in which a carbanion generated from a dialkyl succinate reacts with the aldehyde. Cyclization of the initial intermediate, a β-alkoxide ion, on to the ester carbonyl group in the γ-position drives the equilibrium over, favouring carbon–carbon bond formation, and further reactions lead eventually to one specific half-ester of an alkylidene succinic acid. The overall sequence is illustrated by the example shown in Scheme 22.

A related reaction in which the intermediate alkoxide undergoes a further reaction is the Darzens 'glycidic ester' reaction[13] in which again the equilibrium is driven over in favour of carbon–carbon bond formation. Reaction of an aldehyde with the anion from an



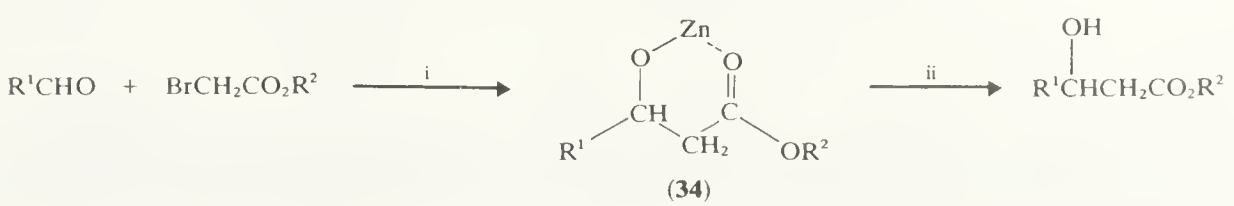
SCHEME 22

α-halo-ester gives an intermediate alkoxide ion which then displaces the neighbouring halogen atom, with the formation of an α,β-epoxy ester (see equation 38).



(38)

Aldehydes will take part in the Reformatskii reaction[116] (see Section 9.2.2). Condensation with an α-bromoester in the presence of zinc leads to a β-hydroxy-ester, as shown in Scheme 23. The success of the Reformatskii reaction is partly because the whole of the α-bromoester is converted into a 'carbanion' form before the aldehyde is added and also because of chelation in the intermediate (**34**).

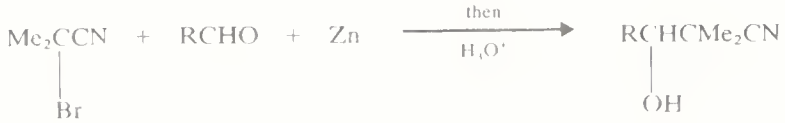


(34)

i, Zn; ii, H_3O^+.

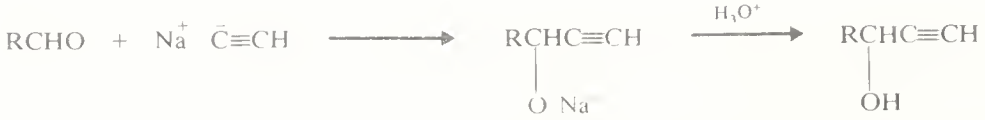
SCHEME 23

There are many modifications[116] of the Reformatskii reaction; for example, α-bromonitriles give β-hydroxynitriles, as shown in equation 39. The reaction of an aldehyde with an α-lithiated ester now provides an alternative to the Reformatskii reaction.[117]



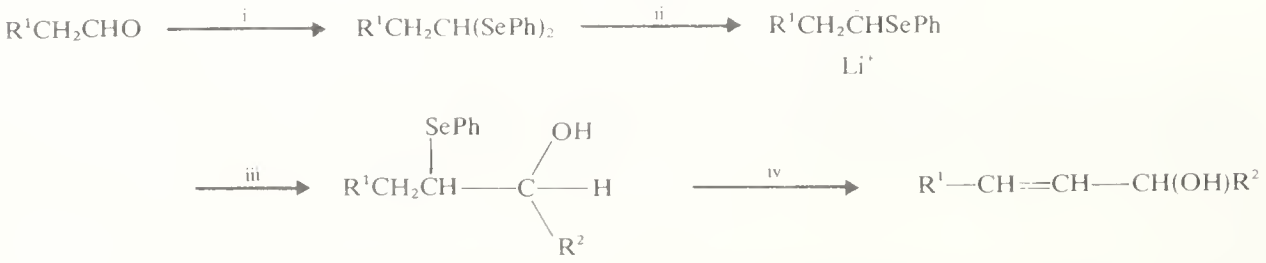
(39)

Aldehydes react with metal acetylides to give propargyl alcohols. On a small scale the reaction is carried out using sodium or lithium acetylides prepared and used in liquid ammonia. The reaction for acetylene itself is illustrated by equation 40. On a technical scale, aqueous formaldehyde is condensed with acetylene under 3–5 atm pressure in the presence of a supported copper(I) acetylide catalyst to give but-2-yne-1,4-diol and some propargyl alcohol.



(40)

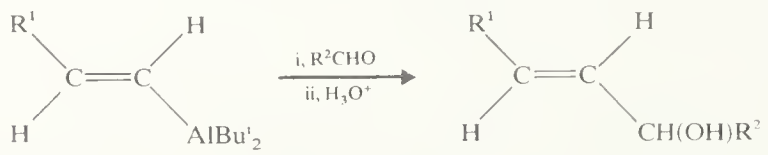
Aldehydes react with lithiated selenyl ethers[102] to give intermediates convertible into allylic alcohols by selenoxide elimination. The whole synthetic sequence[118] is shown in Scheme 24.



i, PhSeH, H^+; ii, BuLi; iii, R^2CHO, H^+; iv, H_2O_2.

SCHEME 24

Aldehydes react with *trans*-vinylalanes, to give[119] *trans*-allylic alcohols (see equation 41) and with α-trimethylsilylvinyl-lithiums to give trimethylsilyl-substituted allylic alcohols.[120]



(41)

Aldehydes react with lithiated α-alkoxycarbonyl isocyanides to give α-formylamino-α,β-olefinic esters,[121] and with the potassium salt of α-*p*-tolylsulphonylmethyl isocyanide to give products hydrolysable to the homologous acid.[122] The overall sequence is shown in Scheme 25.

SCHEME 25

Aldehydes react with alkyl- and aryl-magnesium halides (Grignard reagents) to give adducts which can be hydrolysed to give alcohols by dilute mineral acids or, under neutral conditions, by aqueous ammonium chloride.[123] Formaldehyde gives primary alcohols (equation 42) and other aldehydes give secondary alcohols (equation 43). The methylene bis(Grignard) reagent reacts to give a terminal olefin,[124] as illustrated in equation 44, and

$$CH_2O + RMgX \longrightarrow RCH_2OMgX \longrightarrow RCH_2OH \quad (42)$$

$$R^1CHO + R^2MgX \longrightarrow R^1R^2CHOMgX \longrightarrow R^1R^2CHOH$$

$$RCHO + CH_2(MgX)_2 \longrightarrow RCH{=}CH_2 \quad (44)$$

provides an alternative to the Wittig procedure. Polyfunctional organomagnesium compounds can also be used; for example, the Ivanov reaction[125] (see Scheme 26) is an alternative to the Reformatskii reaction.

$$CH_3CO_2Bu^t + Pr^iMgCl \xrightarrow{i} ClMgCH_2CO_2Bu^t$$

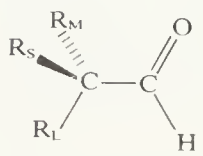
$$\xrightarrow[iii]{ii} CH_3(CH_2)_5CH(OH)CH_2CO_2Bu^t$$

i, ether, petrol; ii, $CH_3(CH_2)_5CHO$; iii, H_3O^+.

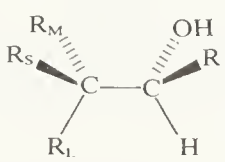
SCHEME 26

Aldehydes react with organozinc[126] and organocadmium[127] derivatives. For example, the diallyl metal derivatives provide a useful route to homoallylic alcohols. Aldehydes also react with alkyl-lithiums, although the method usually has no advantage over the alternative Grignard method.[128]

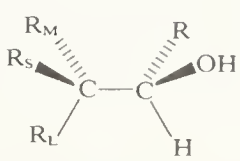
The sterochemistry of the addition of organometallic reagents to chiral aldehydes has been much studied and discussed, and the proportions in which the two diastereoisomeric secondary alcohols are formed can normally be correctly predicted by Cram's rule.[93] For an aldehyde in which the groups attached to a chiral centre in the α-position can be identified as small, medium, and large [R_S, R_M and R_L in (**35**)] the rule predicts that, for reaction of (**35**) with an organometallic reagent (RMgX or RLi), diastereoisomer (**36**) will predominate over diastereoisomer (**37**). Discussion on the rationale behind the observed asymmetric induction has largely been concerned with steric considerations,[93] but it is possible that orbital factors may be at least partly responsible.



(**35**)



(**36**)



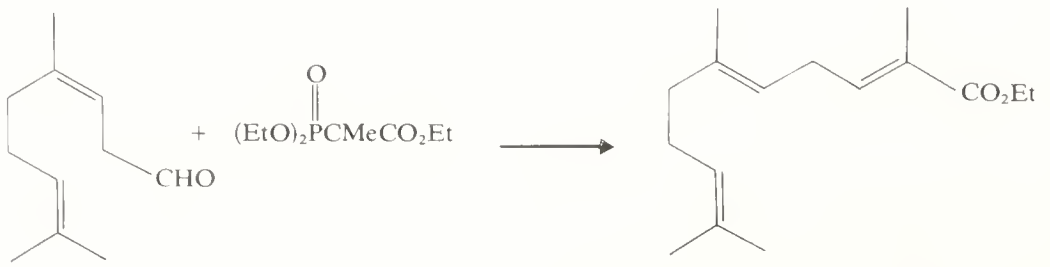
(**37**)

Aldehydes can be converted into olefins by the Wittig and related reactions (see Section 10.8.3). In the Wittig reaction itself[129] the aldehyde is condensed with a phosphorus ylide, as shown in equation 45. The stereochemistry of this reaction has been

$$R^1CHO + R^2CH{=}PPh_3 \longrightarrow R^1CH{=}CHR^2 + Ph_3PO \quad (45)$$

investigated in detail;[130] for the condensation of simple saturated aldehydes with triphenylphosphonium alkylids the reaction gives ~95% of the (*Z*)-olefin. Aldehydes also

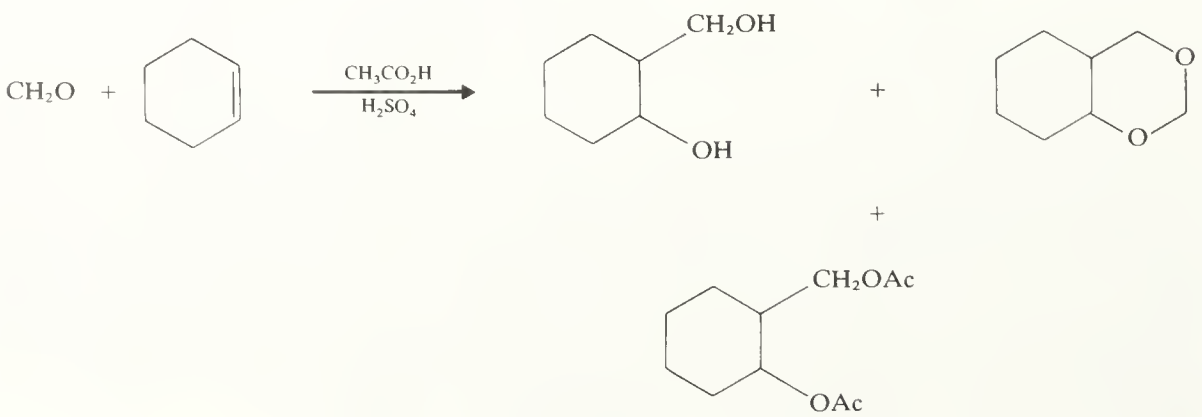
condense with phosphonate carbanions to give olefins.[131] Equation 46 illustrates a case in which the new double bond is formed with the (*E*) configuration. Another useful reagent is a lithiophosphon-bis-*N*,*N*-dialkylamide; pyrolysis of the first-formed β-hydroxyphosphonamide gives the olefin.[132] A related synthesis involves the initial reaction of an aldehyde with the dilithio derivative of methanesulphin-*p*-toluidide.[133]



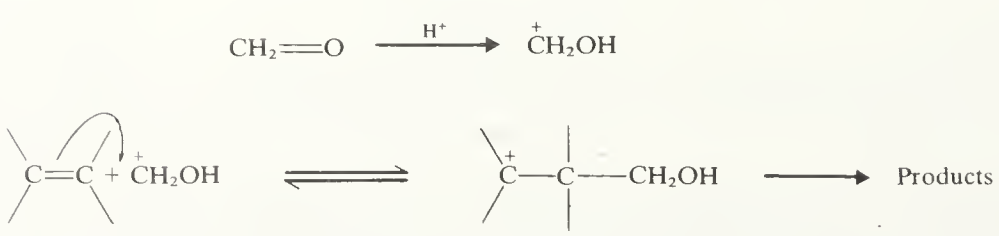
(46)

Formaldehyde condenses with phenol under both basic and acidic conditions (see Section 4.2.3.3). Subsequent reactions lead to the technically important phenol–formaldehyde resins.[55] The phenol, or phenolate ion, acts as a carbon nucleophile towards the formaldehyde at the *ortho* or *para* position and the initial product is the hydroxymethylphenol or its anion.

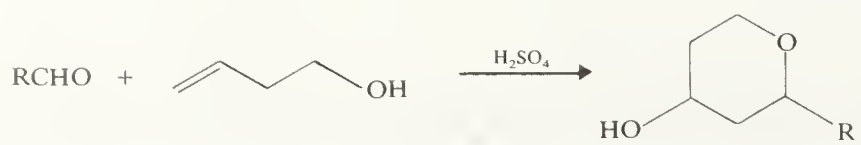
Aldehydes react with olefins to give allylic alcohols, 1,3-dioxans, and related products in the Prins reaction.[134] The reaction is catalysed by mineral or Lewis acids. The products from the reaction of cyclohexene with formaldehyde in acetic acid are shown in Scheme 27. The reaction involves nucleophilic attack by the olefin on the protonated form of the aldehyde, as shown in Scheme 28. Substituted olefins can also take part in this type of reaction. An example is shown in equation 47.



SCHEME 27



SCHEME 28

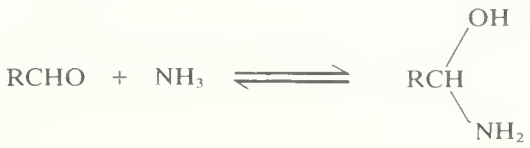


(47)

The chloromethylation of arenes, *e.g.* the synthesis of benzyl chloride from benzene, employs a mixture of formaldehyde and hydrogen chloride with, for example, zinc chloride as catalyst.[135]

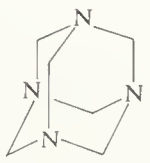
5.1.5.3 Nitrogen nucleophiles

Aldehydes react with ammonia. The initial step leads reversibly to the geminal hydroxyamine (**38**), as shown in equation (48), but these are normally too unstable to be isolated (*cf.* hemiacetals) and the isolable products are considerably more complicated. Formaldehyde gives the high-melting solid 'hexamine', (**39**), a tetra-aza-adamantane. The next higher homologues give products which have been described as 'aldehyde-ammonias', but which are not the hydroxyamines or their simple dehydration products. Acetaldehyde, for example, reacts with anhydrous ammonia in ether to give a trihydrate of a hexahydrotriazine which can be dehydrated over sulphuric acid to give[136] 2,4,6-trimethylhexahydro-1,3,5-triazine (**40**), the nitrogen analogue of 'paraldehyde'. Secondary and tertiary aldehydes react with aqueous ammonia and rapid distillation then leads to products of the 'hydroamide' type (see equation 49).

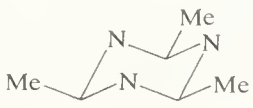


(48)

(**38**)



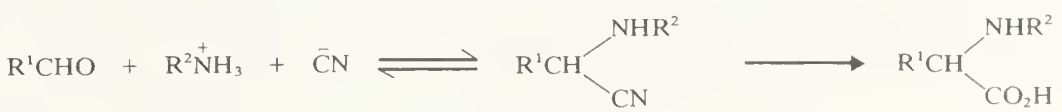
(**39**)



(**40**)

(49)

The Strecker reaction, a useful route to some α-amino acids, involves the interaction of an aldehyde and an ammonium cyanide which leads to an α-aminonitrile that can be hydrolysed to the amino acid. The reaction (see equation 50) probably involves the addition of cyanide ion to the imine, or its protonated form, generated by dehydration of the geminal hydroxyamine. Aldehydes react with primary amines (see equation 51) to give *N*-alkylaldimines,[137] a class of compound often referred to as Schiff bases; solid potassium hydroxide is used to remove the water formed in the elimination step.



(50)

(51)

Aldehydes react with secondary amines in a 1:2 molar ratio to give aminals,[138] geminal diamines, which on distillation give the enamine, together with the secondary amine (see equation 52). The condensing agent is anhydrous potassium carbonate. The use of

butylisobutylamine gives an enamine which can be alkylated on carbon, but in which nucleophilicity at nitrogen is restricted for steric reasons.[139] Aldehydes react with secondary ammonium perchlorates to give iminium salts[140] (see equation 53).

$$R^1CH_2CHO + 2HNR^2R^3 \underset{}{\overset{-H_2O}{\rightleftharpoons}} RCH_2CH(NR^1R^2)(NR^1R^2) \longrightarrow R^1CH{=}CH{-}NR^2R^3 \quad (52)$$

$$R^1CHO + H_2\overset{+}{N}R^2R^3\,ClO_4^- \longrightarrow R^1CH{=}\overset{+}{N}R^2R^3\,ClO_4^- + H_2O \quad (53)$$

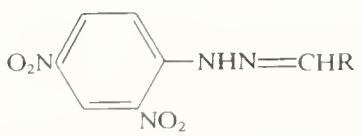
Aqueous formaldehyde reacts with urea and with melamine (2,4,6-triamino-1,3,5-triazine) at 50–100 °C at a slightly alkaline pH to give commercially important polymeric materials.[55] The condensations begin by the formation of α-hydroxyamines and lead to structures with a three-dimensional space network.

Aldehydes react with hydroxylamine to give aldoximes, as shown in equation 54. Aldehydes react with hydrazine and normally give aldazines by a double condensation reaction (see equation 55). Aldehydes react with substituted hydrazines to give the

$$RCHO + NH_2OH \longrightarrow RCH{=}N(OH) \quad (54)$$

$$2RCHO + NH_2NH_2 \longrightarrow RCH{=}N{-}N{=}CHR \quad (55)$$

corresponding hydrazones. Of these, the most important is 2,4-dinitrophenylhydrazine, which gives orange-yellow crystalline 2,4-dinitrophenylhydrazones (**41**) that can be used for the characterization of aldehydes, and which are convenient for chromatographic separations and purifications. Aldehyde semicarbazones (**42**) prepared from aldehydes and the substituted hydrazine semicarbazide often crystallize well.



(**41**)

$NH_2CONHN{=}CHR$

(**42**)

An enormous amount of work has been done on the detailed mechanisms of aldehyde and ketone addition–elimination reactions involving nitrogen nucleophiles and on the stereochemistry of the products in cases where two configurations about a C=N bond are possible; however, very little of it has been concerned with aliphatic aldehydes. Overall the formation of the carbinolamine in the addition step is commonly the rate-determining step in acid solution, but in neutral or basic solution the rate-determining step is commonly the loss of water in the elimination step.

5.1.5.4 Other reactions

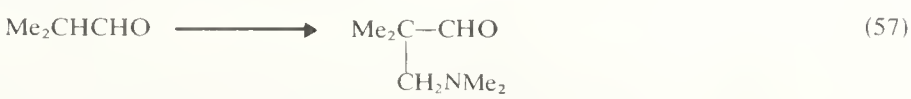
Aldehydes can be polymerized under acidic conditions.[141] 1,3,5-Trioxan and 2,4,6-trimethyl-1,3,5-trioxan, the trimers of formaldehyde and acetaldehyde, respectively, can be prepared by the acid-catalysed trimerization of the aldehyde, *e.g.* with a trace of sulphuric acid. 2,4,6-Trimethyl-1,3,5-trioxan, 'paraldehyde', b.p. 124 °C, can easily be depolymerized and is used as a convenient source of acetaldehyde, b.p. 21 °C. For

example, it is used in the industrial preparation[55] of 2-methyl-5-ethylpyridine, in which 'paraldehyde' in acetic acid is mixed with aqueous ammonia and then reacted at 200–250 °C and 50 atm pressure. Slow evaporation of 'formalin', the commercial solution of formaldehyde in aqueous methanol, gives low molecular mass, water-soluble polymers of formaldehyde, but higher molecular mass, high-melting polymers can also be obtained either by the polymerization of formaldehyde or 1,3,5-trioxan. After stabilization of the end groups, which are of the hemiacetal type, and therefore unstable with respect to loss of water and of formaldehyde, these are of commercial interest,[141] as are copolymers of trioxan and oxiran.

The Mannich reaction[142] is an important general synthetic method which involves the acid-catalysed condensation of an aldehyde, a primary or secondary amine, or ammonia, and a substance which is enolic or potentially enolic. Equation 56 shows a typical

(56)

example. In practice, the reaction is largely confined to formaldehyde (or trioxan) and in such cases serves to introduce a one carbon unit into a structure when a crossed aldol condensation would lead to polycondensation, the Cannizzaro reaction, *etc.* The reaction can be applied to a wide range of compounds, including other aldehydes, as shown in equation 57. The reaction probably involves the formation of the species (**43**) from the formaldehyde and the amine, which then reacts as an electrophile towards the enolic or aromatic substrate.



(57)

(**43**)

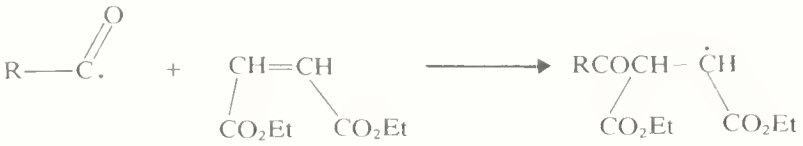
Radicals only rarely add to carbon–oxygen double bonds, in marked contrast to their ready addition to carbon–carbon double bonds. Radicals abstract the trigonal hydrogen atom from aldehydes to give acyl radicals (see equation 58). Such a process initiates the autoxidation of aldehydes; the acyl radical then reacts with molecular oxygen to give a new peroxy radical (see equation 59) and this abstracts a further hydrogen atom to give the peracid and a new acyl radical (equation 60) so that a chain reaction ensues. Acyl

(58)

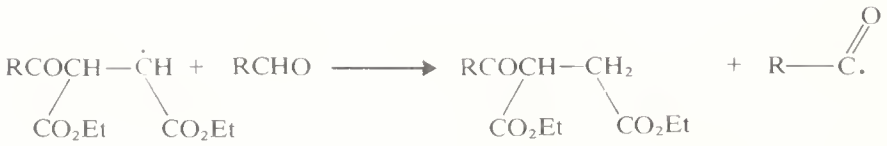
(59)

(60)

radicals can react with olefins,[143] especially those conjugated with electron-withdrawing groups, leading to overall addition of the aldehyde to the olefin with the formation of a ketone. A chain reaction, *e.g.* equations 61 and 62, is again involved.



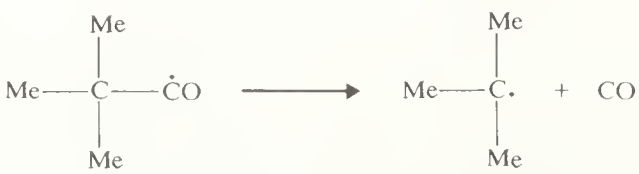
(61)



(62)

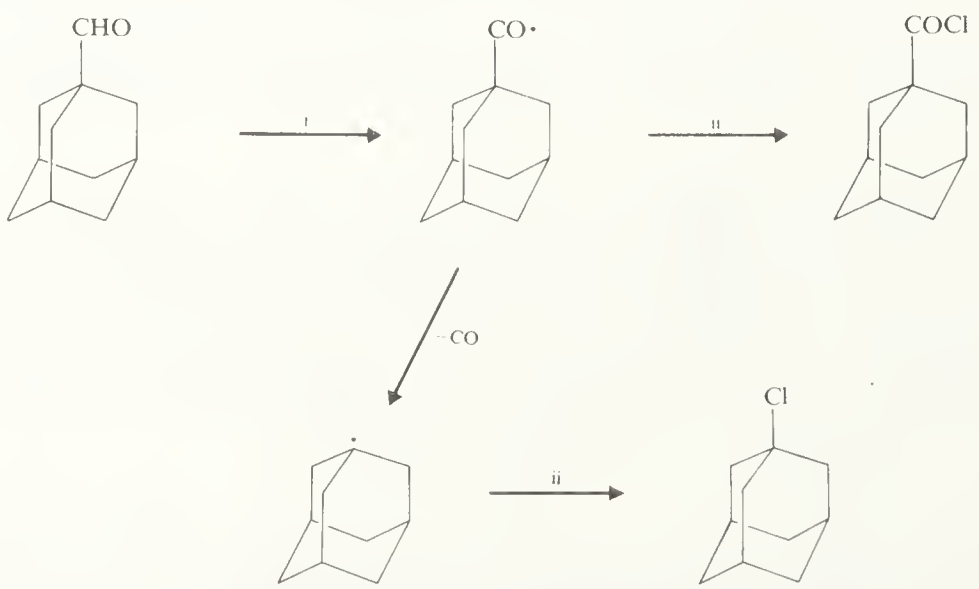
(**44**)

The reaction can be initiated conveniently by the thermal decomposition of dibenzoyl peroxide or azobisisobutyronitrile (to provide the radical Ẋ, equation 58). The example chosen illustrates an excellent route to γ-ketoacids through hydrolysis and decarboxylation of the addition product (**44**). In general, telomerization does not interfere and good yields of 1:1 adducts are formed from conjugated olefins.[143] Decarbonylation of the intermediate acyl radicals may prevent the desired reaction, especially at temperatures >100 °C, and decarbonylation is always an important side reaction with aldehydes such as pivaldehyde (see equation 63). Acyl radicals can also be trapped in other ways, *e.g.* by



(63)

reaction with tetrachloromethane.[144] An example of the preparation of an acid chloride directly from an aldehyde is shown in Scheme 29; some of the alkyl halide formed by the trapping of the decarbonylated intermediate radical is also produced.

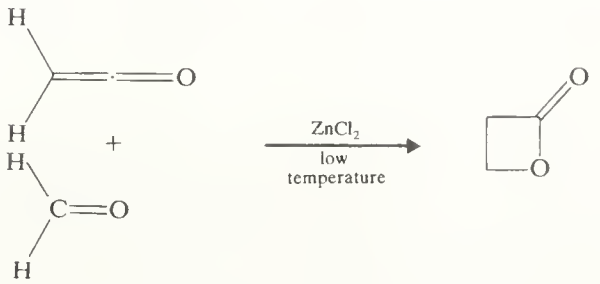


i, Bu^{t}OOBu^t, heat; ii, CCl_4.

SCHEME 29

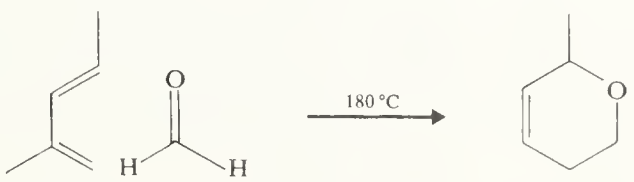
Aldehydes undergo a number of pericyclic reactions.[145] In the Paterno–Buchi reaction[146] the addition of a photoexcited state of an aldehyde to the ground state of an olefin leads to an oxetan (see Section 4.4.4.3). Equation 64 shows a typical example which illustrates the high regioselectivity[145] of this type of photochemical [2+2] cycloaddition. Aldehydes undergo [2+2] cycloadditions with keten, usually catalysed by Lewis acids, to give β-lactones;[147] the commercial route to β-propiolactone (see equation 65) is based on the use of formaldehyde in this reaction.

(64)



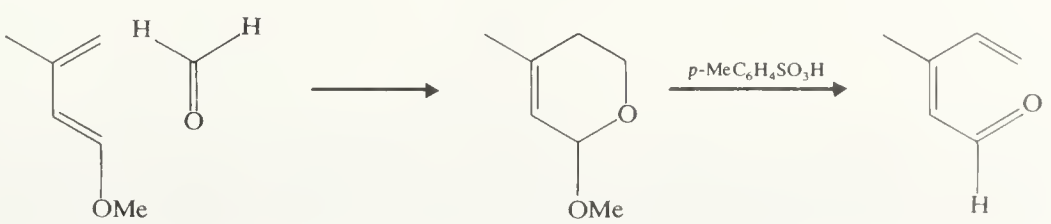
(65)

Formaldehyde can act as a dienophile. Such [4+2] cycloadditions lead to reduced pyran derivatives,[148] in marked contrast to the products formed by the acid-catalysed Prins reaction of formaldehyde with dienes. Equation 66 shows an example; the reaction fails



(66)

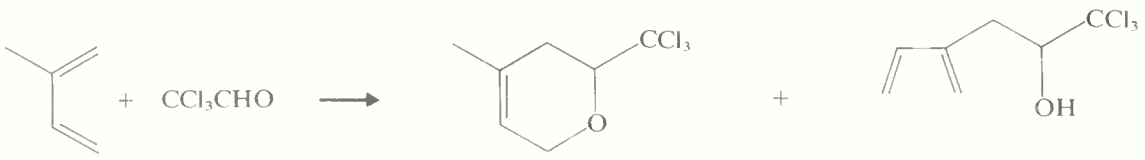
with less highly substituted dienes. Certain heterosubstituted dienes also react with formaldehyde. 1-Alkoxyalka-1,3-dienes, *e.g.* (**45**) (the enol-ethers of α,β-olefinic aldehydes), react to give unsaturated cyclic hemiacetals, *e.g.* (**46**), which can be used further in synthesis, as shown in Scheme 30.[149]



(**45**) (**46**)

SCHEME 30

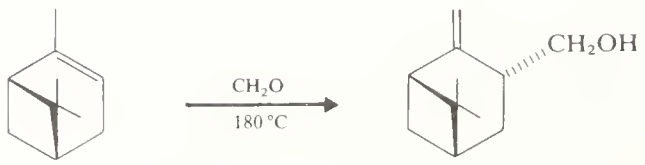
In some cases the 'ene' reaction competes with the [4+2] cycloaddition process; the proportion of the 'ene' product may be enhanced by the use of Lewis acid catalysts.[150] This is illustrated for the reaction of isoprene with chloral in Scheme 31. The 'ene' reaction of



Reaction conditions	*Temperature*	*Cycloaddition product*	*'Ene' product*
Uncatalysed	150 °C	90%	10%
$SnCl_4$ in CH_2Cl_2	25 °C	5%	95%

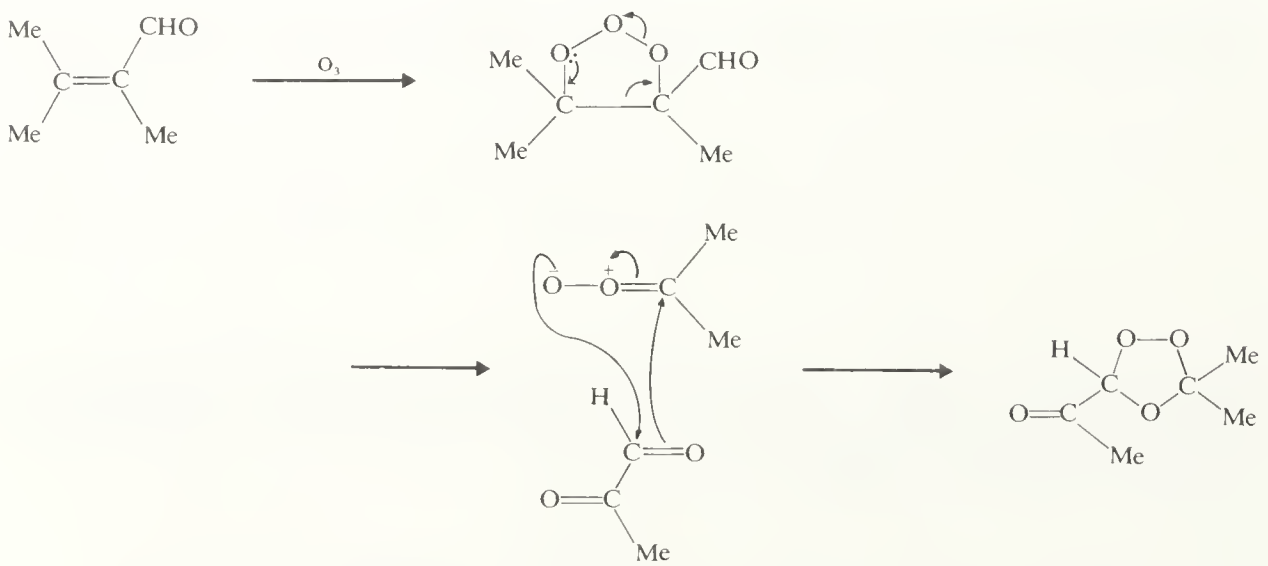
SCHEME 31

formaldehyde with simple olefins[150] can be a useful route to certain primary homoallylic alcohols, (*e.g.* see equation 67).



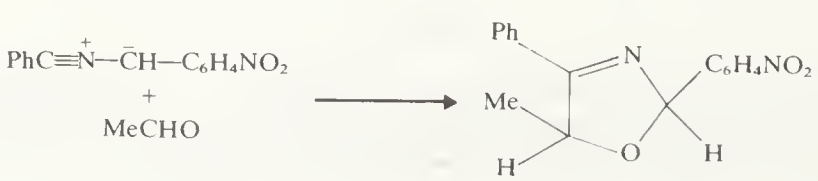
(67)

Aldehydes can also act as dipolarophiles,[151,145] but their reactivity in 1,3-dipolar additions is rather low. The reaction of a carbonyl group with a carbonyl oxide, which occurs in the transformation of a 1,2,3-trioxolan (the initial product from the cycloaddition of ozone to an olefin) to the 1,2,4-trioxolan (the ozonide), is a 1,3-dipolar addition of this type. In the example shown in Scheme 32 the addition of the dipolarophile to an



SCHEME 32

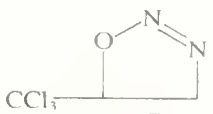
aldehyde in preference to a ketone is illustrated. Aldehydes will not react with nitrile oxides, but will react with azomethine imines,[151] nitrile ylides,[151] and ammonium ylides[152] to give a variety of heterocyclic five-membered systems, *cf.* equations 68 and 69.



(68)

(69)

The 1,3-dipolar addition of diazomethane to an aldehyde leads to a Δ^2-1,2,3-oxadiazoline, and in the case of chloral the unstable cycloaddition compound (**47**) has been isolated.[152] On gentle heating, compound (**47**) loses nitrogen and undergoes a



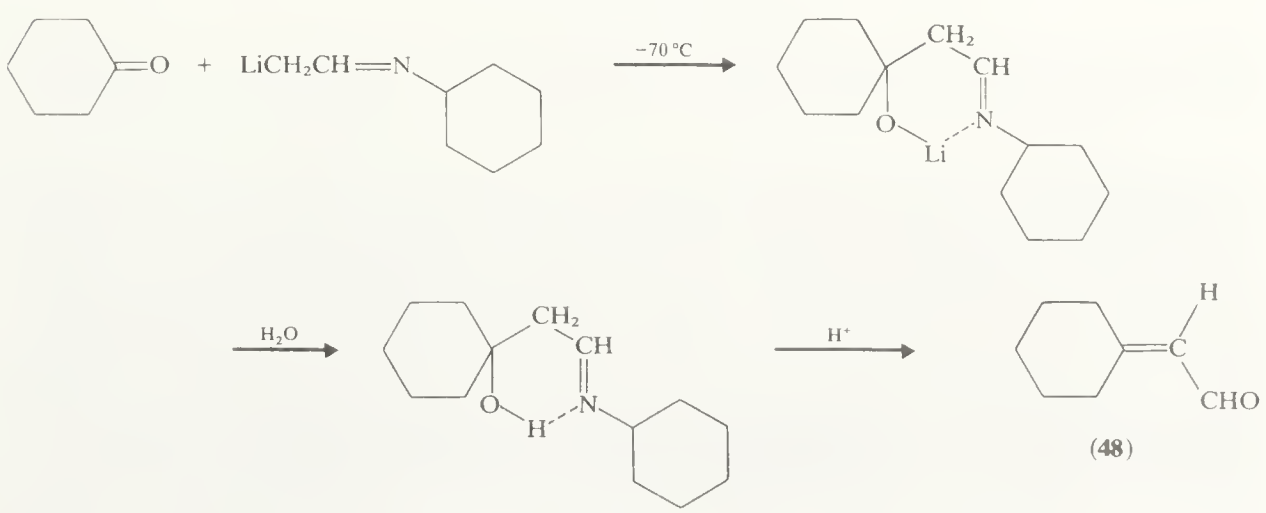
(**47**)

hydride shift to give 1,1,1-trichloroacetone. The oxadiazoline has not been isolated from the reaction of diazomethane with simple unsubstituted aliphatic aldehydes, which, in fact, gives acceptable yields of the methyl ketone. Heptanal, for example, is converted into octan-2-one.[153]

5.1.6 OLEFINIC ALDEHYDES

5.1.6.1 Preparation

Many methods exist for the preparation of α,β-olefinic aldehydes. The classical route is based on the aldol condensation[106] (Scheme 14 in Section 5.1.5.2) since the intermediate β-hydroxyaldehydes, or 'aldols', *e.g.* (**30**), if they possess an α-hydrogen atom, are readily dehydrated, and indeed are frequently not isolated (*cf.* equation 30). High yields are obtained in self-condensation reactions. The best way to condense two different aldehydes is probably to make use of the 'directed aldol' reaction[109] (Scheme 16) which avoids the simultaneous formation of the self-condensation products. Ketones can also be used in the 'directed aldol' reaction,[109] as shown in Scheme 33. β,β-Dialkyl-substituted α,β-olefinic aldehydes, such as the product (**48**) in Scheme 33, cannot be prepared by the ordinary

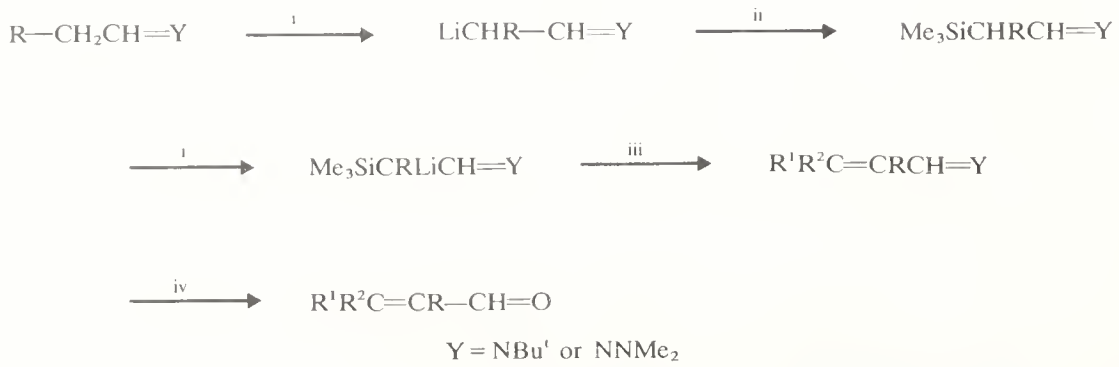


(**48**)

SCHEME 33

base-catalysed aldol condensation. For example, propanone and ethanal give the β-hydroxyketone as the crossed product and not the isomeric β-hydroxyaldehyde when condensed by base, as the aldehyde is more reactive towards nucleophiles than the ketone

and the carbanion from the ketone is more nucleophilic than the anion from the aldehyde. Other versions of the 'directed aldol' reaction have been developed, and used successfully in complex synthetic programmes. For example, a ketone, or an aldehyde, can be condensed with a silyl aldimine or a silyl aldehyde dimethylhydrazone to give a product which can readily be transformed into an α,β-olefinic aldehyde.[154] These methods are illustrated in Scheme 34.



i, LDA; ii, Me_3SiCl; iii, $R^1R^2C{=}O$; iv, $(CO_2H)_2$ (Y=NBu^t); Δ, then MeI, then H_3O^+ (Y = $NNMe_2$).

SCHEME 34

The carbonyl carbon atom of an aldehyde or ketone can also be converted into the β-carbon atom of an α,β-olefinic aldehyde by means of the phosphonate anion (**49**), which provides the formyl and α-carbon atoms.[155] The Wittig routes, using the phosphorus ylides (**50**)[156] or the phosphonate anion (**51**),[157] can only be applied successfully to aldehydes.

$$(EtO)_2PO{-}\bar{C}R{-}CH{=}NC_6H_{11}$$

(**49**)

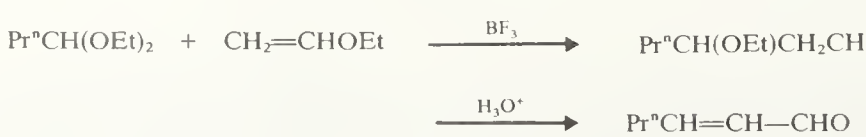
$$Ph_3\overset{+}{P}{-}\bar{C}R{-}CHO$$

(**50**)

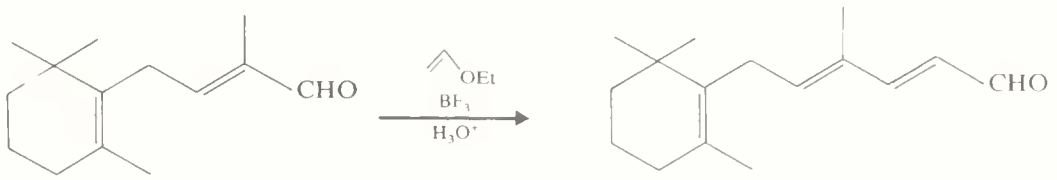
$$(EtO)_2PO{-}\bar{C}HCH(OEt)_2$$

(**51**)

α,β-Olefinic aldehydes can be prepared from β-alkoxyacetals (the protected form of 'aldols'), which are available from the condensation of acetals with vinyl ethers.[158] Scheme 35 illustrates this method. At higher temperatures, and depending on the molar proportions, further condensation may occur to give a product which, on acid hydrolysis, gives a conjugated dienal. The mechanism for this condensation apparently involves the formation of the oxygen-stabilized cation from the acetal, which then adds to the vinyl ether to give a new oxygen-stabilized cation. This method, including the modification using propenyl ethers to give 2-methylalk-2-enals, has been used a lot in the carotenoid and vitamin A fields[159] and is operated on a large commercial scale (see equation 70).

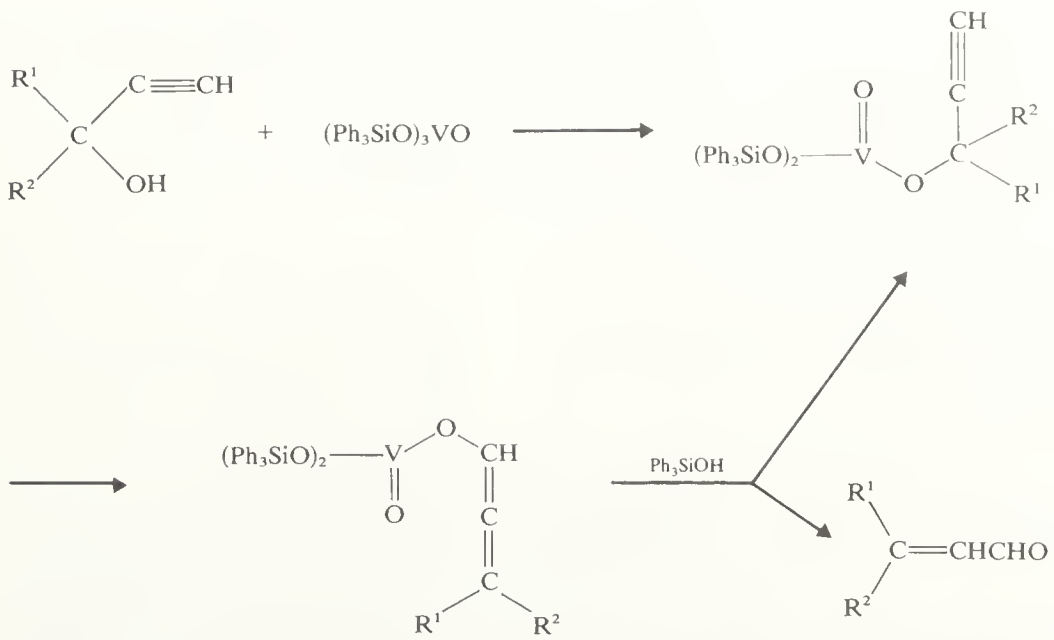


SCHEME 35



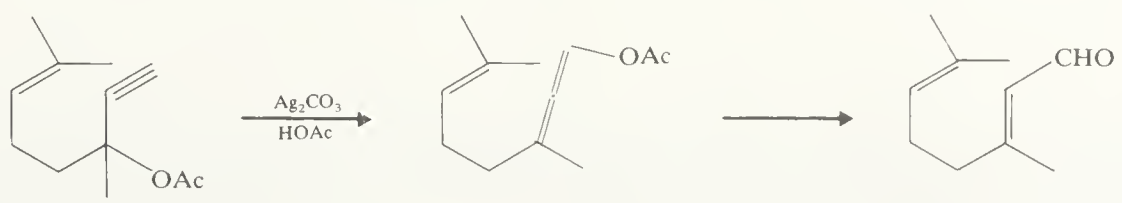
(70)

Several methods by which α-hydroxyacetylenes (readily available from aldehydes and ketones) can be converted into α,β-olefinic aldehydes have been developed. The direct rearrangement can be accomplished using vanadate catalysts, which can be either tris(triphenylsilyl)vanadate–triphenylsilanol[160] in an inert solvent at >100 °C, or a polymeric version of the catalyst[161] which is more stable in air. The rate-determining step is the isomerization of the propargyl vanadate to the allenic vanadate. The overall process is shown in Scheme 36. The acetates rearrange when boiled in acetic acid with a catalyst



SCHEME 36

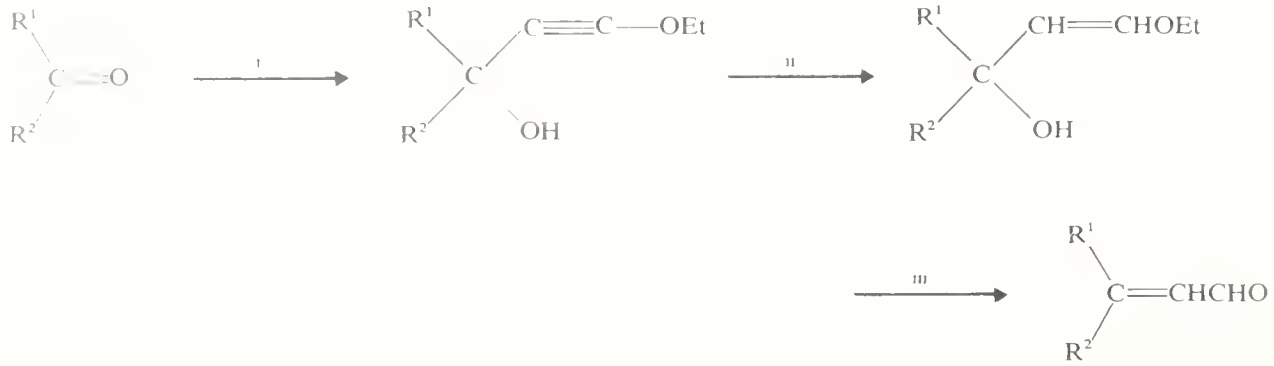
such as silver carbonate, giving allenic acetates which on saponification give α,β-olefinic aldehydes. This procedure[162] has formed the basis for the large-scale preparation of citral (see equation 71). Another possibility is to proceed *via* the chloroethynyl alcohol,



(71)

preparable by the action of hypochlorite on the hydroxyacetylene,[163] or by the condensation of a carbonyl compound with sodio-chloroacetylene.[164] Semihydrogenation and hydrolysis with dilute mineral acid leads to the α,β-olefinic aldehyde. A similar and better known approach[165] is to condense the carbonyl compound with lithio- or sodio-ethoxyacetylene to give an ethoxy-substituted hydroxyacetylene which on semihydrogenation and acid hydrolysis gives the α,β-olefinic aldehyde, as shown in Scheme 37.

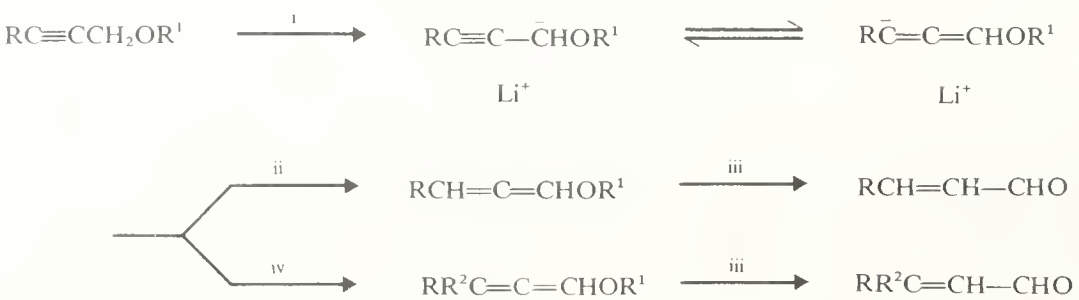
Primary α-alkoxyacetylenes can also be rearranged to their allenic analogues which, as enol ethers, are readily hydrolysed to give α,β-olefinic aldehydes. In this case, in contrast



i, M^+ $C{\equiv}COEt$, liq. NH_3; H^+; ii, H_2, Lindlar catalyst; iii, H_3O^+.

SCHEME 37

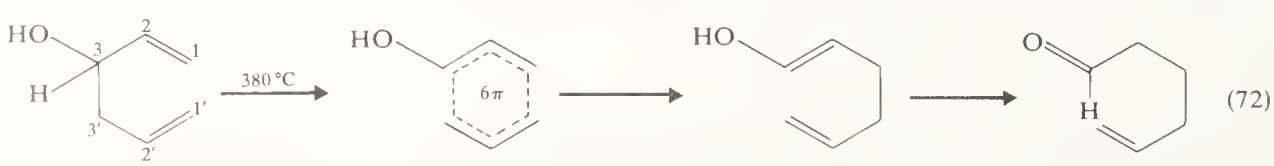
to the vanadate and acetate rearrangements, the propargylic carbon atom becomes the aldehydic carbonyl carbon atom. A β-alkyl group can also be introduced. The possibilities[166] are set out in Scheme 38.



i, BuLi; ii, MeOH; iii, H_3O^+; iv, R^2X.

SCHEME 38

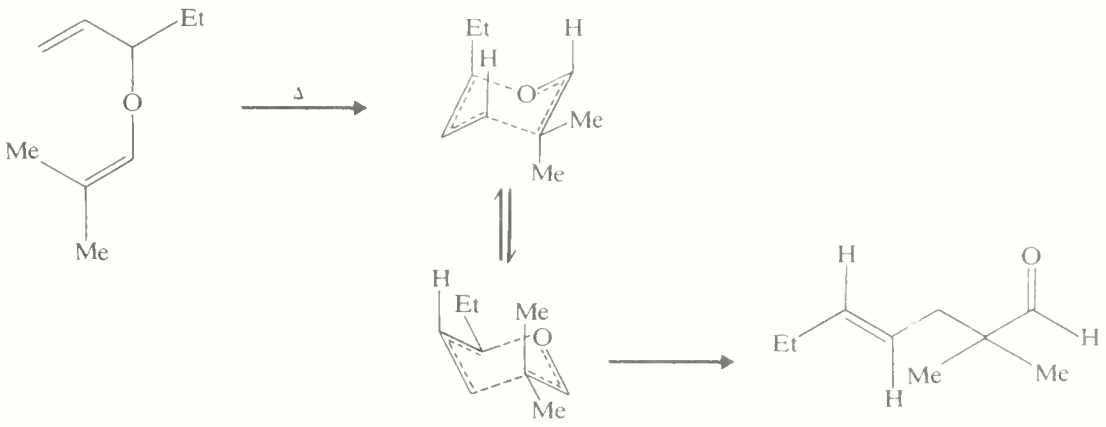
In recent years, a wide variety of olefinic aldehydes has been prepared by sequences relying on pericyclic reactions as the key steps. The Claisen rearrangement, a thermal pericyclic process involving an aromatic transition state, provides a route to many non-conjugated unsaturated aldehydes. Equation (72) shows the simple [3,3]-sigmatropic



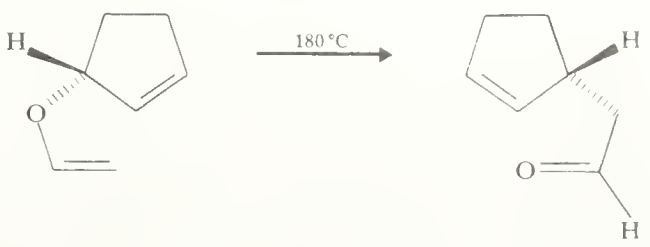
(72)

rearrangement of an allylvinylcarbinol.[167] However, the related rearrangement of allyl vinyl ethers has been generally more useful in synthesis. The allyl vinyl ethers have been prepared in several ways, including transetherification with ethyl vinyl ether in the presence of mercury(II) acetate[168] or phosphoric acid,[169] or by acid-catalysed elimination of allyl alcohol from allyl acetals.[170] The stereochemistry of the new carbon–carbon double bond is predominantly *trans*,[170] a reflection on the reduced non-bonded interactions in the chair-like transition state leading to the major product relative to those in the alternative chair-like transition state, as shown in Scheme 39.

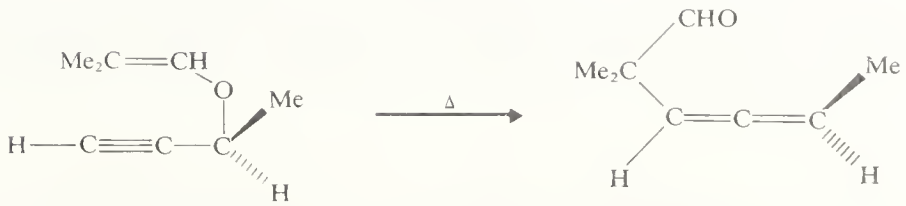
Chirality at the oxygen-bearing atom is transferred stereospecifically to carbon during the rearrangement;[171] for an example, see equation (73). The reaction can also be performed with propargyl vinyl ethers,[172] leading to β,γ,δ-allenic aldehydes of known chirality, as shown in the example in equation (74).



SCHEME 39



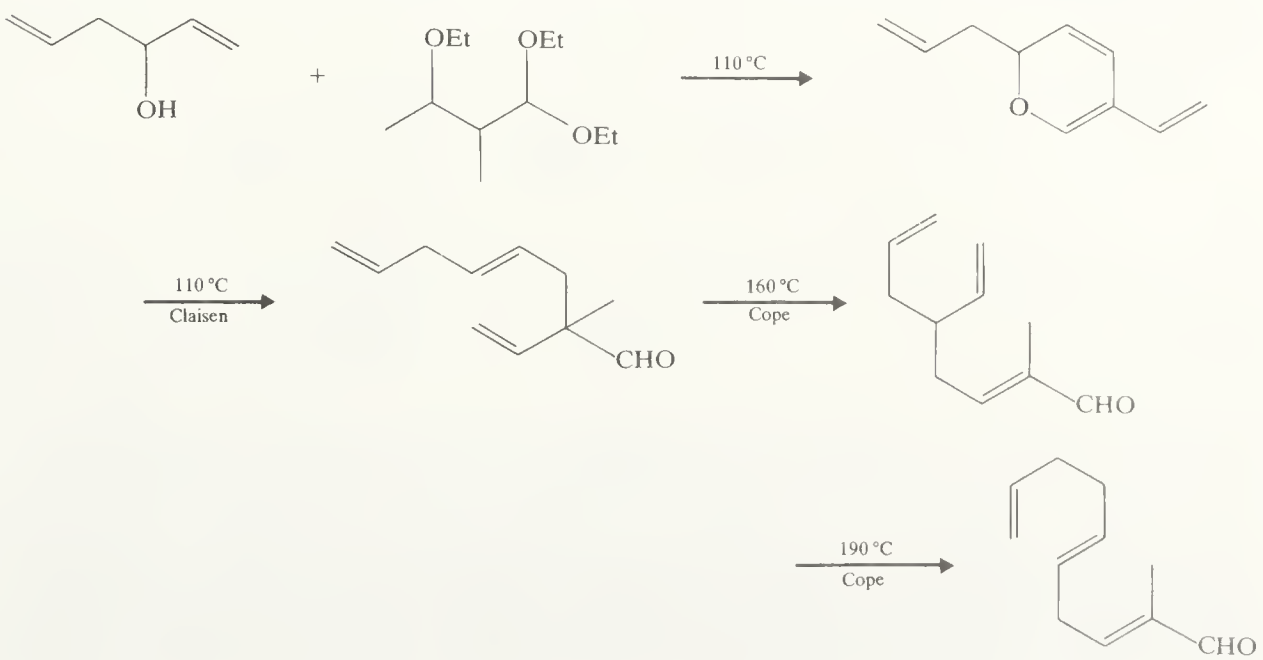
(73)



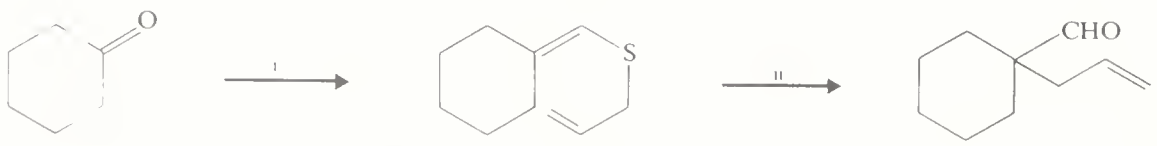
(74)

In more highly unsaturated systems the Claisen rearrangement may be combined with the related [3,3]-sigmatropic rearrangement of 1,5-dienes (the Cope rearrangement). Scheme 40 illustrates a typical example of this approach.[173] The Claisen and Cope rearrangements have been recently reviewed in detail.[174]

The mercury(II) oxide-catalysed thio-Claisen rearrangement can also be used in the synthesis of olefinic aldehydes. An example,[175] in which the allyl vinyl thioether is



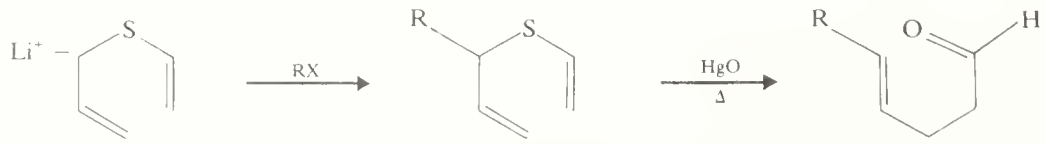
SCHEME 40



i, $(EtO)_2POCH—SCH_2CH=CH_2$; ii, HgO, 3 equiv., 190 °C.

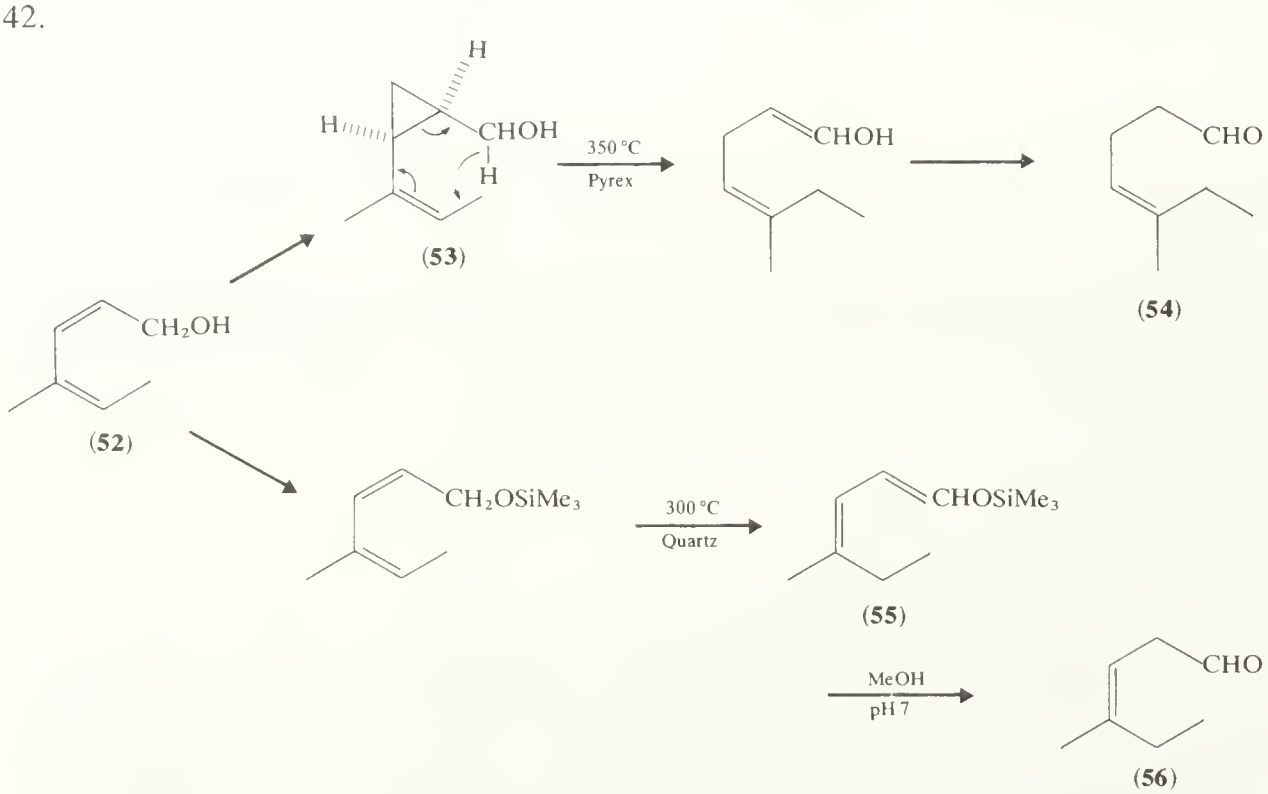
SCHEME 41

prepared by the phosphonate modification of the Wittig reaction, is shown in Scheme 41. Allyl vinyl sulphide is a synthon for γ,δ-olefinic aldehydes since it can be metallated and then alkylated to give a new thioether which, when subjected to the thio-Claisen rearrangement, gives a γ,δ-olefinic aldehyde,[176] as shown in equation (75).



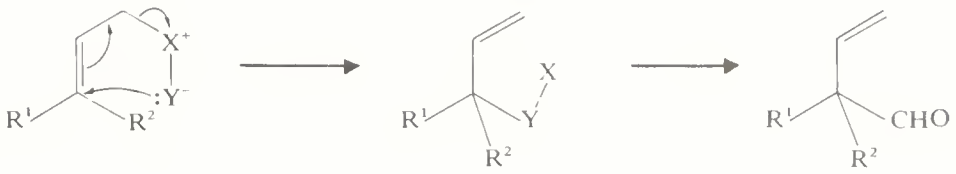
(75)

The γ,δ-olefinic aldehyde (**54**) has been prepared[177] from the dienol (**52**) through the vinylcyclopropylcarbinol (**53**), which at a high temperature undergoes the [1,5]-sigmatropic rearrangement to give (**54**) as shown in Scheme 42. When the trimethylsilyl ether of the same dienol (**52**) is heated to 300 °C, a [1,5]-sigmatropic hydrogen shift is induced, leading to the isomeric enol trimethylsilyl ether (**55**) from which the β,γ-olefinic aldehyde (**56**) is obtained[178] under neutral conditions in which conjugation of the two double bonds does not occur. These highly stereospecific processes are outlined in Scheme 42.



SCHEME 42

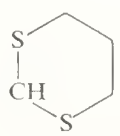
β,γ-Olefinic aldehydes can be obtained by [2,3]-sigmatropic rearrangements of the general type represented by equation (76), and detailed in Table 1. Of these methods, the most useful in terms of the accessibility of the starting materials and the final generation of the aldehyde function is the one due to Lythgoe (Table 1, entry 2); an example of the overall method is shown in Scheme 43.



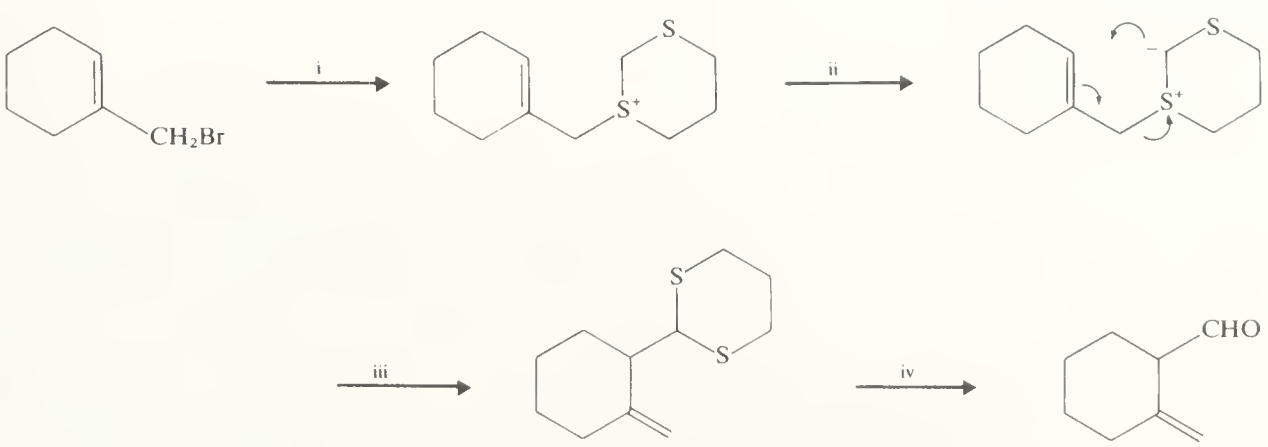
(76)

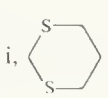
TABLE 1

Preparation of β,γ-Olefinic Aldehydes According to Equation (76)

	X	Y	*Ref.*
1.	SPh	CHSPh	a
2.			b
3.	NMe_2	CHCN	c
4.	NMe_2	CHSPh	d

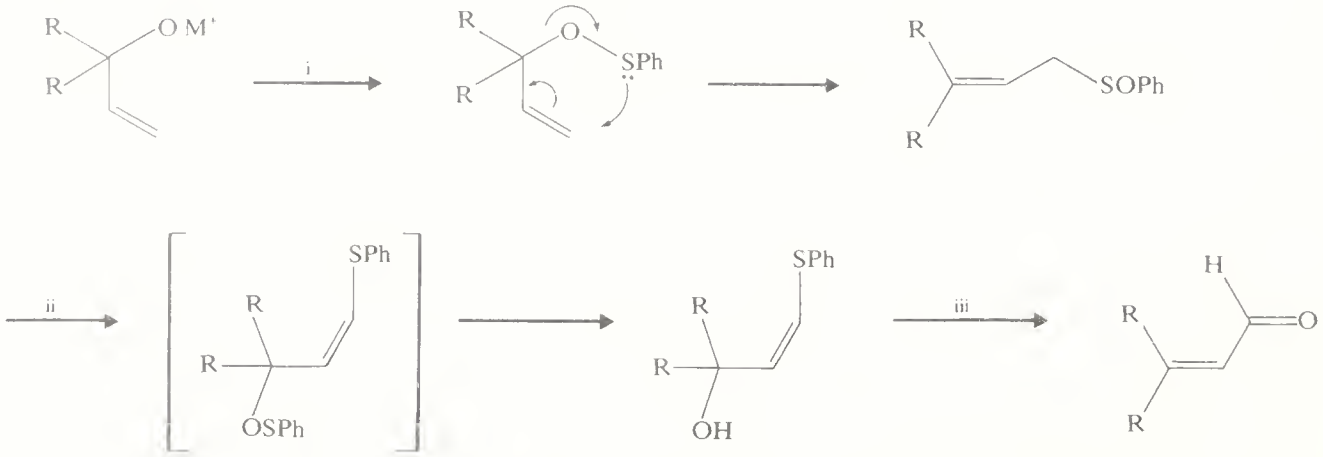
[a] S. Julia, C. Huynh, and D. Michelot, *Tetrahedron Letters*, 1972, 3587. [b] E. Hunt and B. Lythgoe, *J.C.S. Chem. Comm.*, 1972, 757. [c] A. T. Babayan, A. A. Grigoryan, K. P. Kiramidzhyan, and M. G. Indzhikyan, *Armyan. Khim. Zhur.*, 1970, **23,** 602 (*Chem. Abs.*, 1971, **74,** 111 360). [d] C. Huynh, S. Julia, R. Lorne, and D. Michelot, *Bull. Soc. chim. France*, 1972, 4057.



i,  ; ii, BuLi, −78 °C; iii, room temperature; iv, Hg^{2+}, H_2O.

SCHEME 43

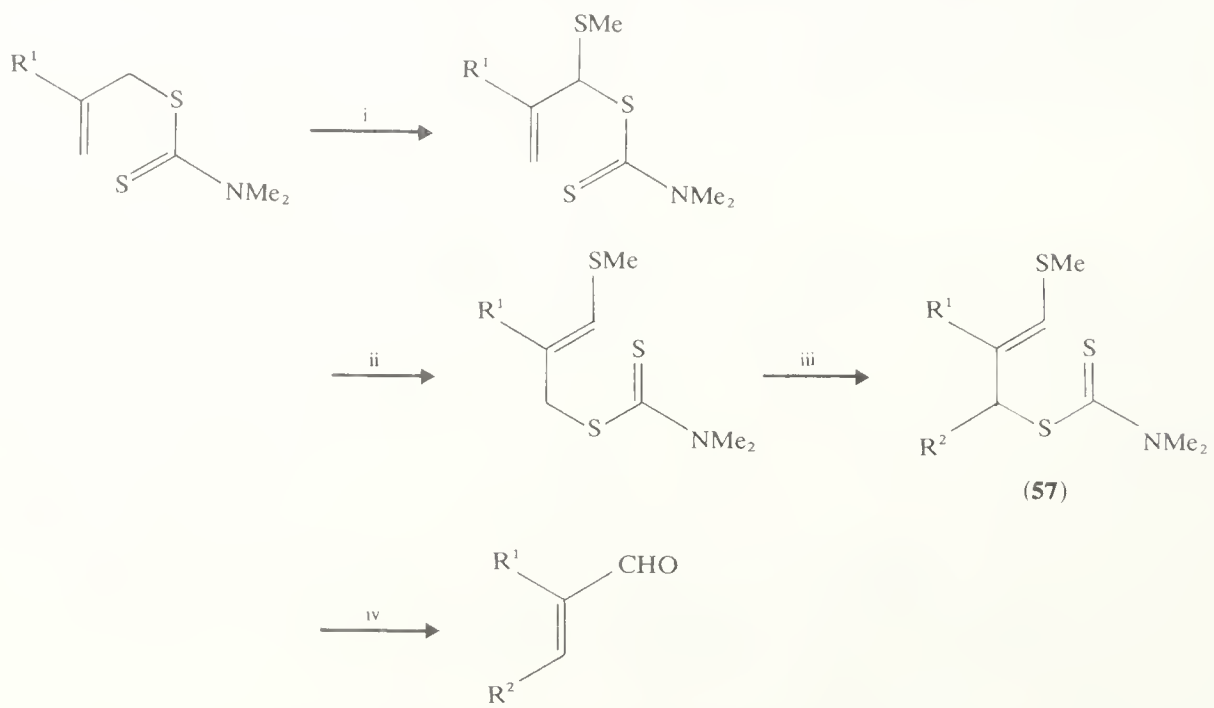
Interestingly, a [2,3]-sigmatropic rearrangement which is of the reverse type to the ones represented by equation (76) is involved in a recent method[179] for the preparation of α,β-olefinic aldehydes from vinylcarbinols. The metal derivative, prepared either by the action of an organovinyl derivative on a carbonyl compound or by the addition of an alkyl-lithium to an enolizable carbonyl compound, is quenched with benzenesulphenyl chloride, and the product undergoes a [2,3]-sigmatropic rearrangement to give an allylic sulphoxide. Sulphenylation gives a γ-hydroxy-α,β-olefinic thioether which is then finally converted into the conjugated olefinic aldehyde. The procedure is given in Scheme 44.



i, PhSCl; ii, LDA, PhSSPh; iii, $HgCl_2$, H_2O.

SCHEME 44

A [3,3]-sigmatropic rearrangement is the key step in another versatile synthesis[180] of α,β-olefinic aldehydes which starts from allyl dithiocarbamates and is set out in Scheme 45. The final intermediate (**57**) is analogous to the final intermediate in Scheme 44 and



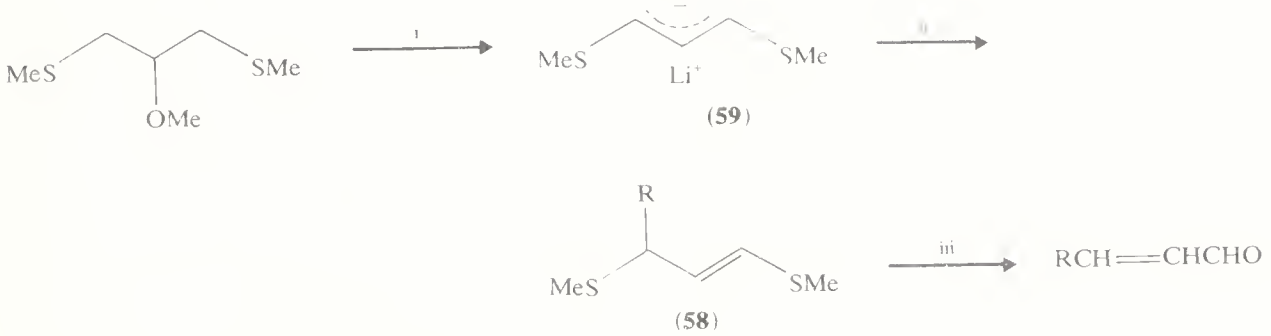
i, LDA, MeSSMe; ii, room temperature rearrangement; iii, LDA, R^2X; iv, Hg^{2+}, H_2O, MeCN.

SCHEME 45

also to the final intermediate (**58**) in a further synthesis[181] (see Scheme 46) in which the anion (**59**) is used as the equivalent of the β-formylvinyl anion.

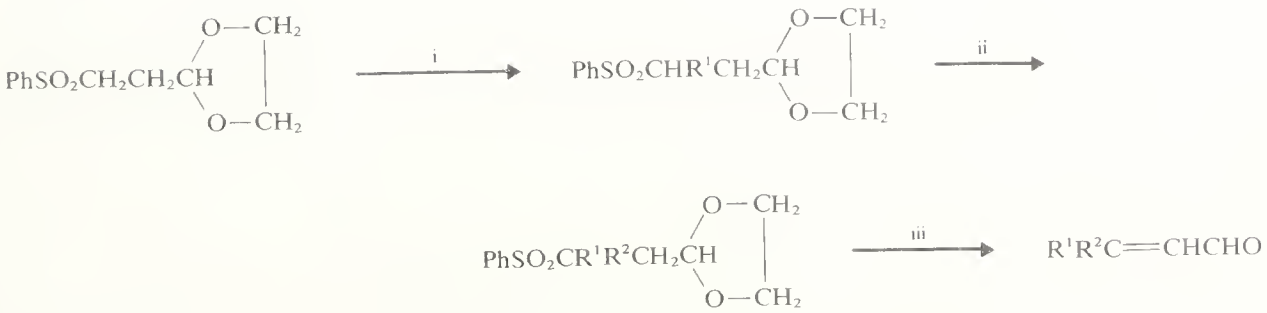
β-Phenylsulphonylacetals can similarly be used as β-formylvinyl equivalents, as shown in Scheme 47.[182] Both *cis*- and *trans*-2-methoxycyclopropyl-lithium can be used for the introduction of a three-carbon unit into a carbonyl compound giving rise ultimately (see equation 77) to a β,γ-olefinic aldehyde.[183]

Eschenmoser has recently introduced two remarkable syntheses of olefinic aldehydes based on the reactions of olefins with α-chloroaldonitrones.[184] In the first of these (see Scheme 48) two carbon atoms are introduced into an olefin to give a β,γ-olefinic aldehyde



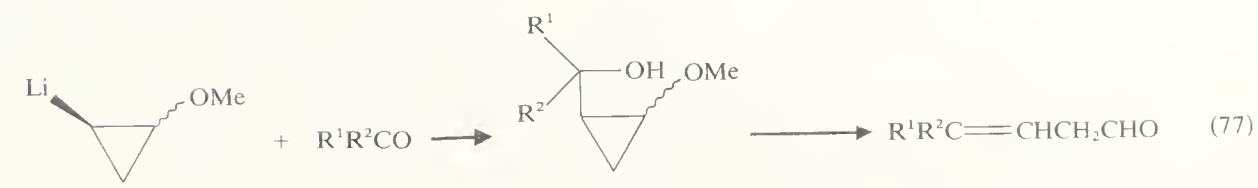
i, LDA, THF, −15 °C; ii, RX; iii, Hg^{2+}, H_2O.

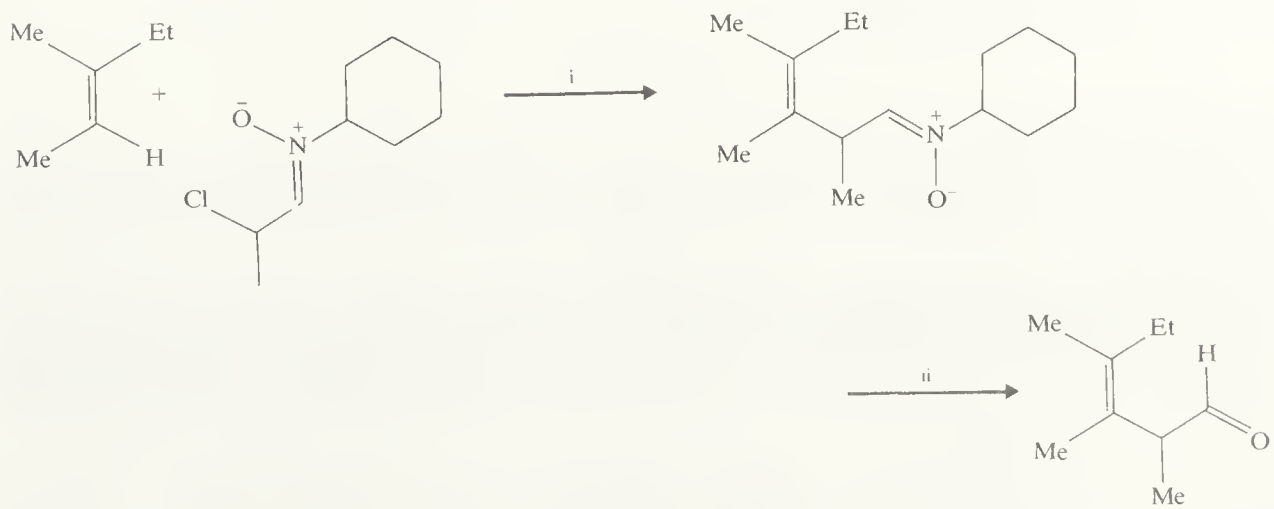
SCHEME 46



i, BuLi, R^1X; ii, BuLi, R^2X; iii, $MeCO_2H$, H_2O; base.

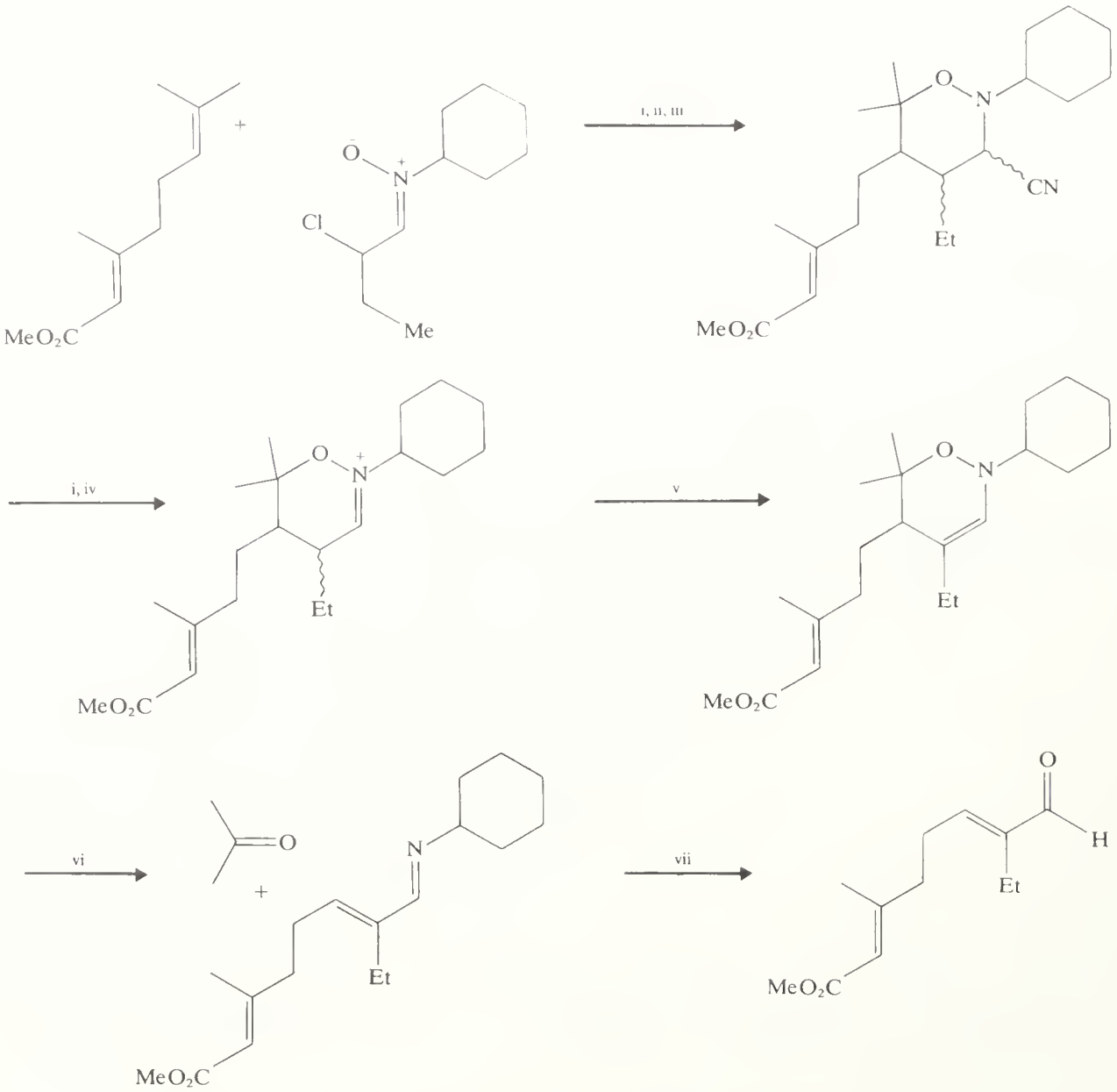
SCHEME 47





i, $Ag^+BF_4^-$ in liq. SO_2; ii, H_3O^+.

SCHEME 48

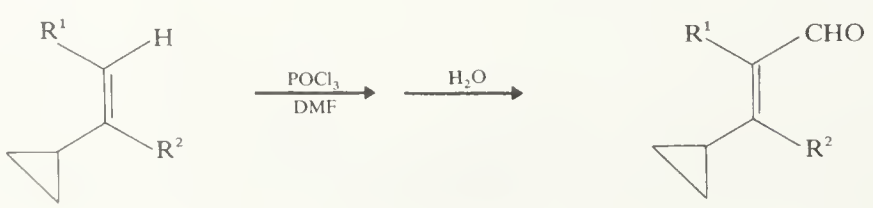


i, $Ag^+BF_4^-$ in $ClCH_2CH_2Cl$; ii, filter off AgCl; iii, KCN, H_2O; iv. $Na^+BPh_4^-$; v, K_2CO_3, CH_2Cl_2; vi, 80 °C, CH_2Cl_2; vii, H_3O^+.

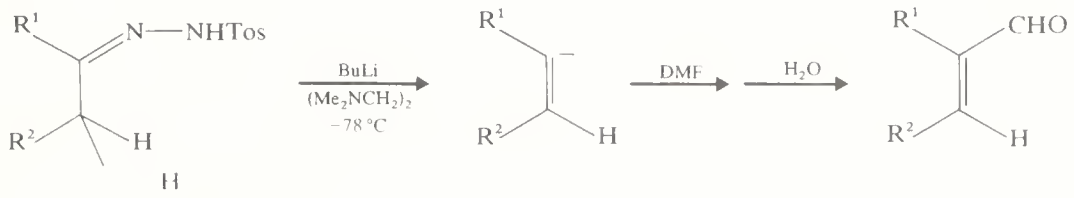
SCHEME 49

in which the position and configuration of the original double bond is retained. In the second (see Scheme 49) the olefin is completely severed at the double bond and one of the two previously connected carbon atoms becomes the β-carbon atom of an α,β-olefinic aldehyde.

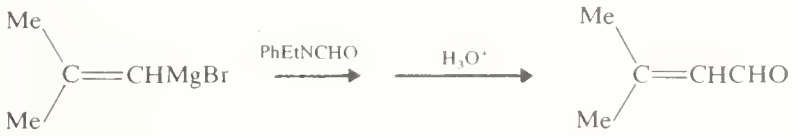
The Vilsmeier formylation has occasionally been applied to olefins[185] (see equation 78). The anion formed intermediately in the Bamford–Stevens olefin synthesis can be trapped by formylation[187] (see equation 79), and similarly vinylmagnesium halides (and less



(78)[186]



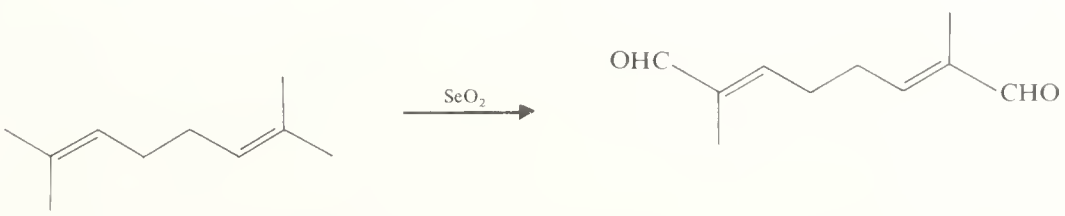
(79)



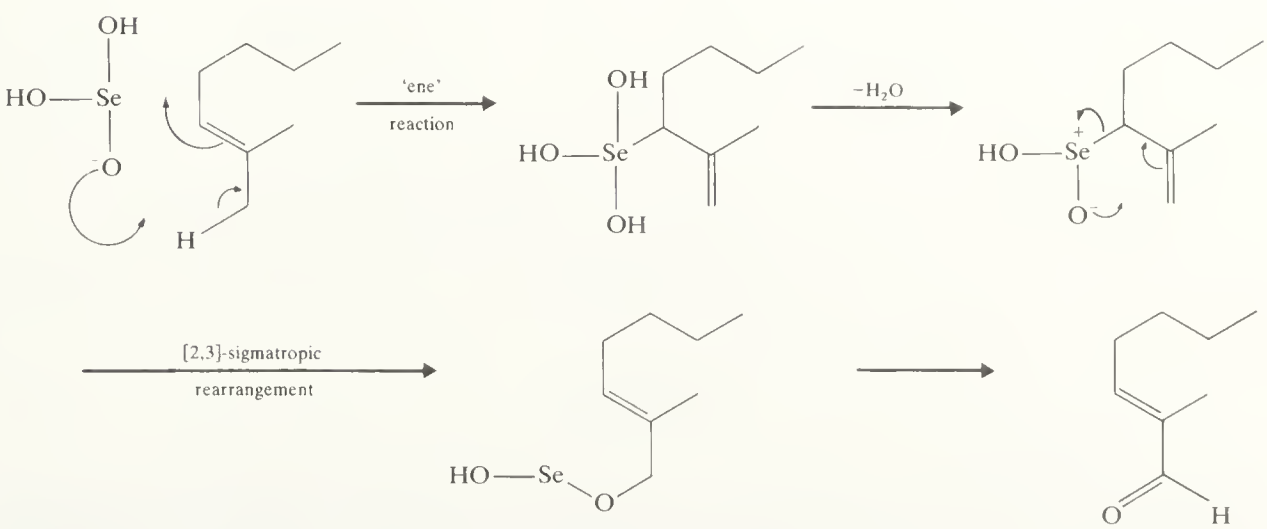
(80)

satisfactorily alkenyl-lithiums) can be formylated[188] (see equation 80). The products from all these methods are α,β-olefinic aldehydes.

Olefins are oxidized to α,β-olefinic aldehydes containing the same number of carbon atoms by selenium dioxide in refluxing 95% ethanol. Geminal dimethyl-substituted olefins give exclusively the (*E*) configuration (see equation 81). The reaction is considered to proceed by the mechanism set out in Scheme 50. Both the (*Z*)- and (*E*)-forms of the

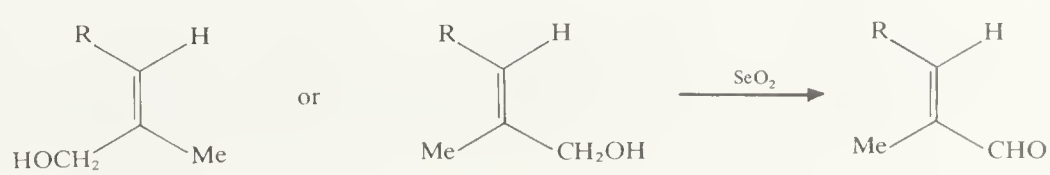


(81)



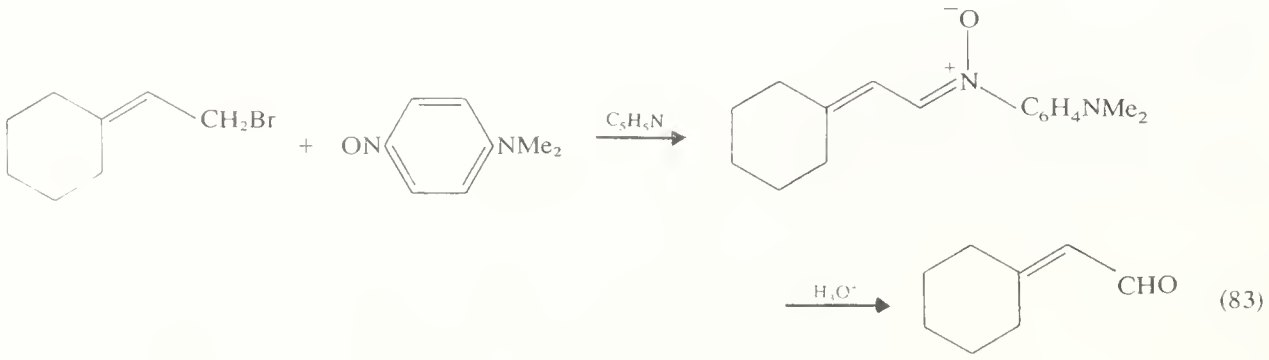
SCHEME 50

corresponding allylic alcohols are oxidized to the (*E*)-aldehyde under these conditions (see equation 82). The reaction has been used in several natural product syntheses and has recently been reviewed.[189]

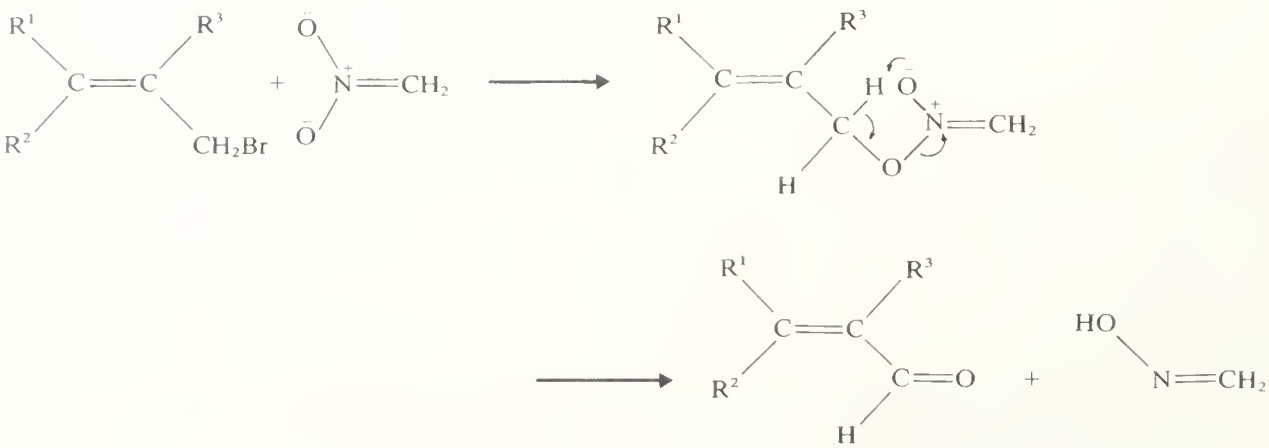


(82)

Propene is oxidized to acrolein (prop-2-enal) (**3**) industrially[55] using air as the oxidant in the presence of a copper oxide catalyst at 350 °C. Allylic alcohols can be specifically oxidized to α,β-olefinic aldehydes by activated manganese(IV) oxide;[190] vitamin A alcohol, in a neutral organic solvent at room temperature, is converted into vitamin A aldehyde (retinal, **4**) by this reagent. Allylic alcohols can also be oxidized in the vapour phase by oxygen over a heated copper catalyst.[55] Several methods are available for the conversion of allylic bromides into the corresponding α,β-olefinic aldehydes. Krohnke's method,[191] employing *p*-nitrosodimethylaniline, is applicable (see equation 83), and treatment with the potassium salt of nitromethane (see Scheme 51) has also proved effective.[192] Reaction with potassium chromate in HMPT in the presence of a crown ether leads to the allylic chromate ester which then collapses in the usual way to generate the aldehyde function.[193]



(83)

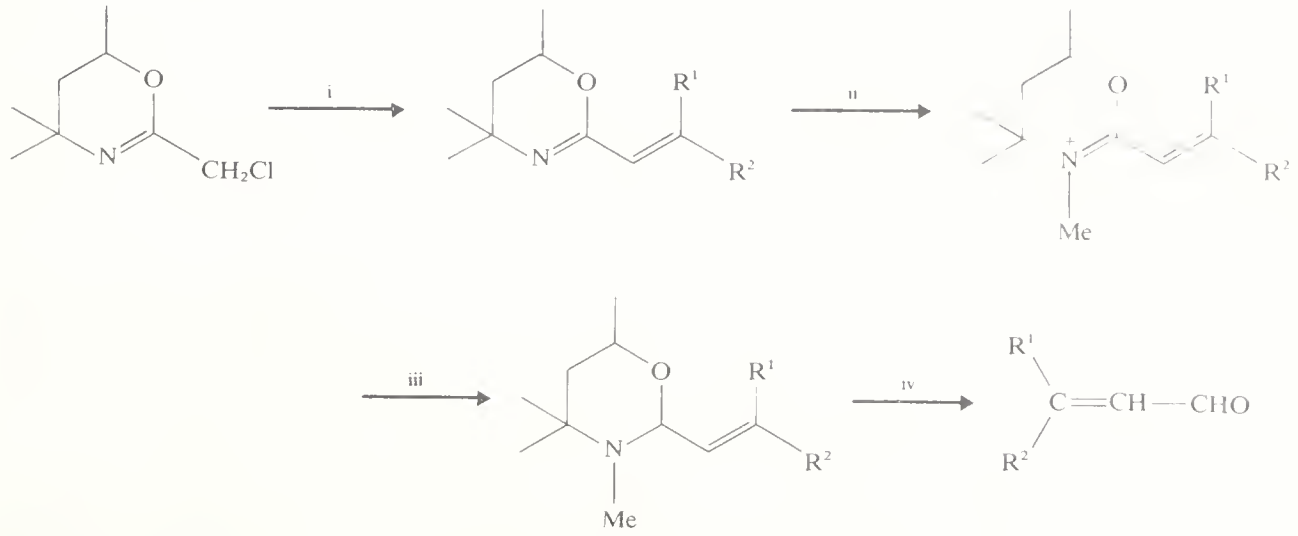


SCHEME 51

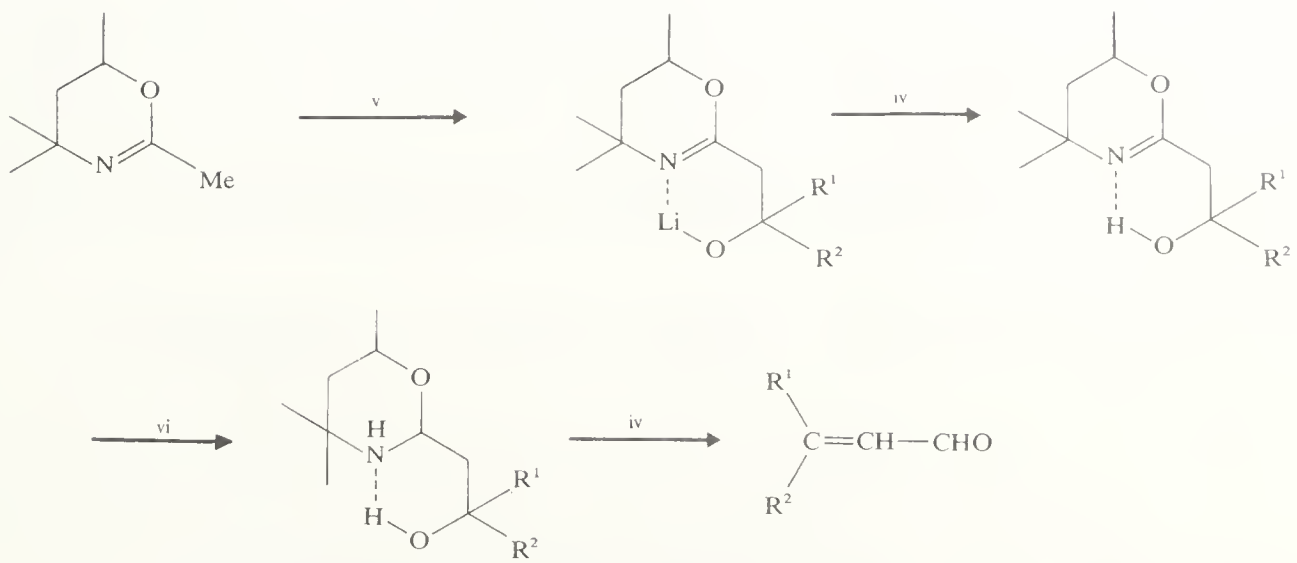
Several of the more recent methods for the synthesis of saturated aldehydes can also be adapted to the preparation of α,β-olefinic aldehydes. For instance, the readily available keten thioacetals on metallation with lithium di-isopropylamide in HMPT give allylic anions which protonate predominantly at the ring carbon atom to give the cyclic thioacetals of α,β-olefinic aldehydes, from which the aldehyde can be regenerated.[194] Two routes[195] based on the dihydro-oxazine approach (see Section 5.1.2.9 and Scheme 4) are shown in Scheme 52.

A ketone can be converted into the α,β-olefinic aldehyde with one extra carbon atom by transforming it into either the α-chloroaldehyde or the β-chloro-α,β-olefinic aldehyde (see Section 5.1.7). The former can then be dehydrochlorinated by the action of calcium carbonate and lithium perchlorate in HMPT,[196] and the latter can be reductively dechlorinated with zinc.[197] An acid chloride can be converted into the α,β-olefinic aldehyde containing two extra carbon atoms by the route[198] illustrated in Scheme 53.

1.

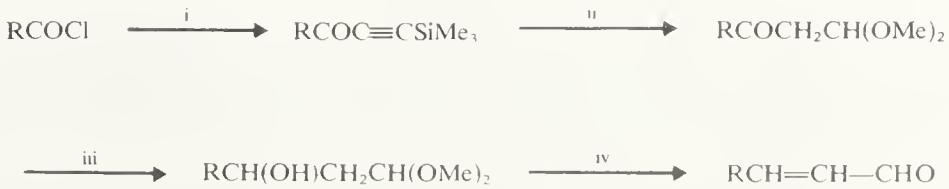


2.



i, Wittig reaction with R^1R^2CO: ii, MeX; iii, BH_4 at −40 °C; iv, H_3O^+; v, BuLi, R^1R^2CO; vi, $\bar{B}H_4$ at 25 °C.

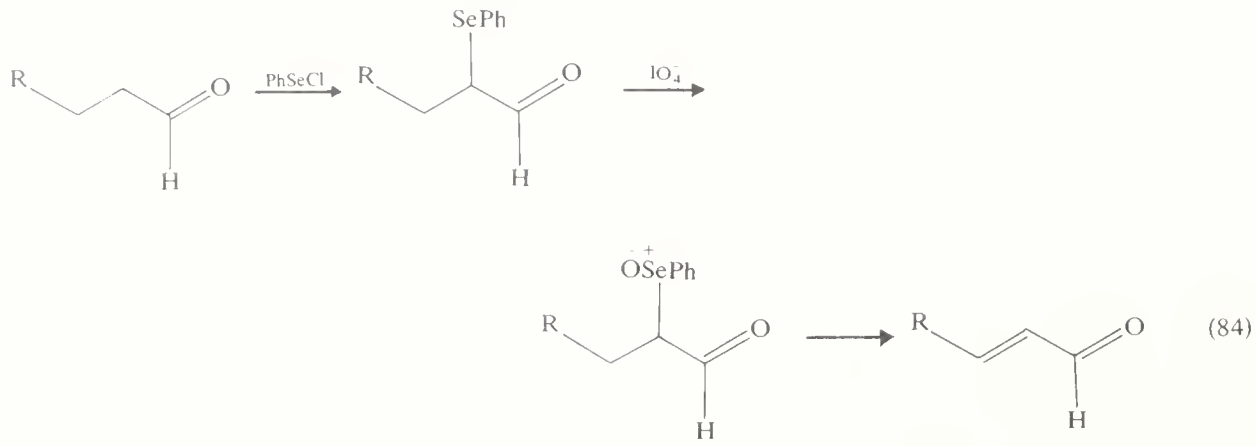
SCHEME 52



i, $Me_3SiC{\equiv}CSiMe_3$, $AlCl_3$, ii, 0.1 M $Me\bar{O}Na^+$ in MeOH; iii, BH_4; iv, H_3O^+.

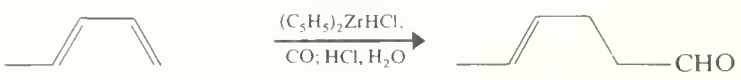
SCHEME 53

Until recently, the introduction of α,β-unsaturation into a saturated aldehyde (equation 84) was not a feasible synthetic step but this can now be easily accomplished[199] by α-selenation, using phenylselenyl chloride, followed by selenoxide elimination, which occurs spontaneously at room temperature when the selenoether is oxidized to the selenoxide with periodate.

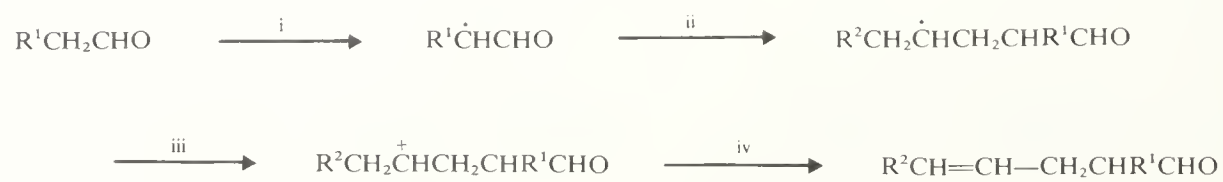


(84)

Hydrozirconation (see Section 5.1.2.7) of a 1,3-diene occurs by 1,2-addition to the less hindered double bond, and carbonylation of the resulant alkenylzirconium complex then gives a high yield of a γ,δ-olefinic aldehyde.[200] The procedure is illustrated by equation (85). More modest yields of γ,δ-olefinic aldehydes[201] are produced by the oxidative addition of aldehydes to olefins in the presence of Mn(III) and Cu(II) salts, as shown in Scheme 54.



(85)



i, Mn^{3+}; ii, $R^2CH_2CH{=}CH_2$; iii, Cu^{2+}; iv, $-H^+$.

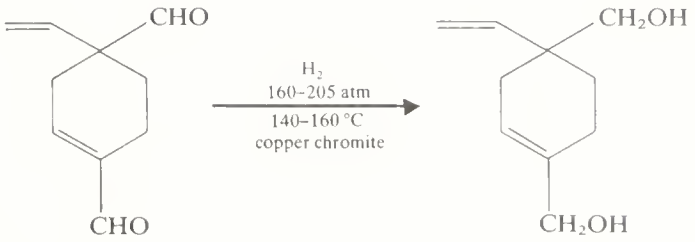
SCHEME 54

5.1.6.2 Reduction of conjugated olefinic aldehydes

The selective reduction of α,β-olefinic aldehydes to the saturated aldehydes is considered in Section 5.1.2.13. It is also possible to reduce them selectively to allylic alcohols. The Meerwein–Ponndorf–Verley reduction[74] with aluminium isopropoxide will do this (equation 86). Lithium aluminium hydride in ether also gives the allylic alcohol and so

(86)

does sodium borohydride in aqueous ethanol, although with a few of the less highly substituted alk-2-enals, *e.g.* acrolein, as much as 15% of the product may be the saturated alcohol formed by initial conjugate reduction.[202] Selective reduction at the carbonyl group can also be achieved by heterogeneous catalytic hydrogenation using as catalyst copper chromite (*e.g.* see equation 87),[203] platinum on carbon in the presence of iron(II) chloride and zinc acetate[78] (equation 86), or rhenium black[204] (equation 86).



(87)

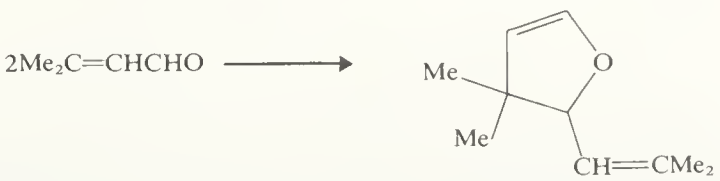
Under more vigorous conditions,[203] heterogeneous catalytic hydrogenation can lead to complete reduction to the saturated alcohol (see equation 88).[56] Homogeneous hydrogenation using tris(triphenylphosphine)rhodium chloride as catalyst may lead to substantial or complete decarbonylation.[79]

$$MeCH{=}CH{-}CHO \xrightarrow[200\ ^{\circ}C]{H_2,\ Cu/SiO_2} MeCH_2CH_2CH_2OH \qquad (88)$$

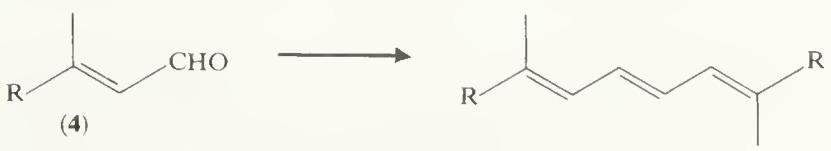
Bimolecular reduction of an alk-2-enal with zinc in acetic acid gives the *meso*- and (±)-forms of the pinacol[205] (see equation 89). Using electrochemical methods,[206] conditions can be found which lead predominantly either to the 3,3-coupled product, a 1,6-dialdehyde[207] (see equation 90) or to a dihydrofuran arising through 1,3-coupling (see equation 91) together with some of the pinacol.[208] Bimolecular deoxygenation can also be achieved[209] using a titanium(III) chloride–lithium aluminium hydride reagent, as in the recent direct synthesis of β-carotene from retinal (**4**) (see equation 92).

$$2CH_2{=}CMeCHO \longrightarrow CH_2{=}CMe{-}CH(OH){-}CH(OH)CMe{=}CH_2 \qquad (89)$$

$$2CH_2{=}CH{-}CHO \longrightarrow OHCCH_2CH_2CH_2CH_2CHO \qquad (90)$$



(91)



(4)

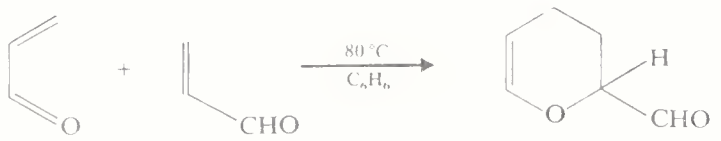
(92)

5.1.6.3 Cycloadditions of conjugated aldehydes

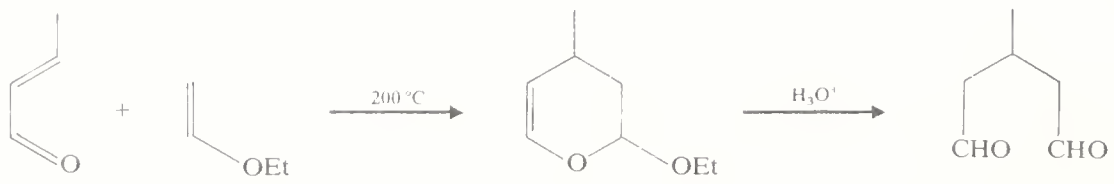
α,β-Olefinic aldehydes can act as heterodienes in [4+2] cycloadditions;[148] the dienophile can be a hydrocarbon, or a vinyl derivative (**60**; X = Me, Ph, OR, CN, CO_2R, CHO, $NHCO_2R$,[210] NHCONHR,[210] *etc.*). Examples of these reactions are the dimerization of acrolein (see equation 93) and the process illustrated in equation 94 which provides a useful 1,5-dialdehyde synthesis.

$$CH_2{=}CH{-}X$$

(**60**)



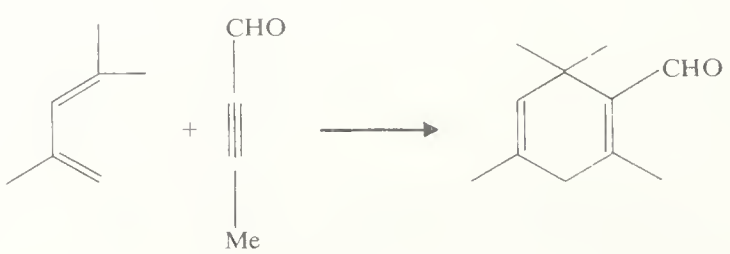
(93)



(94)

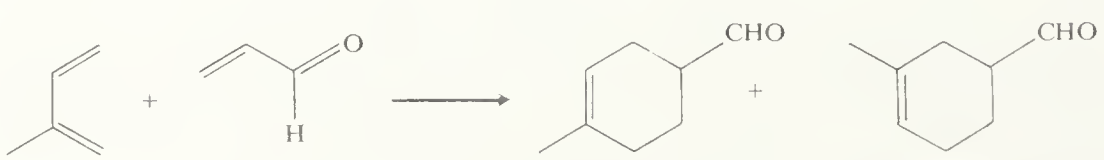
α,β-Olefinic aldehydes, and α,β-acetylenic aldehydes, can also act as the dienophile in the classical Diels–Alder reaction with homodienes.[211] Highly substituted aldehydes, *e.g.* β,β-dimethylacrolein, react sluggishly but α-methylacrolein, crotonaldehyde, *etc.* react readily with cyclopentadiene, isoprene, *etc.* (see equations 95 and 96). These cycloadditions show the usual stereochemical features of the Diels–Alder reaction. The orientation

(95)



(96)

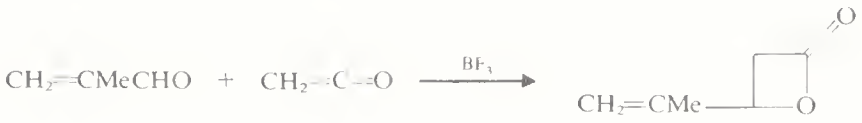
is very much affected by the presence of Lewis acids, which also speed up the reaction (see Scheme 55). This aspect can perhaps be most simply rationalized in terms of frontier orbital theory.[145]



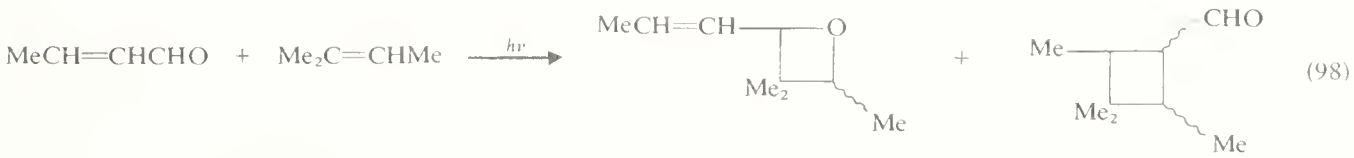
Temperature	*Conditions*	*Product ratio*
150 °C	neat; no Lewis acid	59 : 41
<25 °C	$SnCl_4.5H_2O$ in C_6H_6	96 : 4

SCHEME 55

α,β-Olefinic aldehydes undergo certain [2+2] cycloadditions; for example with keten[147] (see equation 97) and in the Paterno–Buchi reaction,[146] where both cyclobutane and oxetan rings are formed (see equation 98). They undergo 1,3-dipolar addition reactions at

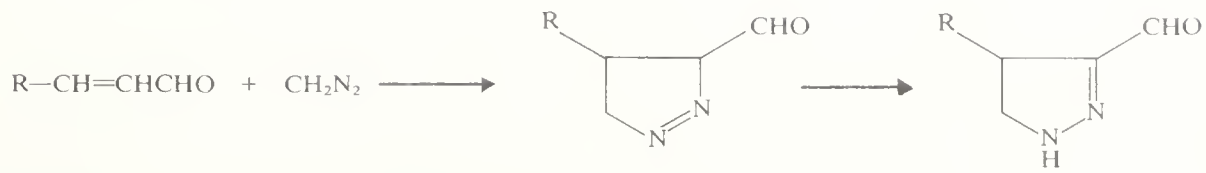


(97)



(98)

the carbon–carbon double bond with diazomethane[152] (see equation 99) and with ozone (see Scheme 32).



(99)

5.1.6.4 Other additions of conjugated aldehydes

In α,β-olefinic aldehydes there is a conjugated system which can be represented in pictorial terms by the two resonance forms shown in Figure 6. It is apparent that there is

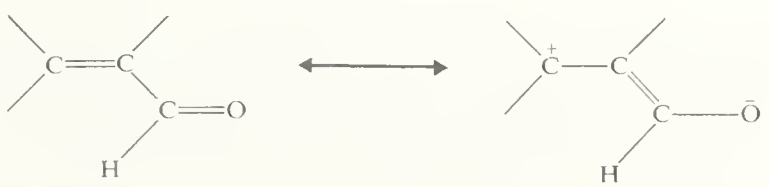
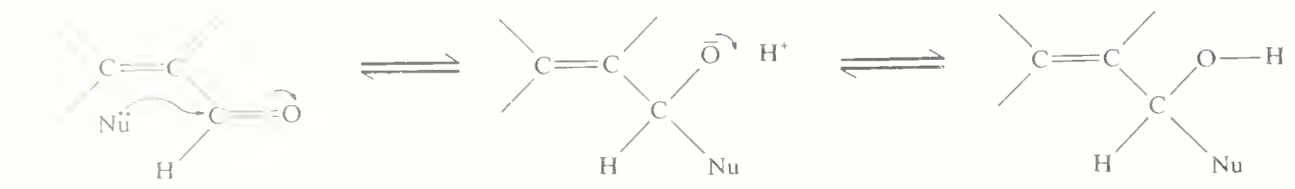


Figure 6 The resonance picture of an α,β-olefinic aldehyde

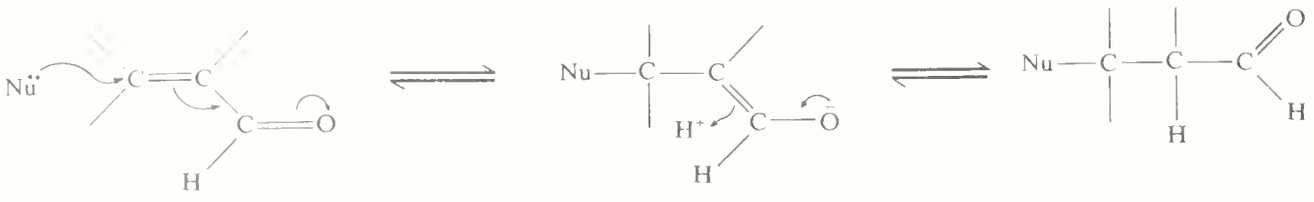
some electrophilic character at both the carbonyl carbon atom and at the β-position; nucleophilic attack can therefore be expected at both these positions. In fact, attack usually occurs preferentially or exclusively at the carbonyl carbon atom, leading to 1,2-addition, with retention of the carbon–carbon double bond, although conjugated addition involving initial attack at the β-position is sometimes encountered, *e.g.* as a minor pathway in certain borohydride reductions (see Section 5.1.6.2). The two processes are compared in Scheme 56 in a general fashion.

Acid-catalysed addition may also occur by either a 1,2- or a 1,4-process, since protonation occurs on oxygen to give the ion (**61**), which is also an allylic cation with electrophilic character at both the 'carbonyl' carbon atom and the β-position (see equation 100).

Grignard[212] and other organometallic reagents[213] react predominantly or exclusively by 1,2-addition to give secondary allylic alcohols (see equation 101). With highly hindered Grignard reagents, *e.g.* t-butylmagnesium chloride, an increase in the amount of the 1,4-addition product, a saturated aldehyde, is noted. The product ratios in these Grignard additions, unlike some others to conjugated systems, are apparently not influenced by the addition of copper(I) chloride. Organocopper derivatives do not undergo conjugate addition to α,β-olefinic aldehydes.

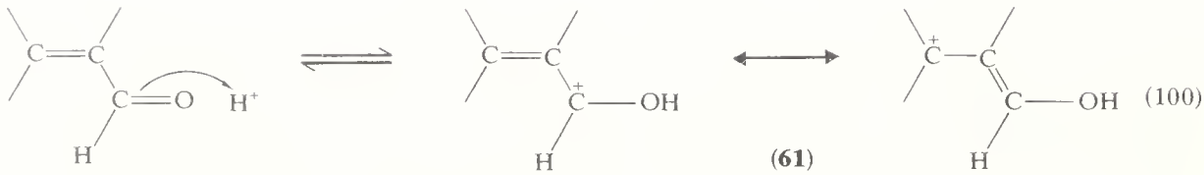


1,2-Addition

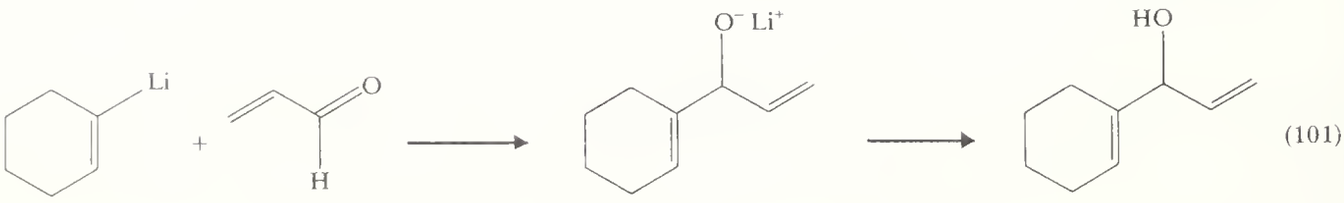


1,4-Addition

SCHEME 56



(100)

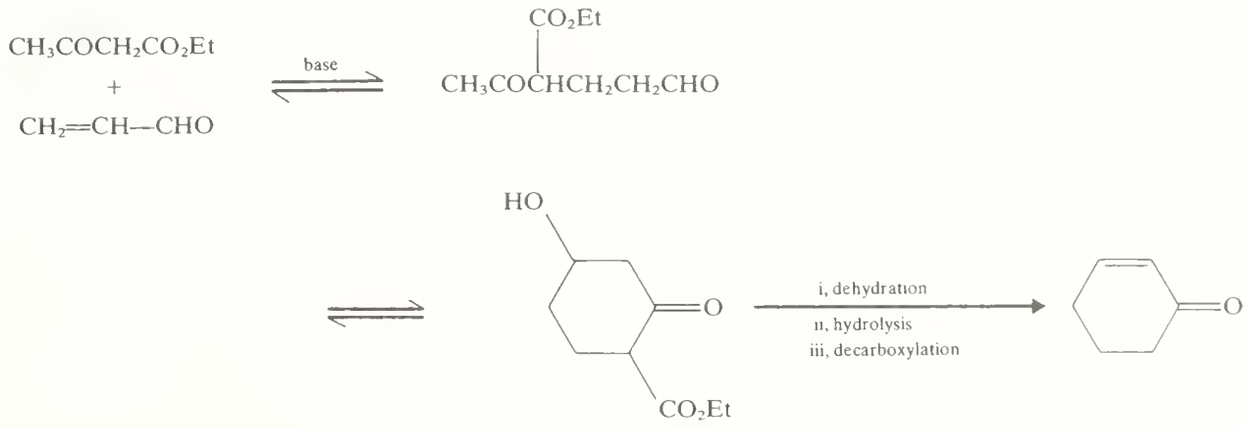


(101)

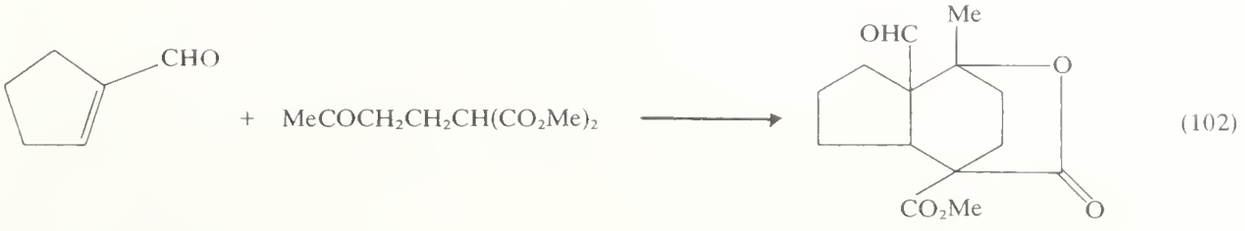
The Michael reaction[214] is one of wide generality and considerable synthetic utility. α,β-Olefinic aldehydes are Michael acceptors and can be condensed with 'active methylene' compounds, *e.g.* dialkyl malonates, β-oxoesters, alkyl cyanoacetates, nitroalkanes, alkyl α-nitroalkanoates, β-diketones, *etc.* The reactions can be catalysed by basic catalysts such as secondary and tertiary amines, metal alkoxides, and basic ion-exchange resins. The reactions are equilibrium processes and proceed better at room temperature than at elevated temperatures. Attempts to bring about the Michael reaction with some highly substituted acceptors, such as β-substituted α,β-olefinic aldehydes, fail, owing to the unfavourable position of the equilibrium.

If one of the activating groups in the Michael donor is a carbonyl group, the adduct from a conjugated aldehyde is a 1,5-dicarbonyl system, which may undergo further reaction under the basic conditions to give a cyclic product. This aspect is made use of in the synthesis[214] of a cyclic ketone which is outlined in Scheme 57. A further example,[215] involving the relatively highly substituted cyclopent-1-enecarbaldehyde as a Michael acceptor, is shown in equation 102.

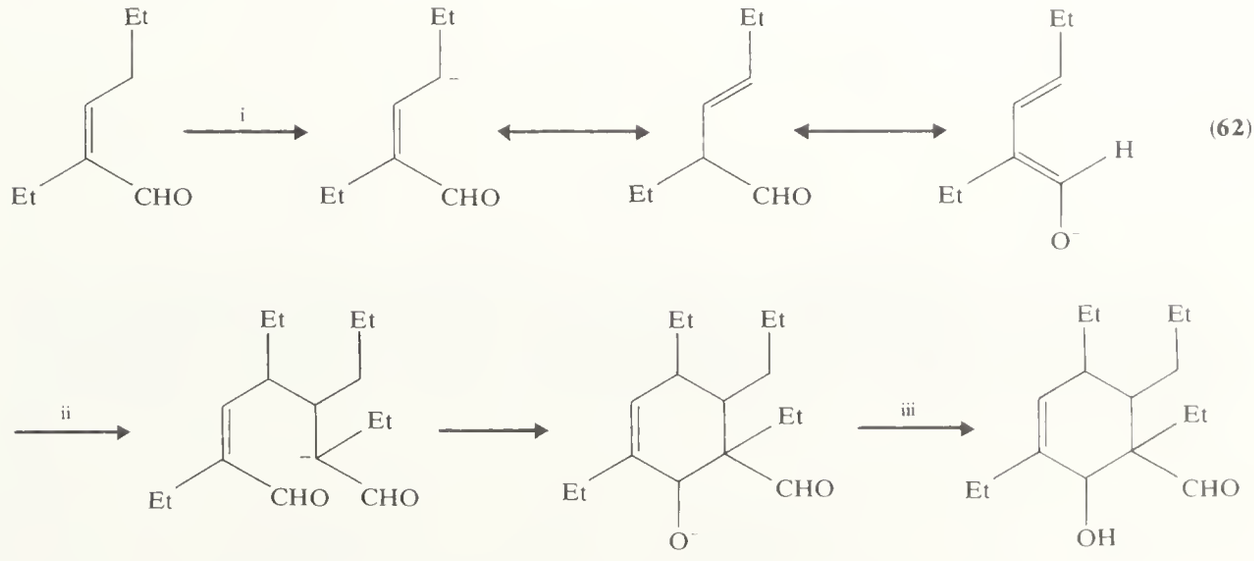
The dimerization of α,β-olefinic aldehydes in the presence of methanolic potassium hydroxide[216] can be formulated with a Michael reaction as the key step (see Scheme 58) in which the nucleophilic species is the anion (**62**) formed by abstraction of the γ-proton. The reaction can also be brought about by lithium metal in ether and under these conditions has been formulated as a cycloaddition process[217] (see equation 103).



SCHEME 57



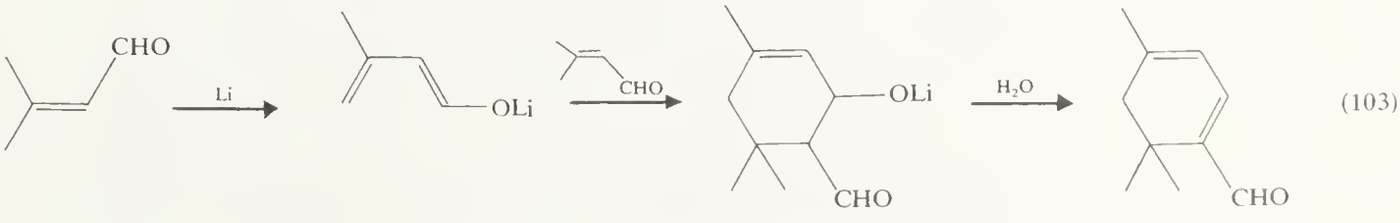
(102)



(62)

i, MeO^-; ii, $EtCH_2CH{=}CEtCHO$; iii, MeOH.

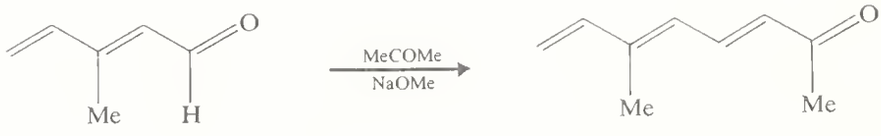
SCHEME 58



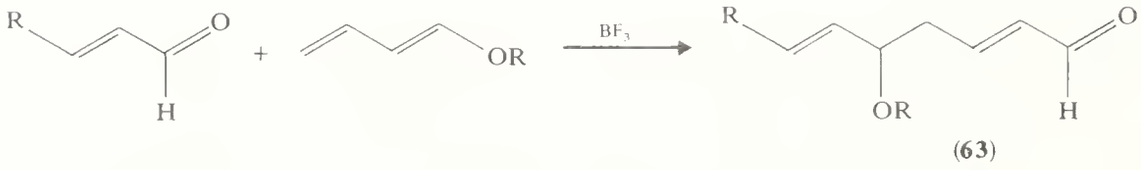
(103)

Linear condensations of the 'aldol' type can be achieved using piperidinium acetate as the catalyst.[106] The yields are low but the route is nevertheless of synthetic importance in view of its simplicity. The reaction is thermodynamically controlled, which results in 1,2-addition to the carbonyl group (α,γ-coupling). Dehydration occurs to give the conjugated trienal (see equation 104). Crossed aldol reactions between two alk-2-enals have been reported,[106] as have condensations between an alk-2-enal and a simple ketone[218] (see equation 105). The 'directed aldol' approach has also been followed; for example, α-lithiated aldehyde dimethylhydrazones (see Scheme 17) undergo 1,2-addition to alk-2-enals.[110] Alk-2-enals react with 1-alkoxyalka-1,3-dienes (the enol ethers of alk-2-enals) to give intermediates (**63**) which with acid yield alka-2,4,6-trienals[149] (see Scheme 59).

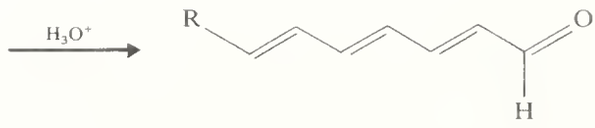
$$2Me_2C{=}CHCHO \longrightarrow Me_2C{=}CH{-}CH{=}CH{-}CMe{=}CHCHO \qquad (104)$$



(105)

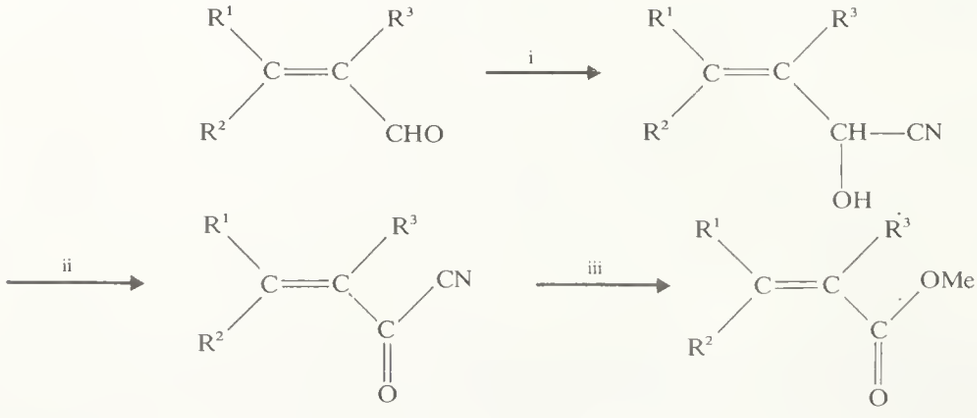


(**63**)



SCHEME 59

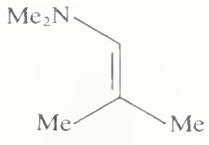
Alk-2-enals give cyanohydrins by exclusive 1,2-addition, with thermodynamic control. The products, as allylic alcohols, can be oxidized with manganese(IV) oxide to give acyl cyanides which can easily be converted into the α,β-olefinic methyl esters by methanol (see Scheme 60). The geometry of the olefinic double bond is preserved. This route is preferable to the oxidation of the alkenal with silver(I) oxide as a route to the α,β-olefinic acid.[219]



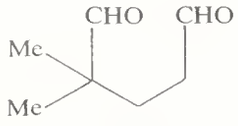
i, ^-CN, HCN; ii, MnO_2; iii, MeOH.

SCHEME 60

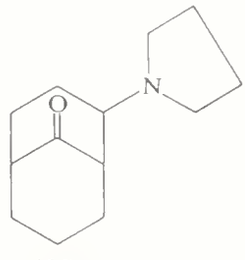
Acrolein (**3**) reacts initially in a conjugated manner with enamines from both aldehydes and ketones, but further reactions follow. Hydrolysis of the product from (**3**) and the enamine (**64**) gives α,α-dimethylglutardialdehyde (**65**), and the reaction of (**3**) with 1-pyrrolidinylcyclohex-1-ene gives the bicyclic aminoketone (**66**).[220]



(**64**)

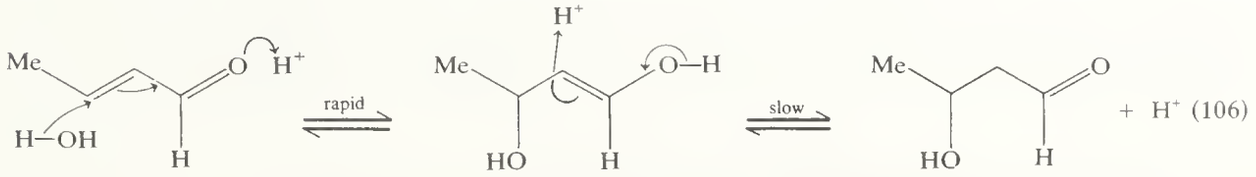


(**65**)

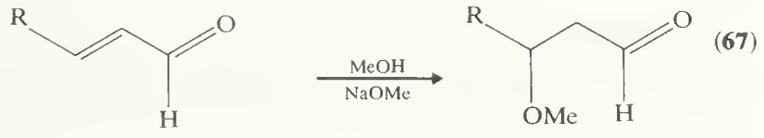


(**66**)

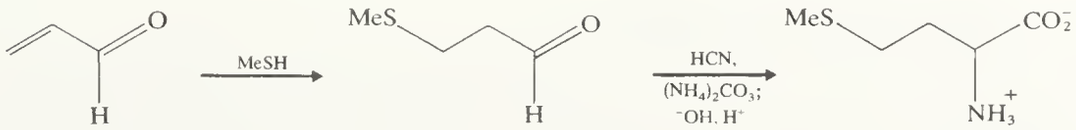
Simple α,β-olefinic aldehydes can be epoxidized under carefully controlled conditions using alkaline hydrogen peroxide.[221] The reaction involves initial attack at the β-position by the hydroperoxide ion, HO_2^-. With dilute sulphuric acid, addition of water to the carbon–carbon double bond can be effected. For example, crotonaldehyde (but-2-enal) is in equilibrium with aldol (3-hydroxybutanal) in water.[222] The position of the equilibrium is largely independent of the acidity. At 25 °C, 47% of the material is present in the hydrated form. It seems likely that the hydration involves a rapid, reversible 1,4-addition of water, followed by a slower acid-catalysed ketonization (see equation 106). In alkaline solution, alcohols add to alk-2-enals to give 3-alkoxyalkanals (**67**) (see equation 107) and thiols undergo an analogous conjugate addition. The product from the addition of methanethiol to acrolein is an important intermediate in the technical synthesis[55] of methionine (**68**) (see equation 108).



(106)



(**67**) (107)



(**3**)

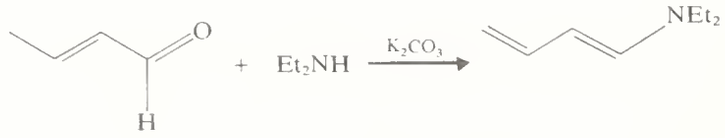
(**68**) (108)

In acidic conditions the products from the reaction of alcohols with alk-2-enals depend on the nature of the acid catalyst and can include the acetal, the 3-alkoxyalkanal, the acetal of the 3-alkoxyalkanol, and, in the presence of hydrogen chloride, the acetal of the 3-chloroalkanal. In the absence of an alcohol, anhydrous hydrogen chloride undergoes 1,4-addition to give the unstable 3-chloroalkanal. The simple olefinic acetals can also be prepared by reacting the olefinic aldehydes with triethyl orthoformate or tetraethyl orthosilicate.

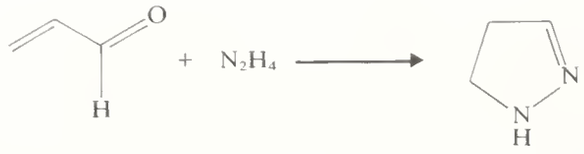
Bromine addition to α,β-olefinic aldehydes in acetic acid in the presence of perchloric or sulphuric acids is very much faster than the corresponding addition to α,β-olefinic

acids. Owing to their greater basicities the aldehydes are first protonated; the next step is then apparently one of the rare examples of nucleophilic attack by bromine. In the absence of perchloric or sulphuric acids, autocatalysis occurs owing to the production of hydrogen bromide in side reactions.[222] Chlorination shows the same general mechanistic features.[222] The useful reagent 2-bromoacrolein (see Section 5.1.7) is prepared by the bromination of acrolein in aqueous solution and is purified by steam distillation.[223]

α,β-Olefinic aldehydes react with some nitrogen nucleophiles to give products formed by 1,2-addition to the carbon–oxygen double bond followed by loss of water, as, for example, in the condensation with the primary amino group of an amino-acid ester to give a Schiff base,[53] or the condensation with secondary amines to give dienamines[224] (see equation 109). With hydrazine and its derivatives,[225] products of this type, for example 2,4-dinitrophenylhydrazones, may also be formed, but cyclic products can also arise. For example, acrolein condenses with hydrazine to give pyrazoline (see equation 110).



(109)



(110)

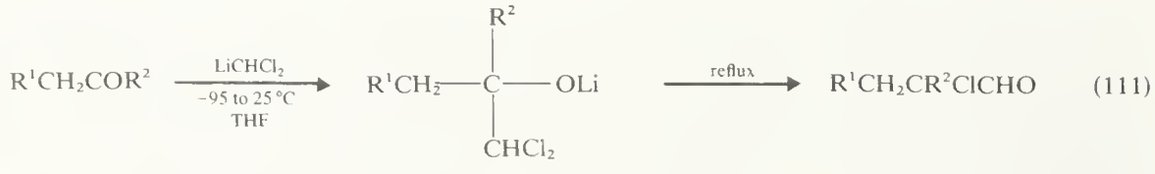
Alkenals react with trialkylboranes by a conjugate radical addition process and the adducts can be transformed into saturated aldehydes incorporating one of the alkyl groups from the borane[22] (see Section 5.1.2.6 and Scheme 2). Alkyl radicals, generated electrochemically from carboxylic acids, add to the β-position of α-methylacrolein to give radicals which dimerize to yield substituted succindialdehydes (see Section 5.1.9).

5.1.7 SOME HALOGENATED COMPOUNDS

The best known halogen-substituted aldehyde is chloral, 2,2,2-trichloroethanal (**2**), the extensive chemistry of which has recently been fully and comprehensively reviewed.[226] The chemistry of bromal, the bromine analogue, has been less fully studied.

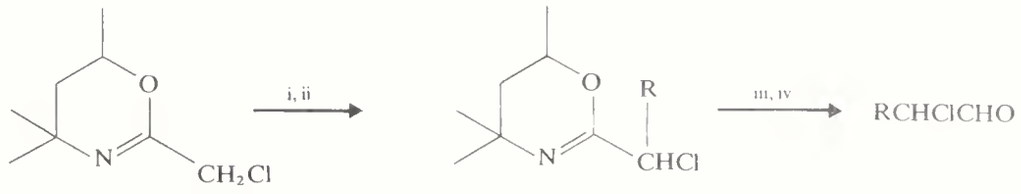
5.1.7.1 α-Monohalogen-substituted aldehydes

Saturated aldehydes can be chlorinated at the α-position with sulphuryl chloride.[227] α-Chloroaldehydes can also be synthesized[196] by the action of lithio-dichloromethane on carbonyl compounds (see equation 111), and by a modification of the Meyers dihydrooxazine route[228] (see Scheme 61).



(111)

Saturated aldehydes can be brominated at the α-position with bromine in DMF containing toluene-*p*-sulphonic acid[229] or in ether containing a small quantity of



i, lithium, hexamethylsilazane; ii, RX; iii, BH_4^-; iv, H_3O^+.

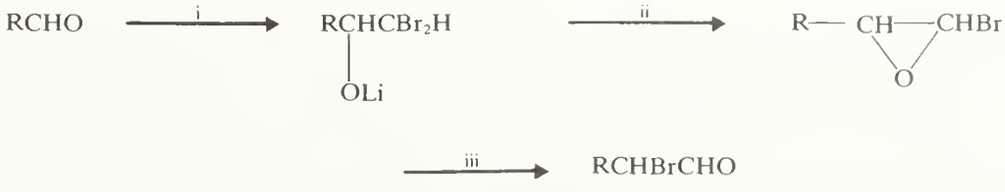
SCHEME 61

dioxan.[230] Bromination of the corresponding enamines,[231] or, in some cases, the trimethylsilyl enol ethers,[232] also gives the α-bromoaldehydes.

Reaction of a trialkylborane with α-bromoacrolein (2-bromoprop-2-enal, see Section 5.1.6.4) in aqueous THF leads to an α-bromoaldehyde[22] (see equation 112); the

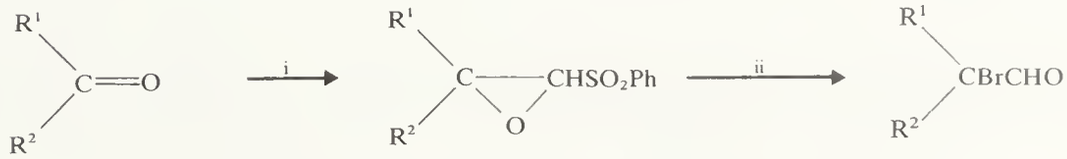
$$R_3B + CH_2{=}CBrCHO \xrightarrow{H_2O} RCH_2{-}CHBrCHO \qquad (112)$$

intermediate enol borinate is instantly hydrolysed. If the reaction is carried out in the presence of triethyl orthoformate the more stable α-bromoacetal can be isolated directly from the reaction mixture.[22] Reaction of aldehydes with lithio-dibromomethane gives bromo-oxirans which rearrange in the presence of pyridine to give the homologous α-bromoaldehyde[233] (see Scheme 62). Another good route to α-bromoaldehydes from carbonyl precursors, set out in Scheme 63, also involves a hetero-substituted oxiran as an intermediate.[234]



i, $LiCHBr_2$, low temperature; ii, 20 °C; iii, 1 drop C_5H_5N in cyclohexane, 80 °C.

SCHEME 62



i, $PhSO_2CH_2Cl$, phase transfer catalysis; ii, $MgBr_2$, ether.

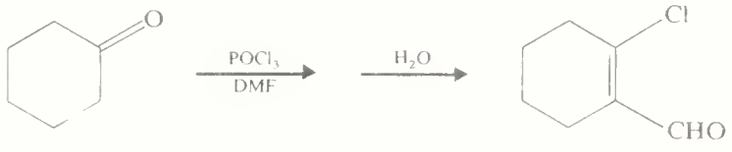
SCHEME 63

α-Halogen-substituted saturated aldehydes, like other α-halocarbonyl compounds, are reactive substances, but they can be converted into the more stable acetals by the reaction with an alcohol in the presence of an acid catalyst. α-Chloroaldehydes undergo an odd reaction with methanolic sodium methoxide, leading to the corresponding α-hydroxy-substituted dimethyl acetal[227] (see equation 113). The dehydrochlorination of α-chloro-aldehydes[196] is dealt with in Section 5.1.6.1.

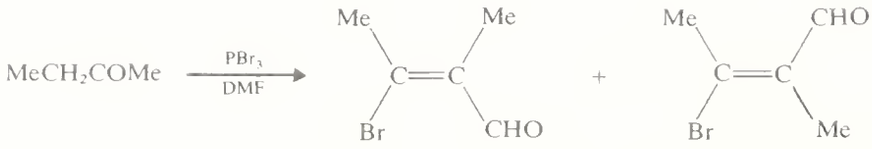
$$RCHClCHO \xrightarrow[MeOH]{NaOMe} RCH(OH)CH(OMe)_2 \qquad (113)$$

5.1.7.2 β-Haloalk-2-enals

β-Halogen-substituted α,β-olefinic aldehydes are readily available from the Vilsmeier reaction on ketones[235] (see equations 114 and 115). Mixtures of the (*Z*) and (*E*) configurational isomers are produced.[236] These compounds are unstable and deteriorate on storage, but are useful synthetic intermediates. Treatment with triethylamine gives the corresponding allenic aldehydes,[237] and reduction with zinc leads to the parent α,β-olefinic aldehydes.[197]



(114)



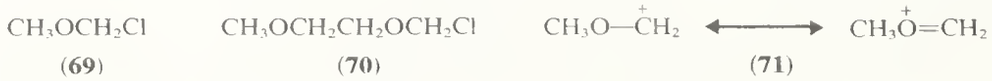
(115)

5.1.7.3 1-Alkoxy-1-chloroalkanes

1-Alkoxy-1-chloroalkanes can be prepared by passing a fast stream of hydrogen chloride into a mixture of an aldehyde and an alcohol (see equation 116). Two important

(116)

compounds made in this way are chloromethyl methyl ether (**69**),[238] which is carcinogenic, and chloromethyl β-methoxyethyl ether, 'MEM chloride' (**70**).[239] The chlorine in these ethers is very easily displaced by nucleophiles. The solvolysis of (**69**) in ethanol is at least 10^{14} times faster than that of chloromethane, owing to the formation of the oxygen-stabilized cation (**71**); the bimolecular reaction of (**69**) with ethoxide ion is also some 10^5 times faster than the reaction of chloromethane.[240] Phenols and alcohols have been protected by conversion into ethers using (**69**) and (**70**) respectively, since such ethers are

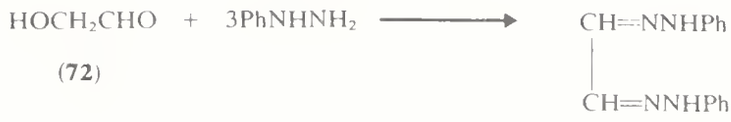


unreactive in basic media but can be cleaved under mild and specific conditions.[239] The Wittig reagents derived from chloromethyl alkyl ethers by reaction with triphenylphosphine followed by deprotonation are used in the method for converting a ketone into the next higher aldehyde[44] discussed in Section 5.1.2.11 (see equation 4). Chloromethyl methyl ether (**69**) forms a Grignard reagent with magnesium which undergoes typical reactions with carbonyl compounds to give the monoethers of 1,2-diols.[241]

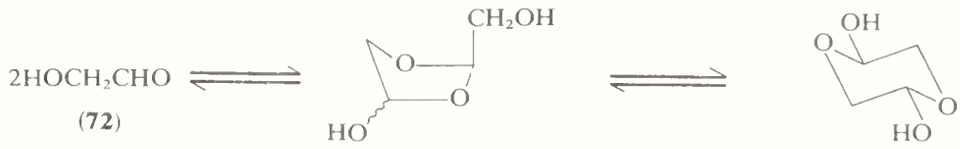
5.1.8 HYDROXYALDEHYDES

5.1.8.1 α-Hydroxyaldehydes

α-Hydroxyaldehydes, *e.g.* hydroxyethanal (glycollaldehyde, **72**), are strong reducing agents and give osazones with phenylhydrazine (see equation 117). They dimerize in the solid state and in solution they exist in equilibrium with five and six-membered ring dimers[242] (see equation 118).

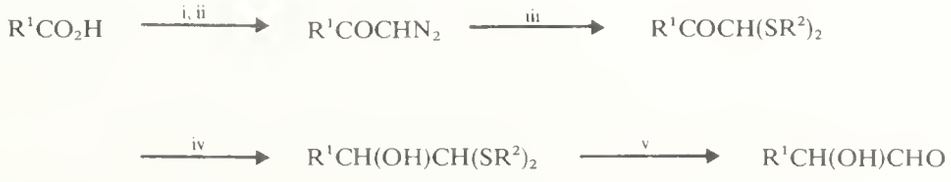


(117)



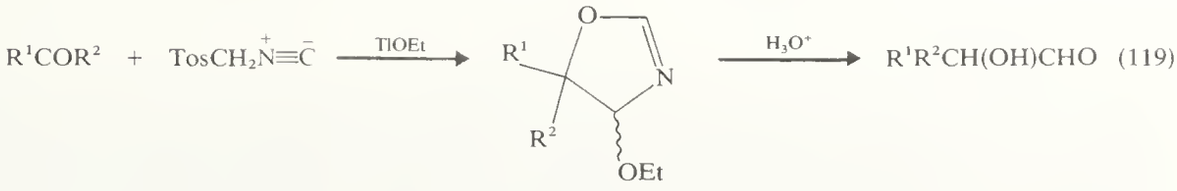
(118)

α-Hydroxyaldehydes can be prepared from α-haloaldehydes (see Section 5.1.7.1) by hydrolysis with aqueous alkali and from carboxylic acids by the route[243] shown in Scheme 64, in which the final step is the regeneration of the α-hydroxyaldehyde from the corresponding thioacetal. They can also be prepared from ketones, with the addition of one carbon atom through 4-ethoxy-2-oxazolines,[244] as shown in equation (119).



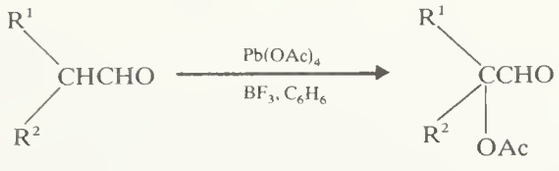
i, $SOCl_2$; ii, CH_2N_2; iii, R^2SCl, then $NaSR^2$; iv, $LiBH_4$; v, $HgCl_2$.

SCHEME 64



(119)

α-Hydroxyaldehydes, like other hydroxyaldehydes, can be prepared by the ozonolysis of olefinic alcohols (in this case, appropriately substituted allylic alcohols) and the route can readily be adapted to the preparation of derivatives, *e.g.* α-acetoxyaldehydes. α-Acetoxyaldehydes can also be prepared by the α-acetoxylation of aldehydes with lead(IV) acetate[245] (see equation 120) and by the thermal rearrangement of α-acetoxyoxirans,[246] which permits the indirect α-acetoxylation of aldehydes (shown in equation 121).



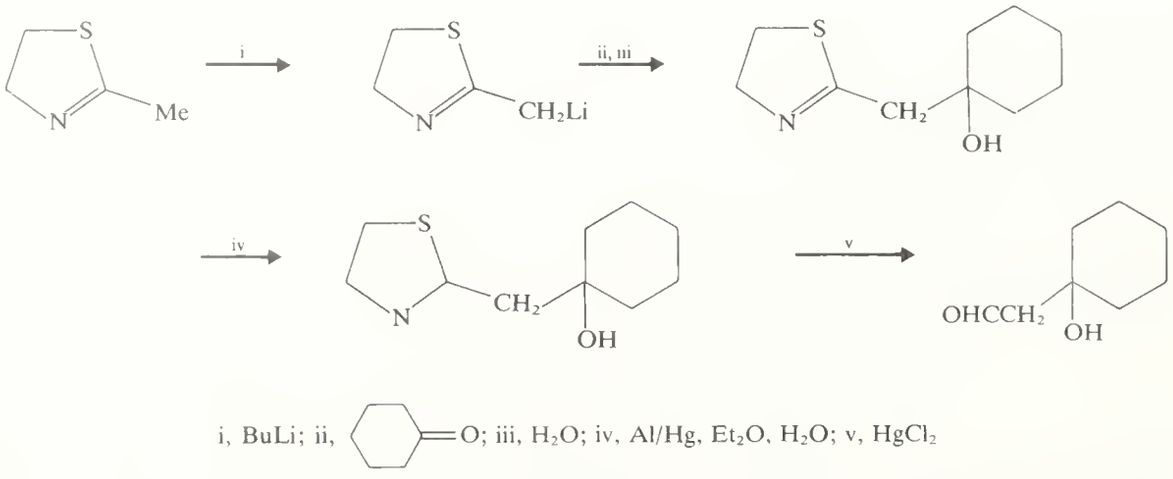
(120)

(121)

α-Acetoxyaldehydes rearrange in acid or base to give the thermodynamically more stable α-acetoxyketones.[246] α-Bromo- and α-chloro-aldehydes can be converted into α-acetoxyaldehydes by treatment with acetate ion in DMF at room temperature with vigorous stirring; use of acetate ion in acetic acid gives the α-acetoxyketone.[246]

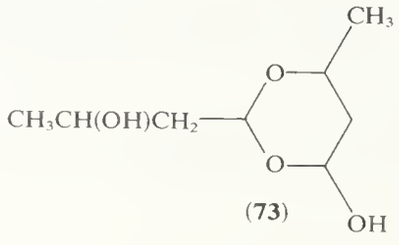
5.1.8.2 β-Hydroxyaldehydes

The β-hydroxyaldehydes are better known as 'aldols', and can be prepared by the aldol condensation.[106] Careful attention to the conditions is necessary, even if the equilibrium favours the formation of the β-hydroxyaldehyde (see *e.g.* Scheme 14), as aldols readily dehydrate, even in basic solution, to give the conjugated olefinic aldehydes (see Sections 5.1.5.2 and 5.1.6.1). Mixtures of *threo*- and *erythro*-isomers are obtained; they can be formed under either kinetic or thermodynamic control, depending on the reaction conditions, and the kinetic and thermodynamic stereoselectivities differ.[247] The 'directed aldol' reaction extends the methods for the preparation of β-hydroxyaldehydes (see Sections 5.1.5.2 and 5.1.6.1). A further example of this approach,[248] used specifically to prepare the β-hydroxyaldehyde and not the α,β-olefinic aldehyde, is shown in Scheme 65. β-Hydroxyaldehydes can also be prepared by the acid-catalysed hydration of α,β-olefinic aldehydes (see Section 5.1.6.4).



SCHEME 65

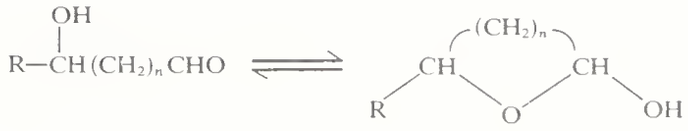
The reactions of β-hydroxyaldehydes are dominated by the ready dehydration of those containing an available α-hydrogen atom. α,α-Disubstituted β-hydroxyaldehydes may undergo the Cannizzaro reaction[75] in aqueous base. α,α-Bis(hydroxymethyl)-β-hydroxypropionaldehyde undergoes a crossed-Cannizzaro reaction under the conditions in which it is formed from acetaldehyde and excess of formaldehyde (see equation 16). Aldols condense with simple aldehydes to give aldoxans (**31**). Aldol (3-hydroxybutanal) gives paraldol (**73**), a solid, on standing, and other β-hydroxyaldehydes also tend to dimerize.



(**73**)

5.1.8.3 γ- and δ-hydroxyaldehydes

γ- and δ-hydroxyaldehydes exist in equilibrium with cyclic hemiacetals, known as lactols (**74**) (see equation 122). The well-known ring–chain tautomerism of glucose and the existence of both five- and six-membered cyclic forms (see Chapter 26.2) is a result of the fact that the open-chain form is both a γ- and a δ-hydroxyaldehyde.



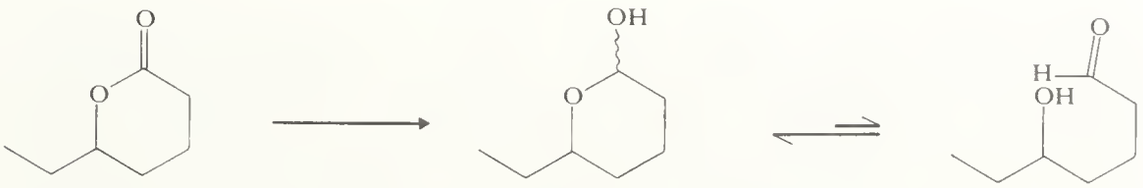
(122)

(74)

γ- and δ-hydroxyaldehydes can be prepared either by routes leading essentially to the hydroxyaldehyde form or by routes leading directly to the lactol form. For example, ozonolysis of pent-4-en-1-ol gives γ-hydroxybutyraldehyde and hydration of the readily available cyclic enol ether dihydropyran (see equation 123) gives the lactol form of

(123)

5-hydroxypentanal. The most important route to lactols is the reduction of lactones (cyclic esters) (see equation 124) which can best be accomplished by low-temperature reduction with di-isobutylaluminium hydride, a very mild and specific reducing agent[249] which has displaced earlier reductants such as lithium triethoxyaluminium hydride. Lactols, generated from γ-lactones in this way, have been much used as masked γ-hydroxyaldehydes in syntheses, especially in the steroid and prostaglandin fields.



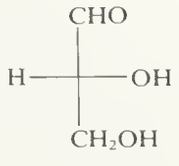
(124)

(75) (76)

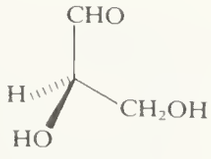
The position of the equilibrium in the simple γ- and δ-hydroxyaldehyde systems is of interest. The cyclization of γ- and δ-hydroxyaldehydes correspond to the favoured 5- and 6-*exo-trig* processes, using Baldwin's terminology,[250] and the equilibrium is rapidly established. In 75% aqueous dioxan, 4-hydroxybutanal and 5-hydroxypentanal exist predominantly in the cyclic forms,[251] there being 11.4 and 6.1%, respectively, of the hydroxyaldehydes and also, presumably, a few per cent of the hydrated (α,α,ω-triol) forms (*cf.* equation 14). For 5-hydroxyheptanal (**76**), in chloroform, the ratio of cyclic to open-chain forms is *ca.* 100:1, and the cyclic hemiacetal (**75**) exists as a mixture of the *cis* and *trans* forms, in the ratio of *ca.* 1:2.[252]

5.1.8.4 Polyhydroxyaldehydes

Aldose sugars (see Chapter 26.2) are polyhydroxyaldehydes. The simplest aldose is glyceraldehyde; D-glyceraldehyde (**77**), which has a positive optical rotation in aqueous solution, and in which the chiral centre has the (*R*) configuration (**78**), is used as the

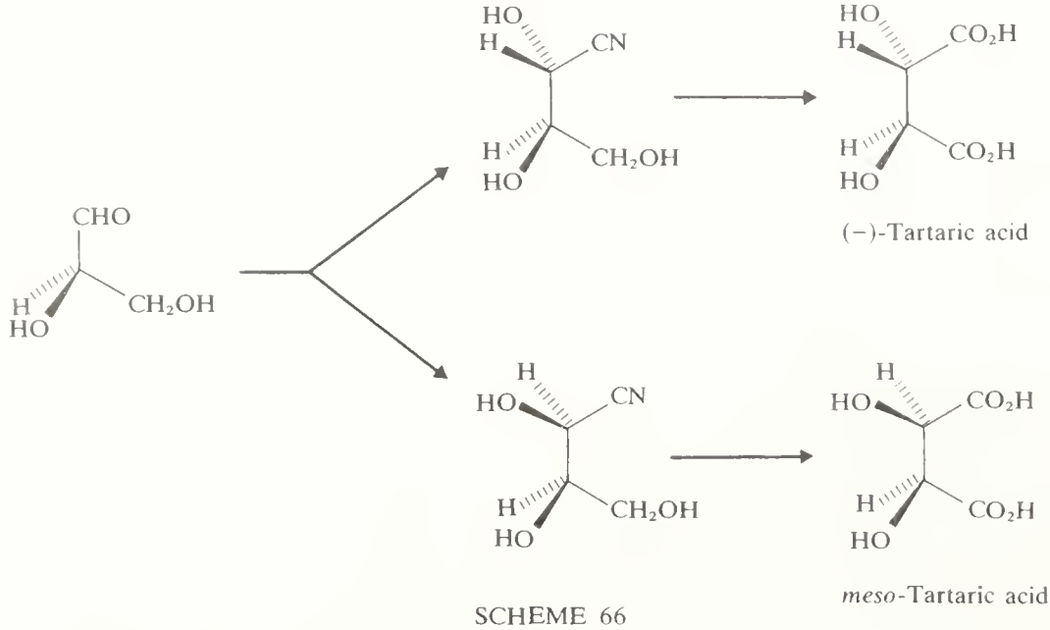


(77)



(78)

standard for configurational assignments in the carbohydrate field. The configuration of (+)-glyceraldehyde was related to that of (−)-tartaric acid by conversion to the cyanohydrin, hydrolysis, and selective oxidation of the primary alcohol group, as shown in Scheme 66, and the absolute configuration of (−)-tartaric acid has more recently been established by the X-ray anomalous dispersion method.

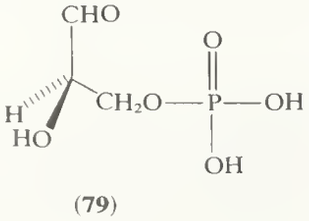


SCHEME 66

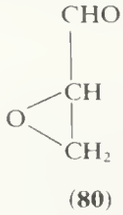
D-(+)-Glyceraldehyde (**77**) is most conveniently prepared from the readily available D-fructose; oxidation with lead(IV) acetate gives 3-*O*-formyl-2-*O*-glycollyl-D-glyceraldehyde, which on hydrolysis with aqueous acid gives the hydroxyaldehyde. L-(−)-Glyceraldehyde can be prepared by a similar method starting from the readily available L-sorbose, and the (±)-modification can be prepared by oxidizing an equimolar mixture of the two keto-sugars.[253] D-Glyceraldehyde can also be prepared by the oxidation of 1,2:5,6-di-*O*-isopropylidene-D-mannitol with lead(IV) acetate and subsequent hydrolysis of the isopropylidene derivative.[254] (±)-Glyceraldehyde can also be prepared by many of the methods for the synthesis of diols and aldehydes, *e.g.* by the hydroxylation of acrolein (**3**) after protection of the aldehyde function as an acetal.[255]

Glyceraldehyde is soluble in water, but insoluble in ether and ethanol. The (±)-modification, but not the pure enantiomers, has been obtained as a crystalline solid dimer. Glyceraldehyde shows the typical chemical reactions of a reducing sugar (see Chapter 26.2). It can be characterized as the dimedone derivative.

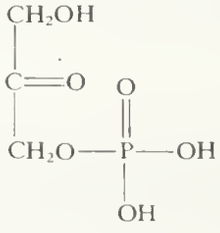
D-Glyceraldehyde 3-phosphate (**79**) is a most important compound in intermediary metabolism. The (±)-modification can be prepared from glycidaldehyde diethyl acetal (**80**) by reaction with dipotassium hydrogen phosphate and subsequent removal of the acetal group with aqueous acid.[256] D-Glyceraldehyde 3-phosphate is formed at a very early stage in the carbon pathway in photosynthesis[257] by the reduction of glyceric acid 1,3-diphosphate. It is also formed in glycolysis by the retro-aldol fission of fructose 1,6-diphosphate, mediated by the enzyme aldolase, which leads to a mixture of D-glyceraldehyde 3-phosphate (**79**) and dihydroxyacetone phosphate (**81**). These two triose



(**79**)



(**80**)



(**81**)

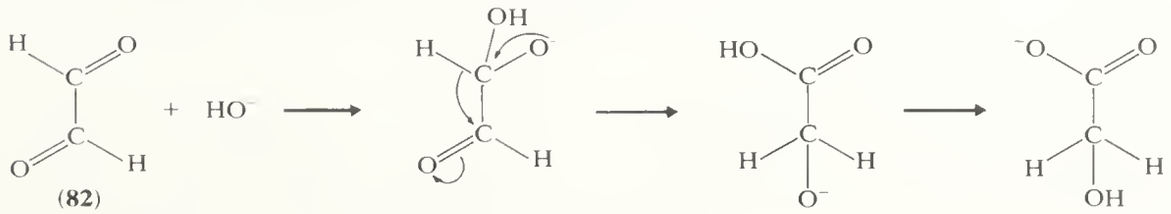
phosphates are rapidly interconverted in the presence of the enzyme triose phosphate isomerase in a manner consistent with an enzyme-bound enediol intermediate. The equilibrium strongly favours dihydroxyacetone phosphate but, in the next step of the glycolytic pathway, it is D-glyceraldehyde phosphate which reacts further, being converted into glyceric acid 1,3-diphosphate in the presence of triose phosphate dehydrogenase.[258]

5.1.9 DIALDEHYDES

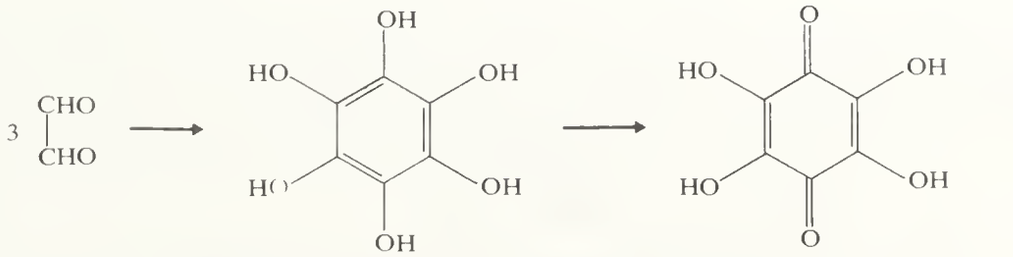
5.1.9.1 Glyoxal

Glyoxal (ethanedial, **82**) is the simplest dialdehyde. It is most conveniently prepared by the oxidation of 2,4,6-trimethyl-1,3,5-trioxan (paraldehyde) with selenium(IV) oxide in aqueous acetic acid.[259] It can also be obtained by the oxidation of chloroacetaldehyde with dimethyl sulphoxide.[260] It is a liquid, b.p. 50 °C, and in the gas phase exists in the *s-trans* conformation (**82**).

On treatment with concentrated alkali, glyoxal is transformed into a salt of glycolic acid (hydroxyethanoic acid) by a reaction analogous to the benzil–benzilic acid rearrangement, an intramolecular Cannizzaro reaction (see equation 125). Glyoxal can be conveniently stored as the solid bis(bisulphite compound). Glyoxal trimerizes in buffered aqueous solution to give hexahydroxybenzene, which is easily oxidized by air to tetrahydroxy-*p*-benzoquinone[261] (see equation 126).



(125)

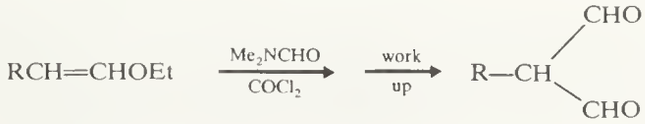


(126)

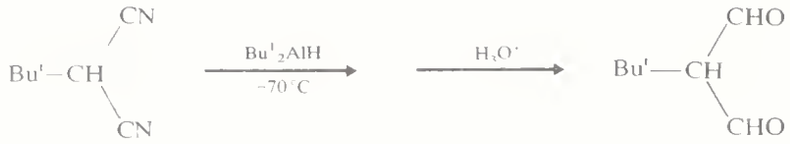
5.1.9.2 Malondialdehydes

Malondialdehydes, being 1,3-dicarbonyl compounds, can be prepared by the Claisen condensation. Equation 127 shows the simplest example. They can also be prepared by the Vilsmeier formylation of aldehyde enol ethers[262] (see equation 128); the Vilsmeier adduct is decomposed by aqueous potassium carbonate at 0 °C and the resultant quaternary salt is then hydrolysed by aqueous alkali at 95 °C. Malondialdehydes can also be prepared by the reduction of the corresponding malononitriles with di-isobutylaluminium hydride[263] (see equation 129).

(127)



(128)

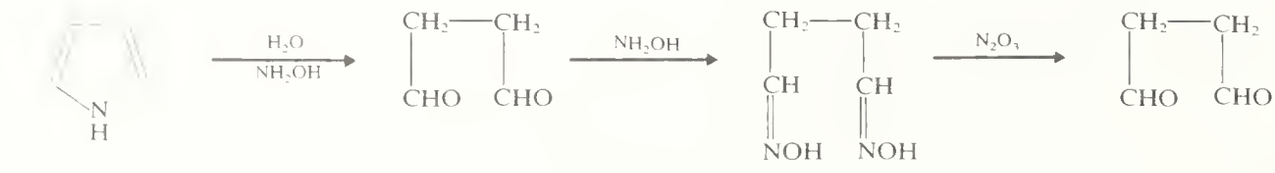


(129)

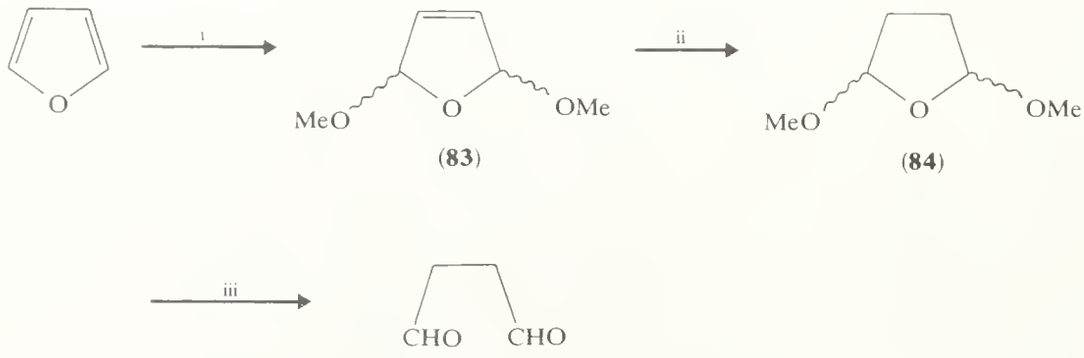
t-Butylmalondialdehyde exists at room temperature in deuteriotrichloromethane as the (*E*)-isomer of the enolic tautomer, with intermolecular hydrogen bonding, but at higher dilution and lower temperatures it exists as the (*Z*)-isomer, with intramolecular hydrogen bonding.[263]

5.1.9.3 1,4-Dialdehydes

Succindialdehyde (butane-1,4-dial) was originally prepared by the hydrolysis of pyrrole, trapped as the bis-oxime, and subsequently regenerated (see equation 130). It is now most conveniently prepared, *in situ*, from 2,5-dimethoxytetrahydrofuran (**84**), available from furan by the route shown in Scheme 67. The dihydrofuran (**83**) similarly gives a mixture of



(130)

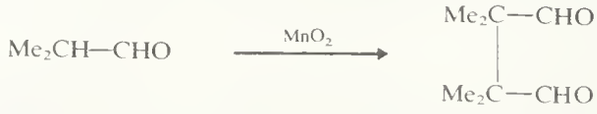


i, MeOH, NH_4Br; electrolyse; ii, H_2, Pt; iii, H_2SO_4, H_2O.

SCHEME 67

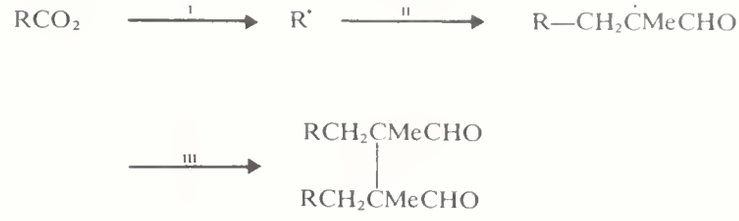
malein- and fumar-dialdehydes, *i.e.* (*Z*)- and (*E*)-but-2-ene-1,4-dials, on hydrolysis and this is the best route to those compounds.

Substituted succindialdehydes can be prepared by the oxidation of aldehydes with manganese(IV) oxide[264] (see equation 131). This is a radical coupling. Considerable



(131)

amounts of the C—O coupled dimer are also formed. The electrolysis of carboxylic acids in the presence of α-methylacrolein leads to radicals of the same type, which likewise dimerize to give substituted succindialdehydes[265] (see Scheme 68).

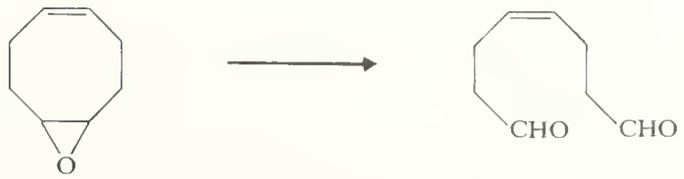


i, electrolyse; ii, CH_2=CMeCHO; iii, dimerization.

SCHEME 68

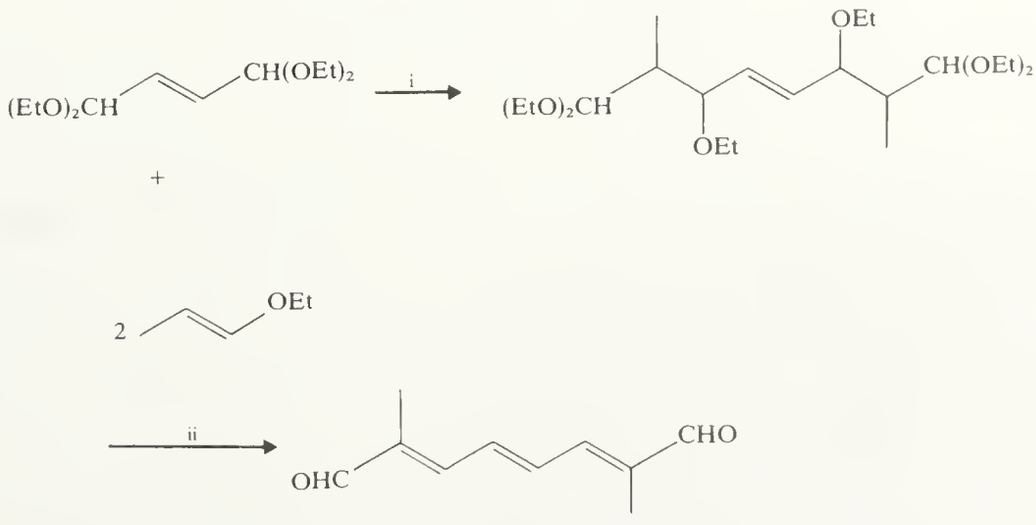
5.1.9.4 Other dialdehydes

Glutaraldehyde (pentane-1,5-dial) is prepared by the hydrolysis of 2-alkoxy-3,4-dihydropyrans, *cf.* equation 94. It can also be prepared by standard aldehyde syntheses, *e.g.* the ozonolysis of cyclopentene, or the periodate oxidation of cyclohexane-1,2,3-triol. Some unsymmetrical glutaraldehydes, *e.g.* (**65**), are available by the hydrolysis of the products from the condensation of aldehyde enamines, *e.g.* (**64**), with α,β-olefinic aldehydes[220] (see Section 5.1.6.4). The electrohydrodimerization of an α,β-olefinic aldehyde to produce a 1,6-dialdehyde[207] is discussed in Section 5.1.6.3 (see equation 90). Other dialdehydes are accessible through obvious applications of the standard methods. The hydrolysis and oxidation of epoxides by aqueous periodate is particularly suitable for the production of dialdehydes,[266] as illustrated in equation 132.



(132)

Several polyolefinic dialdehydes have been used frequently in the synthesis, including the industrial synthesis, of carotenoids and related polyunsaturated systems. They are prepared by the general methods for the synthesis of olefinic aldehydes (see Section 5.1.6.1). An example[159] is shown in Scheme 69.



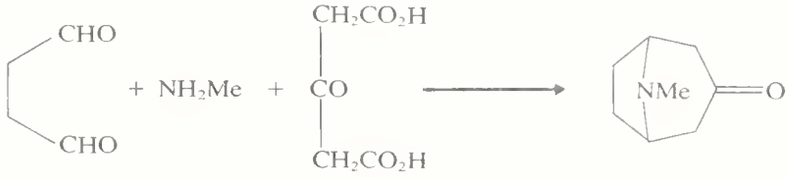
i, Lewis acid; ii, H_3O^+.

SCHEME 69

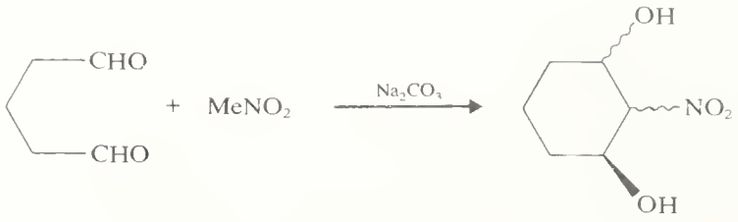
5.1.9.5 General reactions of dialdehydes

The classical Robinson synthesis of tropinone is an example of a dialdehyde undergoing a double Mannich condensation (see equation 133). The use of glutaraldehyde in place of succindialdehyde similarly gives Ψ-pelletierine.[267]

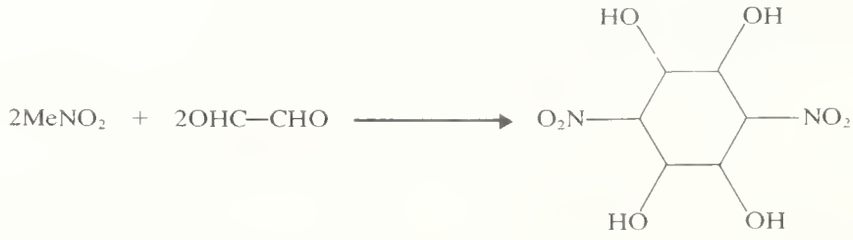
Dialdehydes condense with nitromethane in alkaline solution,[268] as shown by the example in equation 134. The reaction is also shown by glyoxal (see equation 135).



(133)



(134)



(135)

Dialdehydes are frequent reagents in the synthesis of nitrogen heterocyclic systems. The synthesis of quinoxaline from glyoxal and *o*-phenylenediamine (equation 136) is a simple example of this.

(136)

References

1. C. Kata, S. Konaka, T. Iijima, and M. Kimura, *Bull. Chem. Soc. Japan*, 1969, **42,** 2148; T. Iijima and M. Kimura, *ibid.*, 1969, **42,** 2159.
2. M. Traetteberg, *Acta Chem. Scand.*, 1970, **24,** 373.
3. G. J. Karabatsos and D. J. Fenoglio, *Topics Stereochem.*, 1970, **5,** 167.
4. H. E. Nursten, *Rep. Prog. Appl. Chem.*, 1971, **56,** 622.
5. K. Eiter, *Pure Appl. Chem.*, 1975, **41,** 201.
6. O. Bayer, in Houben-Weyl, 'Methoden der Organischen Chemie', Thieme, Stuttgart, 4th edn., 1954, vol. VII, part 1; J. Carnduff, *Quart. Rev.*, 1966, **20,** 169.
7. W. W. Epstein and F. W. Sweat, *Chem. Rev.*, 1967, **67,** 247.
8. B. Ganem and R. K. Boeckman, Jr., *Tetrahedron Letters*, 1974, 917.
9. W. E. Noland, *Chem. Rev.*, 1955, **55,** 137.
10. J. E. McMurry and J. Melton, *J. Org. Chem.*, 1973, **38,** 4347.
11. M. Kocór, M. Gumulka, and T. Cynkowski, *Tetrahedron Letters*, 1972, 4625.
12. J. E. McMurry, J. Melton, and H. Padgett, *J. Org. Chem.*, 1974, **39,** 259.
13. M. S. Newman and B. J. Magerlein, *Org. Reactions*, 1949, **5,** 413.

14. G. Stork and E. Colvin, *J. Amer. Chem. Soc.*, 1971, **93,** 2080.
15. J. Málek and M. Černy, *Synthesis*, 1972, 217.
16. M. Muraki and T. Mukaiyama, *Chem. Letters*, 1974, 1447.
17. M. Muraki and T. Mukaiyama, *Chem. Letters*, 1975, 215.
18. Y. Watanabe, M. Yamashita, T. Mitsudo, M. Igami, K. Tomi, and Y. Takegami, *Tetrahedron Letters*, 1975, 1063.
19. H. Muxfeldt, W. Rogalski, and G. Klauenberg, *Chem. Ber.*, 1965, **98,** 3040.
20. E. Mosettig and R. Mozingo, *Org. Reactions*, 1948, **4,** 362; J. A. Peters and H. van Bekkum, *Rec. Trav. chim.*, 1971, **90,** 1323.
21. E. Mosettig, *Org. Reactions*, 1954, **8,** 218; H. Hauptmann and W. F. Walter, *Chem. Rev.*, 1962, **62,** 375; G. R. Pettit and E. E. van Tamelen, *Org. Reactions*, 1962, **12,** 389.
22. H. C. Brown, 'Boranes in Organic Chemistry', Cornell University Press, 1972.
23. C. A. Tolman, in 'Transition Metal Hydrides', ed. E. L. Muetterties, Dekker, New York, 1971, pp. 289–292.
24. C.-Y. Hsu and M. Orchin, *J. Amer. Chem. Soc.*, 1975, **97,** 3553.
25. A. Stefani, G. Consiglio, C. Botteghi, and P. Pino, *J. Amer. Chem. Soc.*, 1973, **95,** 6504.
26. C. A. Bertelo and J. Schwartz, *J. Amer. Chem. Soc.*, 1975, **97,** 228.
27. M. P. Cooke, Jr., *J. Amer. Chem. Soc.*, 1970, **92,** 6080; W. O. Siegl and J. P. Collman, *ibid.*, 1972, **94,** 2516.
28. H. M. Walborsky, W. H. Morrison, and G. E. Niznik, *J. Amer. Chem. Soc.*, 1970, **92,** 6675.
29. A. I. Meyers and A. Nebeya, *Chem. Comm.*, 1967, 1163.
30. R. R. Schmidt, *Synthesis*, 1972, 333.
31. A. I. Meyers and N. Nazarenko, *J. Amer. Chem. Soc.*, 1972, **94,** 3243.
32. L. J. Altman and S. L. Richheimer, *Tetrahedron Letters*, 1971, 4709.
33. A. I. Meyers, R. Munavu, and J. Durandetta, *Tetrahedron Letters*, 1972, 3929.
34. I. C. Nordin, *J. Heterocyclic Chem.*, 1966, **3,** 531.
35. G. Doleschall, *Tetrahedron Letters*, 1974, 2649.
36. E. J. Corey and D. Seebach, *Angew. Chem. Internat. Edn.*, 1965, **4,** 1075; D. Seebach, *Synthesis*, 1969, 17; E. Vedejs and P. L. Fuchs, *J. Org. Chem.*, 1971, **36,** 366; D. Seebach and E. J. Corey, *ibid.*, 1975, **40,** 231.
37. E. J. Corey and G. Märkl, *Tetrahedron Letters*, 1967, 3201; F. A. Carey and J. R. Neergaard, *J. Org. Chem.*, 1971, **36,** 2731.
38. F. A. Carey and A. S. Court, *J. Org. Chem.*, 1972, **37,** 1926; P. F. Jones and M. F. Lappert, *J.C.S. Chem. Comm.*, 1972, 526; D. Seebach, B.-Th. Gröbel, A. K. Beck, M. Braun and K.-H. Geiss, *Angew. Chem. Internat. Edn.*, 1972, **11,** 443.
39. E. J. Corey and A. P. Kozikowski, *Tetrahedron Letters*, 1975, 925.
40. J. E. Richman, J. L. Herrmann, and R. H. Schlessinger, *Tetrahedron Letters*, 1973, 3267.
41. K. Ogura and G.-I. Tsuchihashi, *Bull. Chem. Soc. Japan*, 1972, **45,** 2203.
42. I. Hori, T. Hayashi, and H. Midorikawa, *Synthesis*, 1974, 705.
43. T. Nakai and M. Okawara, *Chem. Letters*, 1974, 731.
44. S. G. Levine, *J. Amer. Chem. Soc.*, 1958, **80,** 6150; G. Wittig and E. Knauss, *Angew. Chem.*, 1959, **71,** 127.
45. D. S. Matteson, R. J. Moody, and P. K. Jesthi, *J. Amer. Chem. Soc.*, 1975, **97,** 5608; D. S. Matteson, *Synthesis*, 1975, 147.
46. Y. Odić and M. Pereye, *J. Organometallic Chem.*, 1973, **55,** 273.
47. J. M. Conia and C. Girard, *Tetrahedron Letters*, 1973, 2767.
48. Th. Cuvigny and H. Normant, *Bull. Soc. chim. France*, 1970, 3976.
49. I. Ojima and T. Kogure, *Tetrahedron Letters*, 1972, 5035.
50. R. Noyari, I. Umeda, and T. Ishigami, *J. Org. Chem.*, 1972, **37,** 1542.
51. R. K. Boeckman, Jr. and R. Michalak, *J. Amer. Chem. Soc.*, 1974, **96,** 1623.
52. D. Caine, *Org. Reactions*, 1976, **23,** 1.
53. S.-I. Hashimoto, S.-I. Yamada, and K. Koga, *J. Amer. Chem. Soc.*, 1976, **98,** 7450.
54. R. E. Ireland, unpublished results, quoted by L. F. and M. Fieser, 'Reagents for Organic Synthesis', Wiley, New York, 1967, vol. 1, p. 817.
55. J. M. Tedder, A. Nechvatal, and A. H. Jubb, 'Basic Organic Chemistry. Part 5: Industrial Products', Wiley, New York, 1975.
56. T. Bewley and J. A. Keeble, *U.S. Pat.*, 2 501 708 (*Chem. Abs.*, 1950, **44,** 5379).
57. N. O. V. Sonntag, in 'Fatty Acids', ed. K. S. Markley, Interscience, New York, 1961, vol. 2, p. 1023; 1968, vol. 5, p. 3572.
58. 'Hazards in the Chemical Laboratory', ed. G. D. Muir, The Chemical Society, London, 2nd edn., 1977.
59. 'Electronic Absorption Spectroscopy in Organic Chemistry', ed. E. S. Stern and C. J. Timmons, 3rd edn., Arnold, London, 1970.
60. A. F. Thomas and M. Ozainne, *Chem. Comm.*, 1969, 46.
61. M. Ohtsura, M. Teraoka, K. Tori, and M. Takeda, *J. Chem. Soc.* (*B*), 1967, 1033.
62. H. A. Christ, *Helv. Phys. Acta*, 1960, **33,** 572; P. Greenzaid, Z. Luz, and D. Samuel, *J. Amer. Chem. Soc.*, 1967, **89,** 749.
63. H. M. Walborsky, R. H. Davis, and D. R. Howton, *J. Amer. Chem. Soc.*, 1951, **73,** 2590.
64. R. K. Barua and H. B. Barua, *Biochem. J.*, 1964, **92,** 21C.

65. E. J. Corey, N. W. Gilman, and B. Ganem, *J. Amer. Chem. Soc.*, 1968, **90,** 5616.
66. J. R. Ruhoff, *Org. Synth. Coll. Vol. 2*, 1943, 315.
67. R. A. Ellison, W. D. Woessner, and C. C. Williams, *J. Org. Chem.*, 1972, **37,** 2757.
68. P. Deslongchamps and C. Moreau, *Canad. J. Chem.*, 1971, **49,** 2465.
69. P. L. Batten, T. J. Bentley, R. B. Boar, R. W. Draper, J. F. McGhie, and D. H. R. Barton, *J.C.S. Perkin I*, 1972, 739.
70. D. Swern, in 'Organic Peroxides', ed. D. Swern, Wiley-Interscience, New York, 1970, vol. 1, p. 353.
71. R. O. Hutchins and D. Kandasamy, *J. Amer. Chem. Soc.*, 1973, **95,** 6131.
72. G. H. Posner and A. W. Runquist, *Tetrahedron Letters*, 1975, 3601.
73. Y. Yamamoto, H. Toi, A. Sonoda, and S.-I. Murahashi, *J. Amer. Chem. Soc.*, 1976, **98,** 1965.
74. A. L. Wilds, *Org. Reactions*, 1944, **2,** 178.
75. T. A. Geissman, *Org. Reactions*, 1944, **2,** 94.
76. E. G. E. Hawkins, D. J. G. Long, and F. W. Major, *J. Chem. Soc.*, 1955, 1462.
77. I. Lin and A. R. Day, *J. Amer. Chem. Soc.*, 1952, **74,** 5733.
78. P. N. Rylander, 'Catalytic Hydrogenation over Platinum Metals', Academic, New York, 1967, 238.
79. A. J. Birch and D. H. Williamson, *Org. Reactions*, 1976, **24,** 1.
80. D. Evans, J. A. Obsorn, and G. Wilkinson, *J. Chem. Soc.* (*A*), 1968, 3133.
81. V. G. Khomyakov, A. P. Tomilov, and B. G. Soldatov, *Elektrokhimiya*, 1969, **5,** 850 and 853 (*Chem. Abs.*, 1969, **71,** 108 402 and 108 403).
82. J. E. McMurry and M. P. Fleming, *J. Org. Chem.*, 1976, **41,** 896.
83. E. L. Martin, *Org. Reactions*, 1942, **1,** 155.
84. D. Todd, *Org. Reactions*, 1948, **4,** 378.
85. R. O. Hutchins, C. A. Milewski, and B. E. Maryanoff, *J. Amer. Chem. Soc.*, 1973, **95,** 3662.
86. R. H. Shapiro, *Org. Reactions*, 1976, **23,** 405.
87. R. F. Borch, M. D. Bernstein, and M. D. Durst, *J. Amer. Chem. Soc.*, 1971, **93,** 2897; R. F. Borch and A. I. Hassad, *J. Org. Chem.*, 1972, **37,** 1673.
88. K. Ohno and J. Tsuji, *J. Amer. Chem. Soc.*, 1968, **90,** 99; J. Tsuji and K. Ohno, *Synthesis*, 1969, 157.
89. H. M. Walborsky and L. E. Allen, *J. Amer. Chem. Soc.*, 1971, **93,** 5465.
90. H. E. Eschinazi, *J. Amer. Chem. Soc.*, 1959, **81,** 2905.
91. K. Sakai and O. Oda, *Tetrahedron Letters*, 1972, 4375.
92. K. Mislow and M. Raban, *Topics Stereochem.*, 1967, **1,** 1.
93. J. D. Morrison and H. S. Mosher, 'Asymmetric Organic Reactions', Prentice Hall, New Jersey, 1971, chapters 3 and 4.
94. H. B. Burgi, J. D. Dunitz, J. M. Lehn, and G. Wipff, *Tetrahedron*, 1974, **30,** 1563.
95. H. B. Burgi, *Angew. Chem. Internat. Edn.*, 1975, **14,** 60.
96. H. B. Burgi, J. M. Lehn, and G. Wipff, *J. Amer. Chem. Soc.*, 1974, **96,** 1956.
97. R. P. Bell, *Adv. Phys. Org. Chem.*, 1966, **4,** 1.
98. R. Hiatt, in 'Organic Peroxides', ed. D. Swern, Wiley-Interscience, New York, 1971, vol. 2, chapter 1.
99. H. J. E. Loewenthal, in 'Protective Groups in Organic Chemistry', ed. J. F. W. McOmie, Plenum, London, 1973, chapter 9.
100. L. Claisen, *Ber.*, 1896, **29,** 1005.
101. P. Le Henaff, *Bull. Soc. chim. France*, 1968, 4687.
102. D. Seebach and N. Peleties, *Chem. Ber.*, 1972, **105,** 511.
103. E. H. Man, J. J. Sanderson, and C. R. Hauser, *J. Amer. Chem. Soc.*, 1950, **72,** 847.
104. H. J. Hagenmeyer, Jr. and D. C. Hull, *Ind. Eng. Chem.*, 1949, **41,** 2920.
105. A. M. Sladkov and G. S. Petrov, *J. Gen. Chem.* (*U.S.S.R.*), 1954, **24,** 459.
106. A. T. Nielson and W. J. Houlihan, *Org. Reactions*, 1968, **16,** 1.
107. I. Kuwijama, T. Sato. M. Arai, and N. Minami, *Tetrahedron Letters*, 1976, 1817.
108. H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, *J. Amer. Chem. Soc.*, 1973, **95,** 3310.
109. U. Schöllkopf, in Houben-Weyl, 'Methoden der Organischen Chemie', Thieme, Stuttgart, 1970, vol. 13/1, pp. 247–250.
110. E. J. Corey and D. Enders, *Tetrahedron Letters*, 1976, 3, 11.
111. T. Mukaiyama, K. Banno, and K. Narasaka, *J. Amer. Chem. Soc.*, 1974, **96,** 7503.
112. L. Birkofer, S. M. Kim, and H. D. Engels, *Chem. Ber.*, 1962, **95,** 1495.
113. G. Jones, *Org. Reactions*, 1967, **15,** 204.
114. J. R. Johnson, *Org. Reactions*, 1942, **1,** 210.
115. W. S. Johnson and G. H. Daub, *Org. Reactions*, 1951, **6,** 1.
116. M. W. Rathke, *Org. Reactions*, 1975, **22,** 423; K. Nützel, in Houben-Weyl, 'Methoden der Organischen Chemie', Thieme, Stuttgart, 1973, vol. 13/2a, pp. 809–838.
117. M. W. Rathke, *J. Amer. Chem. Soc.*, 1970, **92,** 3222; M. W. Rathke and A. Lindert, *ibid.*, 1971, **93,** 2318; M. W. Rathke and D. F. Sullivan, *ibid.*, 1973, **95,** 3050.
118. D. Seebach and A. K. Beck, *Angew. Chem. Internat. Edn.*, 1974, **13,** 806; W. Dumont, P. Bayet, and A. Krief, *ibid.*, 1974, **13,** 805.
119. H. Newman, *Tetrahedron Letters*, 1971, 4571.
120. W. Mychajlowskij and T. H. Chan, *Tetrahedron Letters*, 1976, 4439.
121. U. Schöllkopf, F. Gerhart, and R. Schröder, *Angew. Chem. Internat. Ed.*, 1969, **8,** 672.
122. U. Schöllkopf and R. Schröder, *Angew. Chem. Internat. Ed.*, 1972, **11,** 311.

123. K. Nützel, in Houben-Weyl, 'Methoden der Organischen Chemie', Thieme, Stuttgart, 1973, vol. 13/2a, pp. 285–302.
124. F. Bartini, P. Grasselli, G. Zubiani, and G. Cainelli, *Tetrahedron*, 1970, **26,** 1281.
125. D. Blagoev and D. Ivanov, *Synthesis*, 1970, 615.
126. K. Nützel, in Houben Weyl, 'Methoden der Organischen Chemie', Thieme, Stuttgart, 1973, vol. 13/2a, pp. 710–727.
127. K. Nützel, in Houben Weyl, 'Methoden der Organischen Chemie', Thieme, Stuttgart, 1973, vol. 13/2a, pp. 916–922.
128. U. Schöllkopf, in Houben Weyl, 'Methoden der Organischen Chemie', Thieme, Stuttgart, 1970, vol. 13/1, pp. 175–183.
129. A. Maercker, *Org. Reactions*, 1965, **14,** 270.
130. M. Schlosser, *Topics Stereochem.*, 1970, **5,** 1.
131. J. Boutagy and R. Thomas, *Chem. Rev.*, 1974, **74,** 87.
132. E. J. Corey and G. T. Kwiatkowski, *J. Amer. Chem. Soc.*, 1968, **90,** 6816.
133. E. J. Corey and T. Durst, *J. Amer. Chem. Soc.*, 1968, **90,** 5548.
134. C. W. Roberts, in 'Friedel-Crafts and Related Reactions', ed. G. A. Olah, 1964, vol. 2, part 2, chapter 27.
135. G. A. Olah and W. S. Tolgyesi, in 'Friedel-Crafts and Related Reactions', ed. G. A. Olah, 1964, vol. 11, part 2, chapter 21.
136. E. W. Lund, *Acta Chem. Scand.*, 1958, **12,** 1768.
137. K. N. Campbell, A. H. Sommers, and B. K. Campbell, *J. Amer. Chem. Soc.*, 1944, **66,** 82.
138. G. Opitz, H. Hellmann, and H. W. Schubert, *Annalen*, 1959, **623,** 112; R. Dunlou, E. Elkik and A. Veillard, *Bull. Soc. chim. France*, 1960, 967.
139. T. J. Curphey and J. C.-Y. Hung, *Chem. Comm.*, 1967, 510.
140. N. J. Leonard and J. V. Paukstelis, *J. Org. Chem.*, 1963, **28,** 3021.
141. S. R. Sandler and W. Karo in 'Polymer Synthesis', Academic, New York, 1974, vol. 1, chapter 5.
142. F. F. Blicke, *Org. Reactions*, 1942, **1,** 303.
143. C. Walling and E. S. Huyser, *Org. Reactions*, 1963, **13,** 91.
144. D. E. Applequist and L. Kaplan, *J. Amer. Chem. Soc.*, 1965, **87,** 2194.
145. I. Fleming, 'Frontier Orbitals and Organic Chemical Reactions', Wiley, New York, 1976.
146. D. R. Arnold, *Adv. Photochem.*, 1968, **6,** 301.
147. H. E. Zaugg, *Org. Reactions*, 1954, **8,** 305.
148. S. B. Needleman and M. C. Chang Kuo, *Chem. Rev.*, 1962, **62,** 405.
149. S. M. Makin, *Russ. Chem. Rev.*, 1969, **38,** 237.
150. H. M. R. Hoffmann, *Angew. Chem. Internat. Edn.*, 1969, **8,** 556.
151. R. Huisgen, *Angew. Chem. Internat. Edn.*, 1963, **2,** 565, 633.
152. I. Zugravescu and M. Petrovanu, 'N-Ylid Chemistry', McGraw-Hill, New York, 1976.
153. C. D. Gutsche, *Org. Reactions*, 1954, **8,** 364.
154. E. J. Corey, D. Enders, and M. G. Bock, *Tetrahedron Letters*, 1976, 7.
155. W. Nagata and Y. Hayase, *Tetrahedron Letters*, 1968, 4359; *J. Chem. Soc.* (*C*), 1969, 460.
156. S. Trippett and D. M. Walker, *J. Chem. Soc.*, 1961, 1266.
157. A. K. Bose and R. T. Dahill, Jr., *J. Org. Chem.*, 1965, **30,** 505.
158. R. I. Hoaglin and D. H. Hirsh, *J. Chem. Soc.*, 1949, **71,** 3468.
159. O. Isler, H. Lindlar, M. Montavon, R. Rüegg, and P. Zeller, *Helv. Chim. Acta*, 1956, **39,** 249.
160. G. L. Olson, H.-C. Cheung, K. D. Morgan, R. Borer, and G. Saucy, *Helv. Chim. Acta*, 1976, **59,** 567; H. Pauling, D. A. Andrews, and N. C. Hindley, *ibid.*, 1976, **59,** 1233; G. L. Olson, K. D. Morgan, and G. Saucy, *Synthesis*, 1976, 25.
161. M. B. Erman, I. S. Aul'chenko, L. A. Kheifits, V. G. Dulova, Yu. N. Novikov, and M. E. Vol'pin, *Tetrahedron Letters*, 1976, 2981.
162. G. Saucy, R. Marbet, H. Lindlar, and O. Isler, *Helv. Chim. Acta*, 1959, **42,** 1945.
163. M. Julia and J.-M. Surzur, *Bull. Soc. chim. France*, 1956, 1615.
164. H. G. Viehe, *Chem. Ber.*, 1959, **92,** 1270.
165. J. F. Arens, *Adv. Org. Chem.*, 1960, **2,** 117.
166. E. J. Corey and S. Terashima, *Tetrahedron Letters*, 1972, 1815; Y. Leroux and C. Roman, *ibid.*, 1973, 2585.
167. A. Viola and L. A. Levasseur, *J. Amer. Chem. Soc.*, 1965, **87,** 1150.
168. W. H. Watanabe and L. E. Conlon, *J. Amer. Chem. Soc.*, 1957, **79,** 2828.
169. R. Marbet and G. Saucy, *Helv. Chim. Acta*, 1967, **50,** 2095.
170. K. C. Brannock, *J. Amer. Chem. Soc.*, 1959, **81,** 3379.
171. R. K. Hill and A. G. Edwards, *Tetrahedron Letters*, 1964, 3239.
172. D. R. Taylor, *Chem. Rev.*, 1967, **67,** 317.
173. R. C. Cookson and N. R. Rogers, *J.C.S. Perkin I*, 1973, 2741.
174. S. J. Rhoads and N. R. Raulins, *Org. Reactions*, 1975, **22,** 1.
175. E. J. Corey and J. I. Shulman, *J. Amer. Chem. Soc.*, 1970, **92,** 5522.
176. K. Oshima, H. Takahashi, H. Yamamoto, and H. Nozaki, *J. Amer. Chem. Soc.*, 1973, **95,** 2693.
177. E. J. Corey, H. Yamamoto, D. K. Herron, and K. Achiwa, *J. Amer. Chem. Soc.*, 1970, **92,** 6635.
178. E. J. Corey and D. K. Herron, *Tetrahedron Letters*, 1971, 1641.
179. B. M. Trost and J. L. Stanton, *J. Amer. Chem. Soc.*, 1975, **97,** 4018.
180. T. Nakai, H. Shiono, and M. Okawara, *Tetrahedron Letters*, 1974, 3625.

181. E. J. Corey, B. W. Erickson, and R. Noyori, *J. Amer. Chem. Soc.*, 1971, **93,** 1724.
182. K. Kondo and D. Tunemoto, *Tetrahedron Letters*, 1975, 1007.
183. E. J. Corey and P. Ulrich, *Tetrahedron Letters*, 1975, 3685.
184. S. Shatzmiller, P. Gygax, D. Hall, and A. Eschenmoser, *Helv. Chim. Acta*, 1973, **56,** 2961; P. Gygax, T. K. Das Gupta, and A. Eschenmoser, *ibid.*, 1972, **55,** 2205; U. M. Kempe, T. K. Das Gupta, K. Blatt, P. Gygax, D. Felix, and A. Eschenmoser, *ibid.*, 1972, **55,** 2187.
185. H. Pommer, *Ger. Pat.*, 1958, 1 025 871 (*Chem. Abs.*, 1960, **54,** 9799).
186. P. C. Traas, H. Boelens, and H. J. Takken, *Rec. Trav. chim.*, 1976, **95,** 57.
187. P. C. Traas, H. Boelens, and H. J. Takken, *Tetrahedron Letters*, 1976, 2287.
188. J. Ficini and H. Normant, *Bull. Soc. chim. France*, 1964, 1294.
189. N. Rabjohn, *Org. Reactions*, 1976, **24,** 261.
190. R. M. Evans, *Quart. Rev.*, 1959, **13,** 61.
191. F. Kröhnke, *Angew. Chem. Internat. Edn.*, 1963, **2,** 380.
192. M. Montavon, H. Lindlar, R. Marbet, R. Rüegg, G. Ryser, G. Saucy, P. Zeller, and O. Isler, *Helv. Chim. Acta*, 1957, **40,** 1250.
193. G. Cardillo, M. Orena, and S. Sandri, *J.C.S. Chem. Comm.*, 1976, 190.
194. E. J. Corey and A. P. Kozikowski, *Tetrahedron Letters*, 1975, 925.
195. G. R. Malone and A. I. Meyers, *J. Org. Chem.*, 1974, **39,** 623; A. I. Meyers, A. Nabeya, H. W. Adickes, J. M. Fitzpatrick, G. R. Malone, and I. R. Politzer, *J. Amer. Chem. Soc.*, 1969, **91,** 764.
196. H. Taguchi, S. Tanaka, H. Yamamoto, and H. Nozaki, *Tetrahedron Letters*, 1973, 2465.
197. A. Hara and M. Sekiya, *Chem. Pharm. Bull. (Japan)*, 1972, **20,** 309.
198. H. Newman, *J. Org. Chem.*, 1973, **38,** 2254.
199. K. B. Sharpless, R. F. Lauer, and A. Y. Teranishi, *J. Amer. Chem. Soc.*, 1973, **95,** 6137.
200. C. A. Bertelo and J. Schwartz, *J. Amer. Chem. Soc.*, 1976, **98,** 262.
201. G. I. Nikishin, M. G. Vinogradov, and G. P. Il'ina, *Synthesis*, 1972, 376.
202. M. R. Johnson and B. Rickborn, *J. Org. Chem.*, 1970, **35,** 1041.
203. R. Pummerer, F. Aldebert, F. Graser, and H. Sperber, *Annalen*, 1953, **583,** 225.
204. H. S. Broadbent, G. C. Campbell, W. J. Bartley, and J. H. Johnson, *J. Org. Chem.*, 1959, **24,** 1847.
205. J. Wiemann and Le Thi-Thuan, *Bull. Soc. chim. France*, 1955, 95.
206. J. Wiemann, *Bull. Soc. chim. France*, 1964, 2545.
207. J. Wiemann, M. Dedieu, and D. Lelandais, *Fr. Pat.*, 1968, 1 591 372, (*Chem. Abs.*, 1971, **74,** 70 990).
208. J. C. Johnston, J. D. Faulkner, L. Mandell, and R. A. Day, Jr., *J. Org. Chem.*, 1976, **41,** 2611.
209. J. E. McMurry and M. P. Fleming, *J. Amer. Chem. Soc.*, 1974, **96,** 4708.
210. R. C. Schulz and H. Hartmann, *Chem. Ber.*, 1962, **95,** 2735.
211. H. L. Holmes, *Org. Reactions*, 1948, **4,** 60.
212. K. Nützel, in Houben-Weyl, 'Methoden der Organische Chemie', Thieme, Stuttgart, 1973, vol. 13/2a, p. 401.
213. E. A. Braude, *Prog. Org. Chem.*, 1955, **3,** 172.
214. E. D. Bergmann, D. Ginsburg, and R. Pappo, *Org. Reactions*, 1959, **10,** 179.
215. H. Marschall, F. Vogel, and P. Weyerstahl, *Tetrahedron Letters*, 1976, 175.
216. A. T. Nielsen, *J. Amer. Chem. Soc.*, 1957, **79,** 2524; A. F. Thomas and R. Guntz-Dubini, *Helv. Chim. Acta*, 1976, 2261.
217. E. A. Braude, B. F. Gofton, G. Lowe, and E. S. Waight, *J. Chem. Soc.*, 1956, 4054.
218. G. L. Olson, H.-C. Cheung, K. D. Morgan, R. Borer, and G. Saucy, *Helv. Chim. Acta*, 1976, **59,** 567.
219. E. J. Corey, N. W. Gilman, and B. E. Ganem, *J. Amer. Chem. Soc.*, 1968, **90,** 5616.
220. A. G. Cook, 'Enamines, Synthesis, Structure and Reactions', Dekker, New York, 1969; S. F. Dyke, 'Chemistry of Enamines', Cambridge University Press, 1973.
221. G. B. Payne, *J. Amer. Chem. Soc.*, 1959, **81,** 4901; *J. Org. Chem.*, 1961, **26,** 250.
222. P. B. D. de la Mare and R. Bolton, 'Electrophilic Addition to Unsaturated Systems', Elsevier, Amsterdam, 1966.
223. A. Berlande, *Bull. Soc. chim. France*, 1925, **37[4],** 1385.
224. S. Hunig and H. Kahanek, *Chem. Ber.*, 1957, **90,** 238; G. Opitz and W. Merz, *Annalen*, 1962, **652,** 139.
225. C. H. Jarboe, in 'Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings', ed. R. H. Wiley, Interscience, New York, 1967, chapter 7.
226. F. I. Luknitskii, *Chem. Rev.*, 1975, **75,** 259.
227. C. L. Stevens, E. Farkas, and B. Gillis, *J. Amer. Chem. Soc.*, 1954, **76,** 2695.
228. G. R. Malone and A. I. Meyers, *J. Org. Chem.*, 1974, **39,** 618.
229. E. M. Chamberlin, E. Tristram, T. Utne, and J. M. Chemerda, *J. Amer. Chem. Soc.*, 1957, **79,** 456.
230. P. Duhamel, L. Duhamel, and J.-Y. Valnot, *Bull. Soc. chim. France*, 1973, 1465.
231. R. Tiollais, H. Bouget, J. Huet, and A. Le Pennec, *Bull. Soc. chim. France*, 1964, 1205.
232. R. H. Reuss and A. Hassner, *J. Org. Chem.*, 1974, **39,** 1785.
233. J. Villieras, C. Bacquet, D. Masure, and J. F. Normant, *J. Organometallic Chem.*, 1973, **50,** C7.
234. F. de Reinach-Hirtzbach and T. Durst, *Tetrahedron Letters*, 1976, 3677; A. Jonczyk, K. Banko, and M. Maskosza, *J. Org. Chem.*, 1974, **40,** 266.
235. Z. Arnold and J. Žemlička, *Proc. Chem. Soc.*, 1956, 227; *Coll. Czech. Chem. Comm.*, 1959, **24,** 2385 (*Chem. Abs.*, 1960, **54,** 1274); Z. Arnold and A. Holy, *Coll. Czech. Chem. Comm.*, 1961, **26,** 3059 (*Chem. Abs.*, 1962, **56,** 15 329).

236. J. M. F. Gagan, A. G. Lane, and D. Lloyd, *J. Chem. Soc. (C)*, 1970, 2484.
237. H. Schelhorn, H. Frischleder, and S. Hauptmann, *Tetrahedron Letters*, 1970, 4315.
238. C. S. Marvel and P. K. Porter, *Org. Synth. Coll. Vol. 1*, 1941, 377.
239. E. J. Corey, J.-L. Gras, and P. Ulrich, *Tetrahedron Letters*, 1976, 809.
240. P. Ballinger, P. B. D. de la Mare, G. Kohnstam, and B. M. Prestt, *J. Chem. Soc.*, 1955, 3641.
241. H. Normant, *Bull. Soc. chim. France*, 1959, 459.
242. C. I. Stassinopoulou and C. Zioudrou, *Tetrahedron*, 1972, **28,** 1257; A. Kirrmann, J. Cantacuzene, L. Vio, and M. Martin, *Bull. Soc. chim. France*, 1963, 1067.
243. F. Weygand, H. J. Bestmann, H. Ziemann, and E. Klieger, *Chem. Ber.*, 1958, **91,** 1043.
244. O. H. Oldenziel and A. M. van Leusen, *Tetrahedron Letters*, 1974, 163, 167.
245. J. J. Riehl and A. Fougerousse, *Bull. Soc. chim. France*, 1968, 4083.
246. J. J. Riehl, J.-M. Lehn, and F. Hemmot, *Bull. Soc. chim. France*, 1963, 224.
247. J. E. Dubois and J.-F. Fort, *Tetrahedron*, 1972, **28,** 1653, 1665.
248. A. I. Meyers, R. Munavu, and J. Durandetta, *Tetrahedron Letters*, 1972, 3929.
249. E. Winterfeldt, *Synthesis*, 1975, 617.
250. J. E. Baldwin, *J.C.S. Chem. Comm.*, 1976, 734.
251. C. D. Hurd and W. H. Saunders, Jr., *J. Amer. Chem. Soc.*, 1952, **74,** 5324.
252. G. Saucy, R. Borer, and A. Furst, *Helv. Chim. Acta*, 1971, **54,** 2034.
253. A. S. Perlin, *Methods Carbohydrate Chem.*, 1962, **1,** 61.
254. E. Baer, J. M. Grosheintz, and H. O. L. Fischer, *J. Amer. Chem. Soc.*, 1939, **61,** 2607.
255. E. J. Witzemann, W. L. Evans, H. Hass, and E. F. Schroeder, *Org. Synth. Coll. Vol.* 2, 1943, 305, 307; F. P. Pingert, *Org. Synth.*, 1945, **25,** 1.
256. C. E. Ballou and D. L. MacDonald, *Methods Carbohydrate Chem.*, 1963, **2,** 289.
257. M. Calvin, *Angew. Chem. Internat. Edn.*, 1962, **1,** 65.
258. J. R. Knowles, P. F. Leadlay, and S. G. Maister, *Cold Spring Harbour Symposium on Quantitative Biology*, 1971, **36,** 157.
259. A. R. Ronzio and T. D. Waugh, *Org. Synth. Coll. Vol. 3*, 1955, 438.
260. S. Horiie, C. Fujii, and Y. Kosai, *Ger. Pat.*, 1970, 2 022 567 (*Chem. Abs.*, 1971, **74,** 41 917).
261. A. J. Fatiadi and W. F. Sager, *Org. Synth.*, 1962, **42,** 90.
262. Z. Arnold and F. Šorm, *Coll. Czech. Chem. Comm.*, 1958, **23,** 452.
263. C. Reichardt and E.-U. Würthwein, *Chem. Ber.*, 1974, **107,** 3454.
264. J. C. Leffingwell, *Chem. Comm.*, 1970, 357.
265. M. Chkir and D. Lelandais, *Chem. Comm.*, 1971, 1369.
266. J. P. Nagarkatti and K. R. Ashley, *Tetrahedron Letters*, 1973, 4599.
267. A. C. Cope, H. L. Dryden, Jr., and C. F. Howell, *Org. Synth. Coll. Vol. 4*, 1963, 816.
268. F. W. Lichtenthaler, *Angew. Chem. Internat. Edn.*, 1964, **3,** 211.

5.2

Ketones

A. J. WARING
University of Birmingham

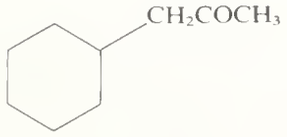
5.2.1 NOMENCLATURE AND BONDING IN KETONES 1019
5.2.1.1 Nomenclature 1019
5.2.1.2 Bonding in ketones 1019
5.2.2 SYNTHETIC ROUTES TO KETONES 1020
5.2.2.1 The major synthetic routes 1020
5.2.2.2 Preparations to which cross-reference has not been made 1021
5.2.3 KETO–ENOL TAUTOMERISM 1024
5.2.4 THE CHEMISTRY OF ENOLS, ENOLATE IONS, AND THEIR DERIVATIVES 1026
5.2.4.1 Reactions of enols and enolate anions 1026
5.2.4.2 Regioselectivity of reactions 1027
5.2.4.3 Enol ester formation: by direct acylation 1028
5.2.4.4 Trimethylsilyl enol ethers: by direct reaction 1028
5.2.4.5 Enol esters and enol silyl ethers from preformed enolate anions 1028
5.2.4.6 Enol ether formation 1029
5.2.4.7 Enolates, enols, and enol derivatives from α,β-unsaturated ketones 1029
5.2.4.8 Synthetic uses of enol derivatives 1030
5.2.4.9 Other routes to enolate anions 1031
5.2.4.10 Spectroscopic data on enol derivatives 1031
5.2.4.11 Equilibration of α,β- and β,γ-olefinic ketones 1031
5.2.5 ALKYLATIONS OF KETONES AT THE α-CARBON ATOM 1032
5.2.5.1 Direct α-alkylation of monoketones 1032
5.2.5.2 Reductive alkylation at the α-carbon atom of α,β-unsaturated ketones 1034
5.2.5.3 Direct alkylation of α,β-unsaturated ketones 1035
5.2.6 HALOGENATION OF KETONES AND THEIR DERIVATIVES 1036
5.2.6.1 Direct halogenation of ketones 1036
5.2.6.2 Regioselective halogenation at the more heavily alkylated α-carbon atom of constitutionally unsymmetrical ketones 1037
5.2.6.3 Regioselective halogenation at the less-alkylated α-carbon atom of constitutionally unsymmetrical ketones 1038
5.2.6.4 Regiospecific halogenation of ketone derivatives 1038
5.2.6.5 Dihalogeno ketones 1038
5.2.6.6 Trihalomethyl ketones 1039
5.2.7 CONDENSATIONS AT THE α-METHYLENE GROUPS OF KETONES 1039
5.2.7.1 Aldol condensations 1039
5.2.7.2 The Mannich reaction 1041
5.2.7.3 Nitrosation of ketones 1042
5.2.7.4 Diazonium coupling of ketones 1043
5.2.8 THE MICHAEL REACTION, AND ADDITIONS OF ORGANOMETALLIC REAGENTS AND YLIDES TO KETONES 1043
5.2.8.1 The Michael reaction 1043
5.2.8.2 Additions of organometallic reagents and ylides to ketones 1046

5.2.9 RING-FORMING REACTIONS AND ANNELATIONS 1049
5.2.9.1 Robinson annelation 1049
5.2.9.2 Other annelation methods 1052
5.2.9.3 Spiroannelations 1054
5.2.9.4 Formation of cyclohexenones 1055
5.2.10 DIKETONES 1056
5.2.10.1 1,2-Diketones (α-diketones) 1056
5.2.10.2 1,3-Diketones (β-diketones) 1058
5.2.10.3 1,4-Diketones (γ-diketones) 1062
5.2.11 HYDROXY KETONES 1065
5.2.11.1 2-Hydroxy ketones (α-hydroxy ketones: α-ketols) 1065
5.2.11.2 3-Hydroxy ketones (β-hydroxy ketones: β-ketols) 1066
5.2.11.3 4-Hydroxy ketones (γ-hydroxy ketones: γ-ketols) 1067
5.2.11.4 Polyhydroxy ketones 1068
5.2.12 KETO ALDEHYDES 1068
5.2.12.1 2-Keto aldehydes (α-keto aldehydes) 1068
5.2.12.2 3-Keto aldehydes (β-keto-aldehydes) 1068
5.2.12.3 4-Keto aldehydes (γ-keto aldehydes) 1069
5.2.12.4 5- and 6-keto aldehydes 1069
5.2.13 UNSATURATED KETONES 1069
5.2.13.1 General preparations 1069
5.2.13.2 Cyclohexenones 1073
5.2.13.3 Cyclopentenones 1073
5.2.14 REDUCTION OF KETONES 1074
5.2.14.1 Catalytic hydrogenation 1074
5.2.14.2 Reduction by alkali and alkaline earth metals in liquid ammonia 1075
5.2.14.3 Complex metal hydride reductions 1077
5.2.14.4 Reduction of α,β-unsaturated ketones mainly at the olefinic bond 1077
5.2.14.5 Reduction of the carbonyl group of α,β-unsaturated ketones 1078
5.2.14.6 Deoxygenation of carbonyl compounds 1079
5.2.14.7 Deoxygenation of ketones to form olefins 1081
5.2.14.8 Reductive cleavage of α-substituted ketones 1082
5.2.15 ADDITIONS TO THE CARBONYL GROUP OF KETONES, PROTECTION METHODS AND BASICITY 1083
5.2.15.1 Additions 1083
5.2.15.2 Protecting groups 1083
5.2.15.3 Basicity of ketones 1084
5.2.16 CLEAVAGE OF KETONES 1085
5.2.17 REARRANGEMENTS OF KETONES 1086
5.2.17.1 Baeyer–Villiger oxidation 1086
5.2.17.2 Ketone isomerizations 1087
5.2.17.3 Ring-expansions and homologations of ketones 1088
5.2.17.4 Rearrangements of α-ketols; the acyloin rearrangement 1090
5.2.17.5 Rearrangements of α-diketones 1090
5.2.17.6 The Favorskii rearrangement of α-halo ketones 1091
5.2.18 PHOTOCHEMICAL REACTIONS OF KETONES 1093
5.2.19 SPECTRA OF KETONES 1093
5.2.19.1 Infrared spectroscopy 1093
5.2.19.2 Ultraviolet spectroscopy 1094
5.2.19.3 ^{1}H Nuclear magnetic resonance spectroscopy 1094
5.2.19.4 ^{13}C Nuclear magnetic resonance spectroscopy 1094
5.2.19.5 Circular dichroism and optical rotatory dispersion 1095
5.2.19.6 Some spectroscopic data 1095

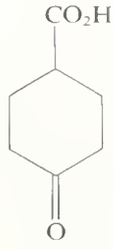
5.2.1 NOMENCLATURE AND BONDING IN KETONES

5.2.1.1 Nomenclature

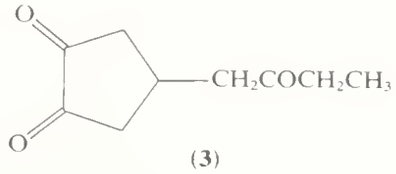
The IUPAC recommendations allow both the substitutive system of nomenclature and the radicofunctional system to be used.[1] In the former, the name of an acyclic ketone is formed by adding the suffix '-one' to the name of the hydrocarbon corresponding to the principal chain, with elision of any terminal 'e' before '-one' (rule C-312). Thus $CH_3COCH_2CH_3$ is butan-2-one and compound (**1**) is cyclohexylpropanone or cyclohexylacetone (rule C-313.1). The priority of the ketone as a 'principal group' in nomenclature is just below aldehydes (which also have the suffix '-one'), and follows cyanides and carboxylic acid derivatives. It precedes alcohols and phenols (rules C-10.1 and C-23). When another group of higher priority is present in the compound the prefix 'oxo-' is used to denote the ketone group. Thus (**2**) is 4-oxocyclohexanecarboxylic acid (rule C-316.2).



(**1**)



(**2**)



(**3**)

The 'oxo-' prefix is used also when more than one ketone group is present and not all can be included in the normal ketone name. Compound (**3**) is thus 4-(2-oxobutyl)-1,2-cyclopentanedione (in American usage) or 4-(2-oxobutyl)cyclopentane-1,2-dione (in British usage) (rules C-12.6 and C-318.1). The prefix 'keto-' is frequently used in the literature of steroids. In the radicofunctional system (which is not, in general, preferred) $CH_3COCH_2CH_3$ is ethyl methyl ketone or methyl ethyl ketone and $CH_3COCH_2CH_2OH$ is 2-hydroxyethyl methyl ketone or methyl 2-hydroxyethyl ketone (rule C-0.2); the preferred name is 4-hydroxybutan-2-one (British usage). The names of acyl or other carbonyl-containing ligands such as acetyl (CH_3CO—), acetonyl (CH_3COCH_2—) or acetonylidene (CH_3COCH=) can be used in certain circumstances, when their carbonyl group is not the only one in the molecule or does not have priority as 'the principal group' (rule C-318.1). Cyclic ketones are named by the substitutive system [see (**3**) above].

5.2.1.2 Bonding in ketones

Ketones have an oxygen atom doubly bound to a single carbon atom, and the carbonyl group ($>C{=}O$) which this constitutes is joined to two carbon atoms. The bonding of the carbonyl group in ketones, R^1COR^2, is essentially the same as that in aldehydes, RCOH (see Section 5.1.1.2). Heats of formation of many ketones have been collected[2,3] and refinements of additive bond-energy methods of calculating these for acyclic ketones have been published.[5]

The length of the carbon–oxygen bond in ketones is about 120 pm and varies when the bond is conjugated with other multiple bonds or attached to strongly electron-donating or -withdrawing groups. Tables of bond lengths, dipole moments, and ionization potentials are given in Ref. 3 and in the theoretical papers which are to be cited. *Ab initio* MO calculations have been made which estimate the charge distribution, dipole moments,[6] and n–π^* excitation energies[7] of acetone, some aldehydes, and many other molecules; the parameters used were discussed. Molecular mechanics (force-field) calculations are valuable in reproducing the conformations of ketones[8] (and have been applied recently to substituted decalones and steroidal ketones[8]) and in estimating many heats of formation and strain energies.[9]

In α,β-unsaturated ketones the polarization $O{=}C{-}C{=}C \leftrightarrow O{-}C{=}C{-}C^{+}$ reduces the strength of the carbonyl bond, places a positive charge estimated at 0.1 to 0.2 electron units at the β-carbon atom (C-3), and allows the existence of *s-cis* and *s-trans* conformers which differ in their stereochemistry about the partially double C-1, C-2 bond. Experimental data on molecular geometries[10,11] and calculations of the conformational behaviour and π–π^* excitation energies of many α,β-unsaturated ketones and aldehydes have been given.[10]

The conformational analysis of cyclic ketones has been extensively discussed (see Refs. 8 and 12).

5.2.2 SYNTHETIC ROUTES TO KETONES

5.2.2.1 The major synthetic routes

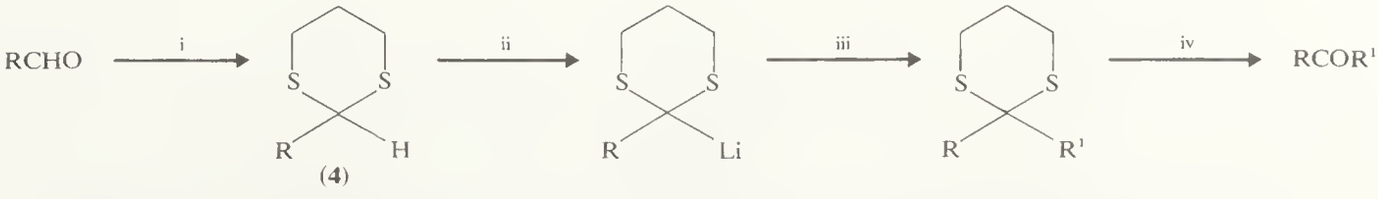
These are outlined, with a cross-reference to the section where more details and references may be found.

1. Ozonolysis of alkenes: $R^1R^2C{=}CHR^3 \rightarrow R^1R^2CO + R^3CHO$ (Sections 2.2.3.5 and 5.2.10).
2. Allylic oxidation of alkenes or alkynes: $>C{=}C{-}CH_2 \rightarrow >C{=}C{-}C{=}O$ and $-C{\equiv}C{-}CH_2 \rightarrow -C{\equiv}C{-}C{=}O$ (Sections 2.2.3.5 and 5.2.13).
3. Hydration of acetylenes: $RC{\equiv}CH \rightarrow RCOCH_3$ and $R^1C{\equiv}CR^2 \rightarrow R^1COCH_2R^2$ (Sections 2.3.10.4 and 5.2.11.1).
4. Hydrolysis of geminal dihalides: $R^1R^2C(Hal)_2 \rightarrow R^1COR^2$ (Section 3.3).
5. Oxidation of secondary alcohols: $R^1R^2CHOH \rightarrow R^1COR^2$ [Sections 4.1.1.4 (p. 644), 5.2.10.1, and 5.2.13.1]; hydride abstraction from silyl ethers of secondary alcohols.
6. Pinacol rearrangement of 1,2-diols: $R^1R^2C(OH)C(OH)R^3R^4 \rightarrow R^1COCR^2R^3R^4$ (Section 4.1.2.4, p. 688).
7. Oxidative cleavage of 1,2-diols, using glycol cleaving reagents (Section 4.1.2.4, p. 691). Diols $R^1CH(OH)C(OH)R^1R^2$ can be made by reducing α-ketols $R^1COC(OH)R^1R^2$, derived from esters $R^1CO_2R^3$ (Sections 5.2.11.1 and 5.2.14.5).
8. Hydrolysis of vinyl ethers: $>C{=}C{-}OR \rightarrow >CH{-}CO$ (Section 4.3.8).
9. Rearrangements of oxirans (epoxides) (Sections 4.4.4.2 and 5.2.11.1).
10. Birch reduction of phenolic ethers and hydrolysis of the resulting vinyl ethers to cyclohexenones (Sections 4.5.2.2 and 5.2.13.2).
11. Claisen–Cope rearrangement of allyl vinyl ethers to γ,δ-olefinic ketones (Section 4.3.6.2).
12. *C*-Alkylation and other attack on phenols to give cyclohexadienones (Section 4.2.1.3).
13. Friedel–Crafts acylation of alkenes: $RCOCl + >C{=}C< \rightarrow RCOC{-}C{-}Cl$ (Section 5.2.13); for intramolecular cyclizations to give cycloalkenones, see Sections 5.2.13.2 and 5.2.13.3.
14. Acetoacetic ester and other β-keto ester syntheses: $>COC(R^1R^2)CO_2R^3 \rightarrow >COC(R^1R^2)CO_2^- \rightarrow >COCHR^1R^2$.
15. Claisen condensation of esters to β-keto esters; Dieckman condensation for cyclic β-keto esters (Section 9.5.2.1).
16. From β-diketones or β-keto aldehydes: general type $R^1COCH_2COR^2 \rightarrow R^1COC(R^3R^4)COR^2 \rightarrow R^1COCHR^3R^4 + R^2CHR^3R^4$ (Section 5.2.10.2).

17. From β-keto sulphoxides, analogous to the preceding cases (Section 11.7.4).
18. Pyrolysis of salts of carboxylic acids: $2RCO_2M \rightarrow RCOR$; suitable for α,β-diacid salts → cyclic ketones (Section 9.1.4.4).
19. By cyclization of phosphonium salts and phosphoranes (Chapters 10.2 and 10.4).
20. Carbonylation of trialkylboranes: indirectly $>C^{A}=C< + >C^{B}=C< \rightarrow$ $>CH-\overset{A}{C}-CO-\overset{B}{C}-CH<$ (Section 14.3.4.2).
21. From nitroalkanes by the Nef reaction $R^1R^2CHNO_2 \rightarrow R^1R^2\bar{C}NO_2 \rightarrow R^1COR^2$ (Sections 7.2.3, 8.1.1, and 5.2.12), and by reductive hydrolysis.
22. Hydrolysis of vinylic halides: $>C=C(-)-Hal \rightarrow >CH-C(=O)-$; usually difficult unless the halogen is β to an electron-attracting group, as in β-chlorovinyl ketones (Section 5.2.9).
23. Acyl chlorides + organocadmium reagents: $R^1COCl + R^2_2Cd \rightarrow R^2COR^1$ (Section 15.2.5.3). Suitable for α,β-unsaturated acyl chlorides → α,β-unsaturated ketones.[13] Dialkylzincs and Grignard reagents are less satisfactory (review, Ref. 14).
24. Acyl halides, carboxylic acids, alkyl cyanides → ketones, using organometallic reagents (Section 5.2.2.2).
25. Routes *via* 1,3-dithians (Section 5.2.2.2).
26. Routes using dihydro-1,3-oxazines (Section 5.2.2.2).
27. From primary amines, *via* imines: *e.g.* $R^1R^2CHNH_2 + ArCOCHO \rightarrow R^1R^2CH-N=CHCOAr \rightarrow R^1R^2C=NCH_2COAr \rightarrow R^1COR^2$. Other carbonyl compounds can be used in the initial step.[15]
28. From cyanohydrin esters and α-chlorocyanides: application to cyclohexenones (Section 5.2.13.2).
29. Addition of NOCl to (cyclic) olefins → —CH(NO)CHCl— → —C(=NOH)CHCl—; the acetate of this oxime tautomer is converted to the α-chloroketone and reductively dechlorinated to a (cyclic) ketone by chromium(II) acetate.[16]

5.2.2.2 Preparations to which cross-reference has not been made

Ketones are available (Scheme 1) from aldehydes and alkyl halides *via* the 2-alkyl-1,3-dithians (**4**) and their 2-lithio derivatives. The ketone is freed by mild hydrolysis in the presence of mercuric chloride and cadmium carbonate or mercuric oxide, or by other means. The method represents a valuable route to chiral ketones from chiral aldehydes or alkyl halides because only a little racemization of the ketone occurs (*via* its enol forms).[17–19]



i, $HS(CH_2)_3SH$: ii, Bu^nLi; iii, R^1Hal; iv, H_2O + $HgCl_2$ + $CdCO_3$ or HgO, or other cleavage.

SCHEME 1

Many alk-1-enes are easily converted into methyl ketones (alkan-2-ones) by addition of mercury(II) acetate in aqueous organic solvents, to form an organomercurial which is

treated with palladium(II) chloride and copper(II) chloride or with dilithiopalladium tetrachloride. The method is less predictable with non-terminal alkenes.[20]

An important and general synthetic route uses the reaction of carboxylic acids or their derivatives with organometallics (review, Ref. 21). The acids or their lithium salts react with alkyl-lithiums to give a stable intermediate (**5**) which is decomposed by aqueous workup to the ketone (equation 1). Many primary, secondary, and tertiary alkyl-lithiums, aryl-, and alkenyl-lithiums can be used; yields are generally good, except for the last named. Unsaturated acids can be used and retain the position of the double bond. Tertiary alcohols can form if excess of alkyl-lithium is used; proper attention to the procedure reduces this problem.[21,22]

$$R^1CO_2H + 2RLi \longrightarrow R^1CO_2Li \longrightarrow \underset{(5)}{RR^1C(OLi)_2} \xrightarrow{H_2O} RCOR^1 + 2LiOH \quad (1)$$

$$R^1C{\equiv}N + R^2Li \longrightarrow R^1R^2C{=}NLi \xrightarrow{H_2O} \underset{(6)}{R^1COR^2} \quad (2)$$

Alkyl cyanides react with alkyl- (or aryl-) lithiums in an excellent route to ketones which avoids the formation of tertiary alcohol impurities[21] (equation 2). The nature of R^1 and R^2 in (**6**) can be varied widely. For preparations of remote acetylenic ketones, for example, see Ref. 23. Epimerization may occur adjacent to the newly produced carbonyl group,[24] but axial and equatorial cyanocyclohexanes gave the corresponding acetylcyclohexanes stereospecifically.[22]

Lithium dialkylcuprates, LiR_2Cu, are discussed in Section 5.2.8. Reagents which show the same properties for the present purposes are obtained from Grignard reagents and equivalent amounts of copper(I) halides. They each react cleanly with acyl halides, R^2COHal, to form ketones R^1COR^2, with retention of stereochemistry. For a review, see Ref. 25. The lithium dialkylcuprates are highly selective, and can leave untouched α-halogens, α,β- and more remote olefinic groups, and remote halogen, ester, and cyano groups; diacyl chlorides give diketones.[25] The copper-mediated Grignard reaction is particularly valuable for preparing highly hindered ketones, in which both R^1 and R^2 may be tertiary (or simpler) alkyl groups.[26–28] Some hindered carboxylate esters react with alkyl-lithiums to form ketones, but the method is not generally applicable (see Section 9.3.3 and Ref. 21), and many Grignard reagents react with one equivalent of acetic anhydride at low temperature to form methyl ketones in good yield.[21]

Acyl halides, and alkyl halides or other alkylating agents, can be converted (Scheme 2) into constitutionally unsymmetrical or symmetrical ketones by reaction with sodium tetracarbonylferrate(II) (**7**).[29] The intermediate (**8**) can be trapped by ethylene at 1 atmosphere pressure to give alkyl ethyl ketones in high yield; higher alkenes are unsuitable.[30]

For routes to α-cyclopropyl ketones, see Ref. 31.

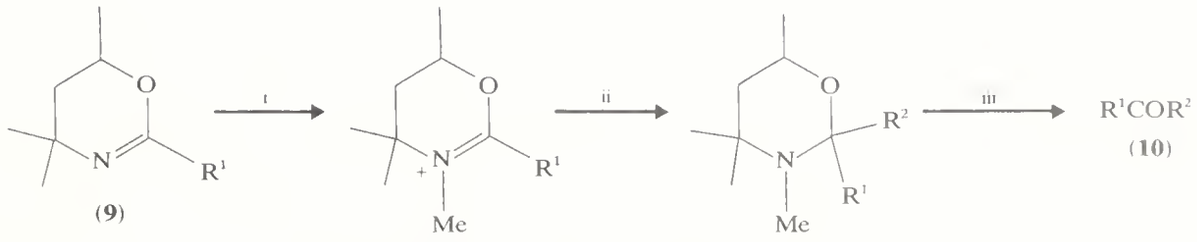
$$1.\ \underset{(7)}{Na_2Fe(CO)_4} \xrightarrow{i} \underset{(8)}{R^1Fe(CO)_4^-} \xrightarrow{ii} R^1COCH_2CH_3$$

$$2.\ \underset{(7)}{Na_2Fe(CO)_4} \xrightarrow[\text{or v}]{\text{i+iii}} R^1COFe(CO)_4^- \xrightarrow{iv} R^1COR^2$$

i, R^1Hal or R^1OSO_2Ar; ii, $CH_2{=}CH_2$; iii, CO; iv, R^2Hal or R^2OSO_2Ar; v, R^1COCl.

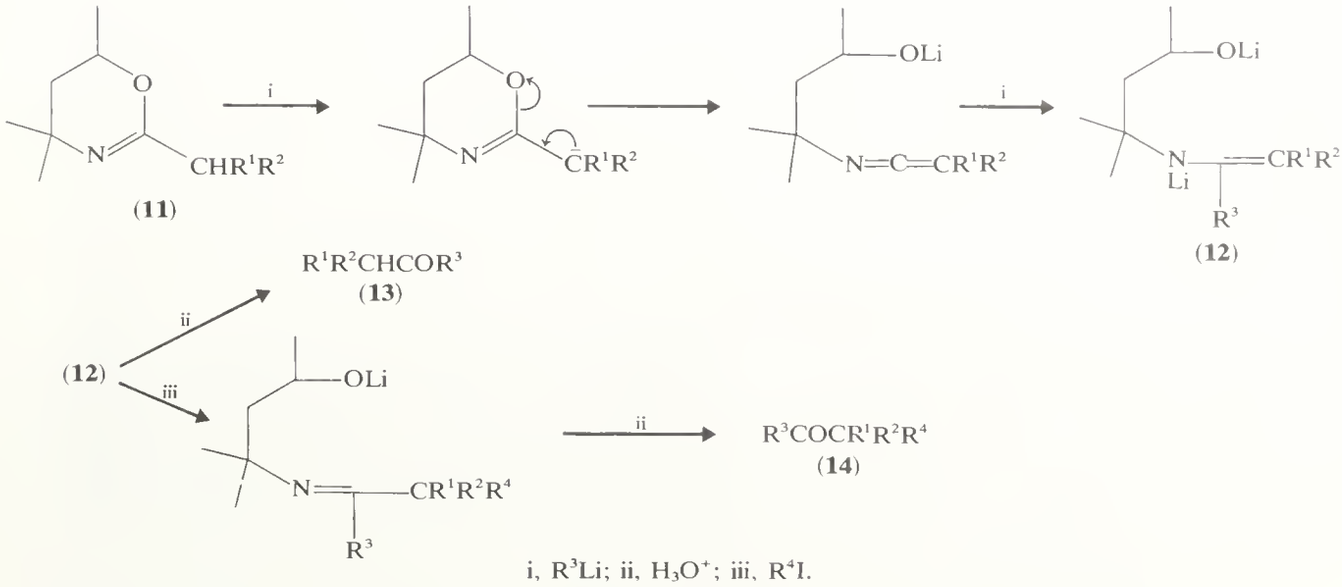
SCHEME 2

A very versatile group of ketone syntheses, which is due to Meyers, uses readily available dihydro-1,3-oxazines as precursors. The 2-substituted dihydro-oxazine (**9**) gives (Scheme 3) the ketone (**10**), in which R^1 and R^2 can be many alkyl, cycloalkyl, or aryl groups, although it is difficult to introduce bulky groups R^2.[32] This problem is overcome by using the sequence (Scheme 4) from (**11**) to (**13**) and (**14**), which effectively allows the stepwise introduction of the groups R^2, R^3, and R^4 and the preparation of hindered



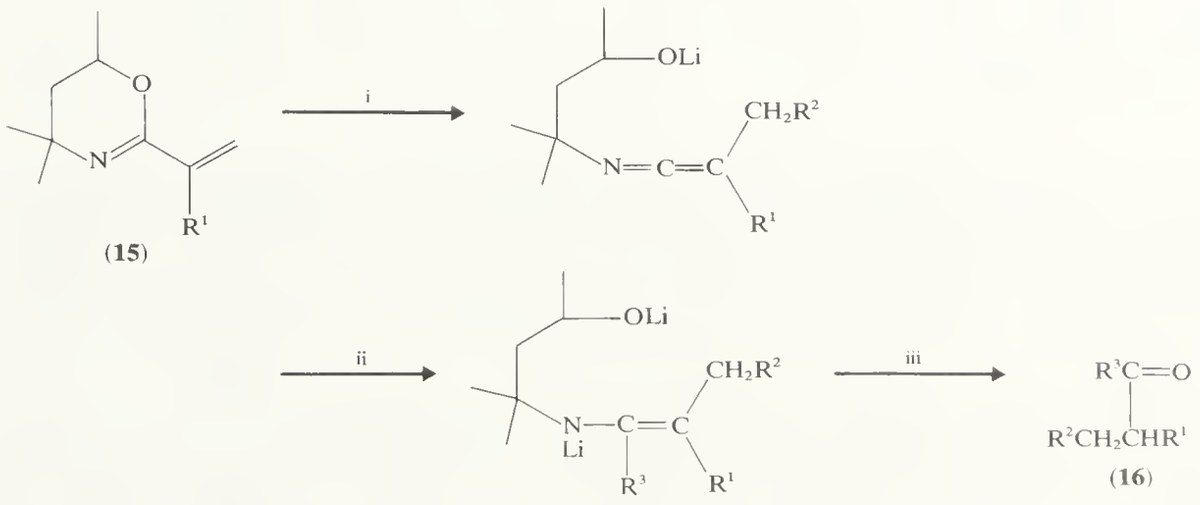
i, MeI or Me_2SO_4; ii, R^2Li or R^2MgHal; iii, H_3O^+.

SCHEME 3



i, R^3Li; ii, H_3O^+; iii, R^4I.

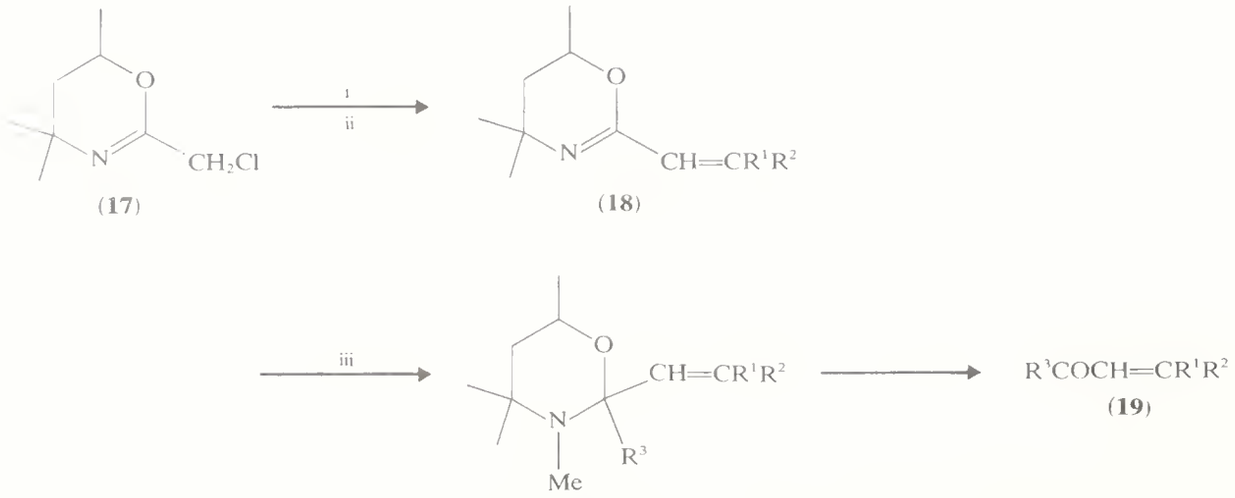
SCHEME 4



i, R^2Li or R^2MgHal; ii, R^3Li or R^3MgHal, or BH_4^- for R^3=H; iii, H_3O^+.

SCHEME 5

ketones. The groups R^1 and R^2 can also represent a cycloalkyl ring.[33] A further variant (Scheme 5) uses 2-alkenyldihydro-oxazines (**15**) which lead to the ketones (**16**).[33,34] None of these syntheses allows the introduction of a ketone group in a new ring. Wittig-type reagents derived from the chloromethyloxazine (**17**) react (Scheme 6) with aldehydes and ketones, including cycloalkanones, to form the compounds (**18**). These are converted, by the sequence used for transforming (**9**) into (**10**), to a wide variety of conjugated olefinic ketones (**19**), including cycloalkylidene ketones.[35]

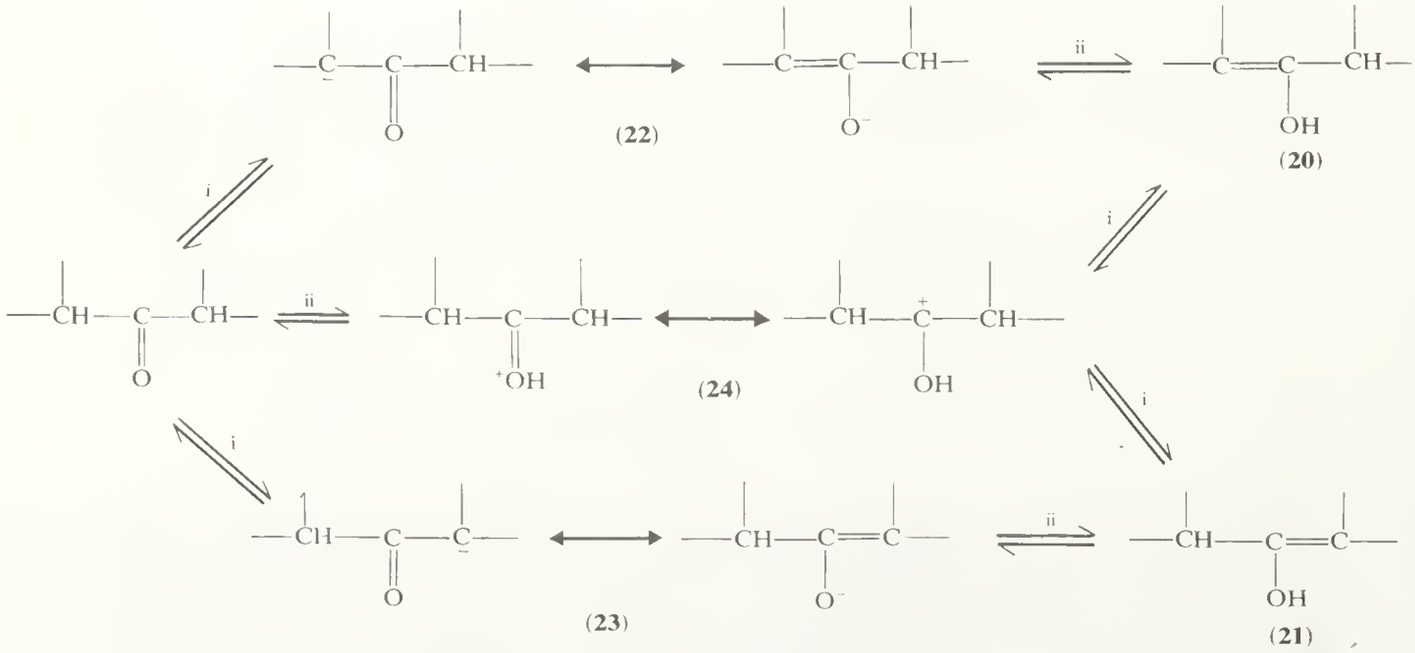


i, Ph_3P or $P(OAlkyl)_3$; base; ii, R^1COR^2: iii, MeI, then R^3Li; iv, H_3O^+.

SCHEME 6

5.2.3 KETO–ENOL TAUTOMERISM

For extensive reviews of keto–enol tautomerism, see Refs. 36 and 37. A ketone having α-hydrogen atoms can be interconverted (Scheme 7) with its enol tautomers (**20**) and (**21**) *via* enolate anions (**22**) or (**23**) under basic conditions or *via* its cation (**24**) under acidic conditions. A constitutionally unsymmetrical ketone having α- and α'-hydrogen atoms can form two enols and two isomeric enolates. The amounts of enol present in equilibrium with simple aliphatic and alicyclic monoketones are very small (*ca.* 1 part in 10^6 for acetone and cyclohexanone in water at 25 °C), but for diketones and other ketones in which the enol double bond is stabilized by conjugation with another unsaturated group the proportion is increased. The method of analysis of the enol content depends on the amount present. Bromine titration under carefully developed conditions can give a reliable measure of large or small enol contents, and spectroscopy — particularly ^1H and ^{17}O nuclear magnetic resonance — is valuable when the enol content is in the range

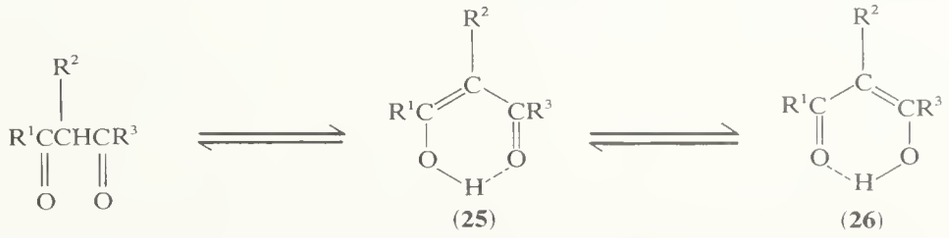


i, base; ii, H^+.

SCHEME 7

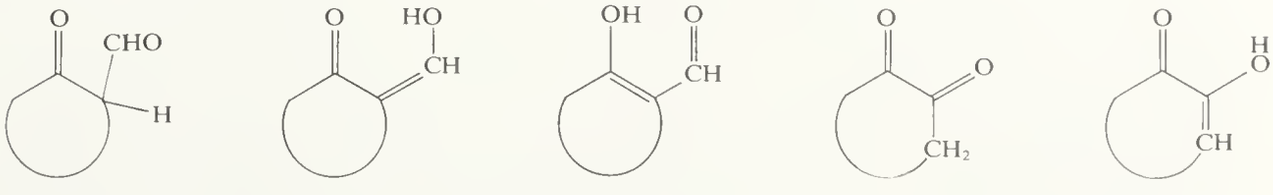
ca. 5–95%. Refs. 36 and 37 give lists of enol contents. The amounts depend strongly on the structure of the ketone, on the ring size of cyclic ketones, and on the properties of any solvent used. For cyclic ketones, the free energies of enolization (—CH—C=O ⇌ —C=C—OH) parallel the free energy differences between methylenecycloalkanes and methylcycloalkenes (—CH—C=CH_2 ⇌ —C=C—CH_3), both series reflecting the same conformational changes. Many attempts have been made to correlate the enol contents and preferred direction of enolization with the structures of acyclic alkyl ketones.[36,37] Although some broad rules can be given (see Section 5.2.4.2), there is no satisfactory quantitative or semi-quantitative correlation as yet.

The enol forms of β-diketones and β-keto esters are conjugated, and the enol contents are relatively high. Pentane-2,4-dione (acetylacetone) is *ca.* 76% enolic in the gas phase, and *ca.* 80% in the pure liquid at 25 °C. Acyclic β-diketones can have *cis* or *trans* stereochemistry (equation 3) about the enol double bond, the *cis*-isomers (**25**) and (**26**) being chelated and much more stable than the *trans*. Unsymmetrical diketones can have two constitutionally isomeric enols. Ref. 37 lists thermodynamic data for the tautomerism of many β-diketones and β-keto esters. The enolization process is exothermic in the gas phase, in the neat liquids, and in solution. Electron-withdrawing groups R^1, R^2, and R^3 increase the stability of the keto-enol relative to the diketone form, but alkyl groups and bulky groups R^2 reduce it. An interesting study of the rates of all the steps in the base-induced enolization of a series of 3-alkylpentane-2,4-diones, using relaxation methods, showed that the variation in enol contents depends almost entirely on the variation of the rate constant for the step from the ketone to enolate anion.[39]



(**25**) (**26**) (3)

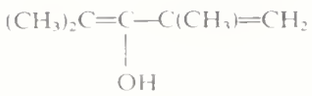
β-Aldehydo ketones (α-formyl ketones) are in equilibrium with two enolic tautomers. The α-formylcycloalkanones (**27**), which are important in synthesis, exist heavily in the enol forms, but sometimes the hydroxymethylene ketone form (**28**) may predominate and sometimes ('2-formylcyclohexanone') the alternative (**29**).[37] The total enol content varies from *ca.* 75% in the cyclopentanone series and 25% in the cyclohexanone, to 65% falling to 20% for the seven- to ten-membered ring ketones.



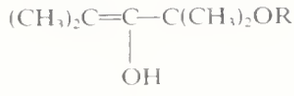
(**27**) (**28**) (**29**) (**30**)

Cycloalkane-1,3-diones are also tautomeric. In dilute solution in non-polar solvents the β-diketone form predominates heavily, but the keto-enol form can become more important in concentrated solution. Acyclic α-diketones are less enolic than the analogous β-diketones, but cyclopentane-1,2-dione and cyclohexane-1,2-dione exist largely or almost entirely in the keto-enol form (**30**).[37]

A number of enols of acyclic ketones have been prepared — indirectly — in high concentration in solution. Although they are unstable, and easily revert to the ketones,



(31)



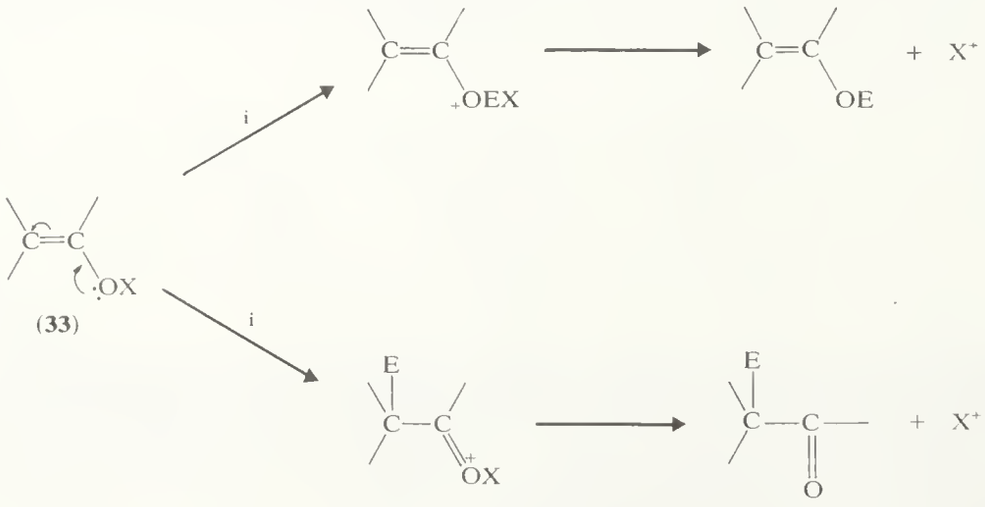
(32)

they are sufficiently long-lived for chemical and spectroscopic study. The enol (**31**) of 2,4-dimethylpent-1-en-3-one is stabilized by conjugation. The enols (**32**; R = H, D, CH_3, or $COCH_3$) derived from (**31**) by the addition of water, methanol, or acetic acid, can be even more stable, probably due to chelation; all are more stable in dipolar aprotic solvents (dimethyl sulphoxide or dimethylformamide) than non-polar solvents.[40] Some other stable enols have been claimed,[40] and another has been disproved.[41]

5.2.4 THE CHEMISTRY OF ENOLS, ENOLATE IONS, AND THEIR DERIVATIVES

5.2.4.1 Reactions of enols and enolate anions[36,42]

For understanding reactions of ketones which proceed *via* the enols or enolates[42] a clear distinction must be made between kinetically and thermodynamically controlled processes. Under kinetic control, the two possible isomeric enols or enolates are formed relatively slowly and then react rapidly with a reagent to form products in an irreversible manner. If this reaction is sufficiently fast, the rate of product formation equals the rate of enol or enolate formation, and the ratio of products from α- and α'-attack equals the ratio of rates of enolization towards the α- and α'-carbons. Under thermodynamic control the reaction of enol or enolate is reversible so that, in time, the products of α- and α'-attack reach an equilibrium. It is also possible to allow equilibration of the two enol or enolate isomers, and then to trap the mixture under kinetic control. The ratios of isomeric products arising in these different ways can differ dramatically. The direct halogenation of ketones in acidic solution is an excellent example of kinetic control, in which the halogen rapidly attacks the enol mixture as it is formed (see Section 5.2.6). The same is true of the α- and α'-deuteriation of ketones in acidic deuteriated solvents; analysis by ^1H n.m.r. spectroscopy of the mixture of deuterioketones is convenient and accurate. Quantitative analysis of enolate anion mixtures is carried out by quenching them in an excess of deuterioacetic acid solution (giving α-deuterioketones),[43] acetic anhydride (giving enol acetates),[43,44] or trimethylsilyl chloride (giving trimethylsilyl enol ethers).[45,46] The enols or enolates can react (Scheme 8) with electrophiles at either the oxygen or α-carbon atom — see (**33**). They are typical ambident nucleophiles; for a review of the factors affecting the



(33)

i, electrophile, E^+.

SCHEME 8

spectrum of *C versus O* reactivity, see Refs. 36 and 47. Alkylating agents give enol ethers and α-alkyl ketones (Section 5.2.5), acylating agents give enol esters and α-acyl ketones (β-diketones) (Section 5.2.10.2), aldehydes and ketones give the aldol reaction (Section 5.2.7), halogens give α-halo ketones (Section 5.2.6), and α,β-unsaturated ketones, *etc.*, give the Michael addition (Section 5.2.8).

In preparations of enol derivatives the ketone is frequently treated with the reagent in the presence of a base or acid to allow the reaction to proceed through low concentrations of the enolate or enol. More recently, methods have been developed which convert the ketone completely into its enolate anion(s); they can allow greater regioselectivity between the two sides of unsymmetrically substituted carbonyl groups. Slow addition of the ketone to an excess of strong base in an aprotic solvent allows formation of the enolates under kinetic control. If a slight excess of un-ionized ketone is present, the α- and α'-enolate anions can interconvert *via* the ketone to give their equilibrium mixture. This is the case if the base is added slowly to the ketone, or if some other proton donor (*e.g.* the solvent) has an acidity comparable with that of the ketone. The rate of approach to equilibrium varies with the metal cation used: it is particularly slow for lithium enolates, which are recommended in order to avoid enolate interconversion.[44] The bases which are suitable for preparing enolates are lithium di-isopropylamide, lithium diethylamide, lithium piperidide, sodium bistrimethylsilylamide, lithium isopropylcyclohexylamide, potassium, sodium, or lithium hydrides or triphenylmethides, sodamide, and potassamide. They are frequently used in 1,2-dimethoxyethane, tetrahydrofuran, or diethyl ether (which slowly decompose), and the amide bases in liquid ammonia or the parent amine. The sodium derivative of dimethyl sulphoxide is used in that solvent. All these bases are much stronger than the alkali metal salts of alcohols; the latter give only small equilibrium concentrations of enolate anions, which can undergo competing aldol condensation with un-ionized ketone. To ensure complete formation of enolates, a little triphenylmethane can be used as an indicator in dimethoxyethane and THF; 2,2-bipyridyl or 1,10-phenanthroline are used as indicators with the lithium dialkylamides in these solvents or in diethyl ether.[36,48]

5.2.4.2 Regioselectivity of reactions

The rates of acid-catalysed enolization have been studied by halogenation, deuteriation, or by the racemization of a chiral α-carbon atom in optically active ketones.[36,49–51] The introduction of alkyl groups at the α-carbon atom reduces the rate of enolization there, and affects that at the α'-carbon atom also. Methyl n-alkyl ketones and α-alkylcycloalkanones normally give the more-stable, more-substituted enol faster than the alternative. Methyl s-alkyl ketones form the less-stable, less-substituted enol faster, presumably because of steric effects on the deprotonation step. However, the differences in rates are small and it has been stated that no general rules can be given for predicting the preferred direction of enolization.[51] The rates of formation of enolate anions vary with the structure of the ketone, the nature of the solvent, and the strength and size of the base. This last factor allows the hindered lithium dialkylamides to exert their high selectivity in forming preferentially the less-substituted, less-stable enolate from unsymmetrically alkyl substituted ketones. The introduction of α-alkyl groups generally reduces the rate of enolate formation at that centre.[43,49,50,52] The stability is usually as stated for lithium enolates, but the change to sodium and potassium cations increases the stability of the less-substituted enolate ions. The equilibrium composition of enolate isomer mixtures is also quite strongly solvent dependent. Tetrasubstituted enolate double bonds from s-alkyl ketones seem to be strongly destabilized. For many useful data, see Refs. 36, 43, 44, and 52. A related series of lithium, sodium, zinc, and magnesium enolates, and of α-iodomercuri ketones, has been made, and their spectra, structures in solution, and acetylation have been studied.[53]

The lithium enolates of ketones can be made regiospecifically by reacting the corresponding enol acetate or enol silyl ether with methyl-lithium (two and one mole equivalent,

respectively).[45,46,48] The by-products are lithium t-butoxide or tetramethylsilane. The recommended route to the more highly substituted enol derivative uses equilibrating conditions, sometimes with selective hydrolysis of the undesired minor isomer. Trapping of the kinetically controlled enolate mixture, formed using a hindered strong base on the ketone, gives a mixture of enol derivatives in which the less highly substituted isomer predominates. Efficient distillation or gas–liquid chromatography are usually needed to purify the isomers.[48]

5.2.4.3 Enol ester formation: by direct acylation

Many enol acetates are made by heating the ketone with acetic anhydride or isopropenyl acetate, and a little perchloric, sulphuric, or toluene-*p*-sulphonic acid to catalyse enolization. The acetic acid or acetone by-products may be distilled off to ensure complete reaction. Solvents such as benzene or carbon tetrachloride may be used. The isomeric enol acetates of constitutionally unsymmetrical ketones are equilibrated by prolonged heating with a little toluene-*p*-sulphonic acid.[44] Many examples and conditions are given in Refs. 43, 44, 48, 54, and 56. The isomers having more heavily alkylated enol double bonds are more stable than the less-substituted isomers, the preference being more marked than that found for enolate anions and enol ethers.[43] The selectivity between ketone groups in steroids, and the directions of enol acetate formation, are discussed in Refs. 54 and 56. For detailed studies of the reagents and conditions required to effect kinetically or thermodynamically controlled reaction of many alkylated 3-keto- and Δ^4-3-keto steroids, see Refs. 57 and 58.

5.2.4.4 Trimethylsilyl enol ethers: by direct reaction

For a review of the chemistry of silyl enol ethers, see Ref. 59. The ketone is heated with excess of trimethylsilyl chloride and triethylamine or 1,4-diazabicyclo[2.2.2]octane (DABCO) in DMF.[45] These are equilibrating conditions, with equilibrium usually being reached within *ca.* 20 hours. The composition of the mixtures is qualitatively similar to that found for enol acetates, but with a smaller ratio of major/minor isomers. For many preparations and equilibrations, see Refs. 45 and 46.

5.2.4.5 Enol esters and enol silyl ethers from preformed enolate anions

Of the bases used to prepare enolate ions under kinetic control, the hindered lithium di-isopropylamide offers good regiospecificity and is the most used. Alkyl methyl ketones, for example, can form the terminal enolate [$RC(O)=CH_2$] with >95% specificity.[61] Sodium bistrimethylsilylamide is also valuable.[62] Sodium hydride in 1,2-dimethoxyethane[46] is most useful for ketones which do not easily suffer aldol condensation;[63] however, potassium hydride is superior in this respect.[64] Lithium diethylamide is cheap and easily made[65] but reacts rather rapidly with trimethylsilyl chloride.[45] Trapping of the mixture of enolate isomers with acetic anhydride[43] or trimethylsilyl chloride[45,46] gives the same ratio of products,[46] although the enol acetate procedure was believed to slightly overestimate the more substituted enolate.[43] The trimethylsilyl ethers are very rapidly hydrolysed, especially by acid, but t-butyldimethylsilyl enol ethers are more stable. Equilibration of isomeric silyl ethers is achieved by prolonged heating with a trace of toluene-*p*-sulphonic acid in carbon tetrachloride[46] or with triethylammonium chloride in DMF.[45] For alternative, regiospecific routes to trimethylsilyl ethers, see Refs. 59 and 66.

It should be noted that the alkali metal enolates of monoketones are acylated by excess of acetic anhydride, acid chlorides, or ketens in aprotic solvents to give the enol esters as kinetic products.[43] The use of less-polar solvents, acid chlorides instead of anhydrides, or

magnesium enolates leads to more acylation at the α-carbon atom, to form β-diketones.[53] It is assumed that the clean *C*-acylation found when enolates react with 0.5 mole equivalents of acyl halides[61] occurs by attack of further enolate on the initially formed enol ester.

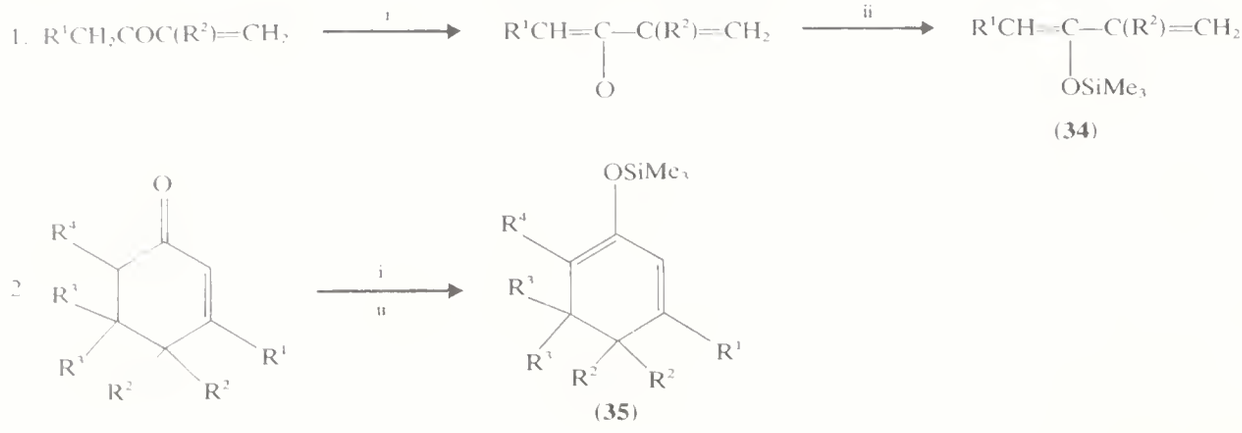
5.2.4.6 Enol ether formation[54,56]

The ketone may be treated with 2,2-dimethoxypropane in the presence of ethanol (for ethyl ethers), or of methanol, or alone (for methyl ethers), usually in DMF solution. Triethyl or trimethyl orthoformate are also used, without solvent or in ethanol and/or dioxan or THF, together with catalytic amounts of toluene-*p*-sulphonic or sulphuric acid.[67] Benzyl and other alcohols with toluene-*p*-sulphonic acid in benzene give enol benzyl or enol alkyl ethers; the last two methods give good yields of monoenol ethers from 1,3-diketones.[68,69] The conditions allow reversibility and give equilibrium mixtures of isomeric enol ethers; the side products can be distilled off as they are formed, to displace the reaction. A hemiacetal is formed by attack of an alcohol on the protonated ketone, or by transacetalization with the di- or tri-alkoxyalkane reagents, followed by elimination of water. Alternatively, the ketone can be converted into an acetal (*e.g.* by a trialkyl orthoformate in an alcohol, with toluene-*p*-sulphonic acid or hydrogen chloride gas as a catalyst).[67] The acetal is then pyrolysed at 190–215 °C, or distilled, or heated at reflux in xylene with or without an acidic catalyst, such as ammonium dihydrogen phosphate,[43,70] to eliminate a mole of alcohol. These preparations are different from those of the enol derivatives mentioned before, because they do not involve the enol. Enolate ions can be alkylated using alkyl halides, which give mainly the *C*-alkylation products (Section 5.2.5), but the use of dissociating solvents such as DMSO,[71] or alkylation by the more reactive dialkyl sulphates or trialkyloxonium ions, gives larger proportions (up to *ca.* 70%) of the enol ethers.[72] The equilibrium compositions of mixtures of isomeric enol ethers from constitutionally unsymmetrical ketones are quite different from those of the corresponding enol acetates, tending to a more equal balance of more- and less-substituted isomers.[43,70,73] Enol ethers are very easily hydrolysed in acidic media.

5.2.4.7 Enolates, enols, and enol derivatives from α,β-unsaturated ketones

Cyclohex-2-enones and other α,β-unsaturated ketones lose a γ-proton to form a 1,3-dienolate anion upon treatment with strong bases under equilibrating conditions.[74,75] Thus steroidal Δ^4-3-ketones give the $\Delta^{3,5}$-dienolate anions,[56] and their reaction with trimethylsilyl chloride and triethylamine in DMF gives the $\Delta^{3,5}$-dienol trimethylsilyl ethers.[76,77] In the absence of a γ-proton (as in alkyl vinyl ketones) the enolate is formed at the α′-position and silyl ethers of type (**34**) are obtained[77,78] (Scheme 9). Enolate anion formation under kinetically controlled conditions, using lithium dialkylamides, gives predominantly or exclusively the α′-enolate from cyclic and acyclic enones.[56,74,79] Thus many cyclohex-2-enones give the 2,6-dienolate, and then the 1-trimethylsilyloxy-2,6-dienes (**35**) (Scheme 9). Steroidal Δ^4-3-ketones give the $\Delta^{2,4}$-dienolate and -dienol silyl ether.[77]

Protonation of a 1,3-dienolate anion probably occurs at oxygen to give the 1,3-dienol which tautomerizes to a β,γ-unsaturated 3-en-1-one by protonation at the α-carbon atom. Protonation by acetic acid often allows this non-conjugated isomer to be isolated, and the overall procedure allows isomerization of α,β- to β,γ-unsaturated ketones.[36,56] Stronger acids allow production of the thermodynamically controlled mixture of α,β- and β,γ-unsaturated ketones (see later). Acid-catalysed enolization of Δ^4-3-keto steroids occurs to give the more stable $\Delta^{3,5}$-dienol faster than the $\Delta^{2,4}$-dienol.[56] Equilibrium



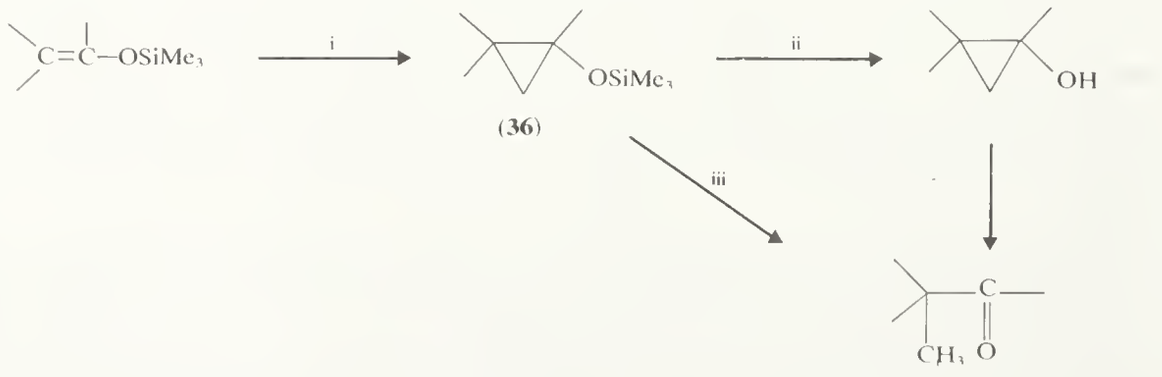
i, $LiNPr^i_2$; ii, Me_3SiCl.

SCHEME 9

controlled enol acetate and enol ether formation gives the $\Delta^{3,5}$-dienol acetates and enol ethers.[54,56,58]

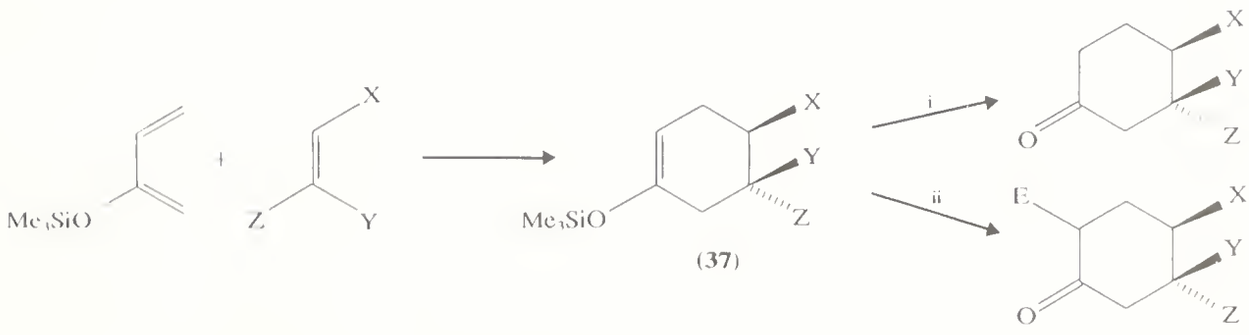
5.2.4.8 Synthetic uses of enol derivatives

For reviews, see Refs. 36, 42, 56, and 59. The major synthetic use of enol acetates and enol silyl ethers is their regiospecific conversion into enolate anions which can then react further. The enol derivatives can also be converted directly by electrophilic reagents [see (**33**) in Scheme 8] into many α-substituted ketones, including α-halo ketones (Section 5.2.6.4), β-hydroxy ketones (aldols: Section 5.2.7.1), α-acetoxy ketones and α-ketols (Section 5.2.11.1), 1,4-diketones (Section 5.2.10.3), β-amino alcohols (Section 5.2.17.3), and Mannich bases (Section 5.2.7.2), and are valuable in new annelation procedures (Section 5.2.9) and in preparations of β-diketones (Section 5.2.10.2). The treatment of silyl enol ethers with a modified Simmons–Smith reagent gives (Scheme 10) the silyl ethers of cyclopropanols (**36**). Hydrolysis gives the free cyclopropanols, and mild rearrangement gives α-methyl ketones in a regiospecific manner.[76] Application of this reaction to the silyl ethers (**35**) derived from cyclohex-2-enones in Scheme 9 involves cyclopropanation of the more nucleophilic silyl enol ether group, and thus introduction of the methyl group at C-6. Because Δ^4-3-keto steriods can be converted into either the $\Delta^{2,4}$- or $\Delta^{3,5}$-dienol silyl ethers, the method can give a 2α-methyl- or 4-methyl-Δ^4-3-ketone.[77] A second cyclopropanation of dienol silyl ethers, followed by a similar ring cleavage, gives many α-cyclopropyl ketones.[80] The dienol silyl ethers (**34**), derived from α-acylcycloalkenes or acyclic α,β-enones, give cyclopropanol ethers which can adopt the *cisoid* conformation



i, CH_2I_2; Zn/Ag couple, pyridine; ii, MeOH, reflux; iii, OH^- or H_3O^+.

SCHEME 10



i, H_3O^+; ii, electrophiles, E^+.

SCHEME 11

needed to allow easy acid-induced isomerization to cyclobutanones, and thermal rearrangement to the enol silyl ethers of cyclopentanones. Both reactions are synthetically valuable.[77] The silyl ethers of *cisoid* dienols, for example, (**34**) and (**35**), act as dienes in Diels–Alder reactions to form adducts (**37**) which are hydrolysed to cyclohexanones[75,78,81] or regiospecifically converted[78] into α-substituted cyclohexanones (see Scheme 11 and Section 5.2.5).

5.2.4.9 Other routes to enolate anions

The central position of enolates in ketone chemistry is reflected in a number of indirect routes to them. These are discussed in Sections 5.2.5, 5.2.7.1, 5.2.8, 5.2.9, 5.2.10, 5.2.11, and 5.2.14.

5.2.4.10 Spectroscopic data on enol derivatives

See the references cited. Enol acetates, i.r. and ^{1}H n.m.r.,[43,82] ^{1}H n.m.r.,[83] ^{1}H and ^{13}C n.m.r.,[84] ^{13}C n.m.r.;[85] enol silyl ethers, i.r. and ^{1}H n.m.r.[45,46,86] and ^{13}C n.m.r.;[85] enol ethers, i.r. and ^{1}H n.m.r.,[43,70] ^{1}H n.m.r.,[73] ^{1}H and ^{13}C n.m.r.;[84] metal enolates, ^{1}H n.m.r.,[53,86] and ^{13}C n.m.r.[85,87]

5.2.4.11 Equilibration of α,β- and β,γ-olefinic ketones

It is usually found that conjugated, α,β-olefinic ketones which do not have a γ-alkyl substituent are more stable than their β,γ-olefinic isomers. A γ-alkyl group helps to stabilize the latter isomer, possibly by stabilizing the olefinic bond, and an α-alkyl group stabilizes the conjugated isomer.[88] In cyclohexenones, increasing the size of a 4-substituent from hydrogen through the alkyls changes the equilibrium composition from *ca.* 100% α,β-unsaturated in the unsubstituted compound to 50% of each isomer in the 4-t-butyl compounds.[89] The β,γ-unsaturated isomer becomes more important in larger rings (27%, 80%, and >99.7% in cycloheptenone, cyclo-octenone and cyclononenone).[90] The isomerizations can occur readily under acidic or basic conditions, or even on storage (presumably owing to traces of enolization catalysts). In the former case the α,β-unsaturated isomer enolizes with loss of a γ-proton, and the β,γ-isomer with loss of an α-proton, to form the common 1,3-dienol. Kinetic studies have been made on acyclic ketones, cyclohexenones, and cyclopentenones. Basic isomerization involves the analogous dienolate anion.[91] Similar isomerizations are effected by primary amines, *via* an imine of the ketone and a dienamine tautomer.[92]

5.2.5 ALKYLATIONS OF KETONES AT THE α-CARBON ATOM

5.2.5.1 Direct α-alkylation of monoketones

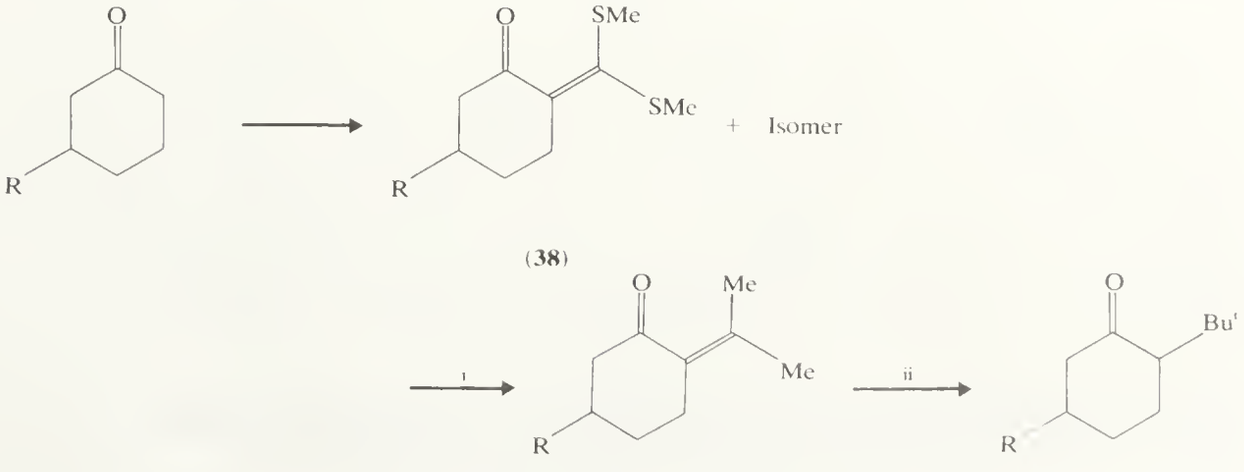
This normally employs reaction with an alkyl halide or alkyl sulphonate (or other alkylating agent) of the enolate anion produced using a strong base (see Section 5.2.4). For a review, see Ref. 36. The method can be satisfactory with ketones which can enolize in only one direction. For mono- and di-alkylations at C-2 of 1-tetralones, see Ref. 93. Additional activation of the α-methylene group of the ketone, as in β-diketones and β-keto esters (Sections 5.2.10 and 9.5.2) improves this route. Normally there are important problems. Di- and poly-alkylation frequently occur, even when only one equivalent of base and alkylating agent are used. The enolate anion can also undergo aldol condensation with the starting ketone or its alkylation products. Two isomeric enolate ions can be formed from constitutionally unsymmetrical ketones and lead to isomeric products. Equilibrating conditions give mainly the more highly alkylated enolate (except for acyclic ketones of type $R_2CHCOCH_2R$) which is alkylated *ca.* 1.7–10 times faster than the less-alkylated isomer.[43,48,94] Thus alkylation at the more alkylated α-carbon can be favoured, but the problems of di- and poly-alkylation, and self-condensation of the ketone usually remain.[43,48] The nucleophilicities of the isomeric enolates, and the effects on the reaction rates and *C*- to *O*-alkylation ratios of varying the nature of the cation, solvent, and alkylating agents have been discussed frequently. All of these factors can affect the ratio of isomeric alkylation products obtained from constitutionally unsymmetrical ketones.[36,43,48,71,95] Rates of alkylation vary greatly with the solvent; in one example, the relative rates in diethyl ether, 1,2-dimethoxyethane (glyme), di-(2-methoxyethyl) ether (diglyme), and DMSO were $1:10^2:10^3:10^6$, respectively, but the last solvent and hexamethylphosphoric triamide promote *O*-alkylation — to form enol ethers — in many cases. The nature of the metal cation does not seem to affect the *C*/*O*-alkylation ratio in some cases,[71] but does affect the equilibrium composition of the isomeric enolate anions.[43] The leaving group in the alkylating agent is important in affecting the *C*/*O* ratio and reaction rate: iodide is better than bromide, which is better than chloride, sulphate, or tosylate for giving a high degree of *C*-alkylation, and faster alkylation.[71,95]

Enol acetates or trimethylsilyl enol ethers (Section 5.2.4) react regiospecifically with methyl-lithium to give the corresponding enolate anions which can then be alkylated.[48,96] It is desirable to use high concentrations of reactants, and especially of the alkylating agent, and a polar aprotic solvent — preferably 1,2-dimethoxyethane, but sometimes HMPT — in order to obtain fast alkylation. Short reaction times reduce the chance of enolate anion equilibration with the ketonic products.[48] The enol acetate reacts with two equivalents of methyl-lithium to give lithium t-butoxide as by-product; this may deprotonate the monoalkylation product and allow dialkylation. This problem is avoided with the trimethysilyl enol ethers, but they are less regiospecifically prepared and less easily purified. The supposed quaternary ammonium enolates, made by cleaving the O—Si bond of trimethysilyl enol ethers with benzyltrimethylammonium fluoride, give good results even with the relatively unreactive n-butyl halides.[97]

Enolate anions can be prepared regiospecifically from α-halo ketones in a number of ways. Treatment of α-bromo ketones with zinc in a 10:1 mixture of benzene:DMSO gives the anion which is alkylated satisfactorily with reactive halides (*e.g.* methyl iodide and allylic halides), but not with the less reactive ethyl or n-hexyl halides.[98] The α-bromo ketones can be treated with trialkylboranes and potassium t-butoxide in THF with good results, but the reaction is inefficient in the use of alkyl groups in the borane and sensitive to steric effects.[99] The use of a *B*-alkyl-9-borobicyclo[3,3,1]nonane with a hindered base (potassium 2,6-di-t-butylphenoxide) allows hindered groups such as cycloalkyl, s-butyl, and isobutyl to be introduced in good yield.[100] Vinyl phosphonates, phosphinates, or phosphates are produced regiospecifically from α-halo ketones and phosphorus nucleophiles. Treatment with an alkyl-lithium or Grignard reagent gives the enolate salt

which can be alkylated; methylation and benzylation are satisfactory, but the slower n-butylation gives loss of regiospecificity.[101] Reaction of α-bromo ketones with lithium dimethylcuprate gives the enolate anion which can sometimes be methylated at the α-carbon atom in high yield[102] (review, Ref. 25). An extension to lithium di-isopropyl- and di-isobutyl-cuprates allows these secondary alkyl groups to be introduced, albeit in lower yield.[103] Some steroidal α-bromo ketones underwent reductive debromination rather than methylation with lithium dimethylcuprate.[104] An α-bromo-α,β-unsaturated ketone has been converted into the α-methyl enone in the same way.[105] A variant allows α,α′-dialkylation of constitutionally symmetrical α,α′-dibromo ketones. Reaction with lithium dialkylcuprates or mixed cuprate reagents is believed to form an α′-bromo-α-enolate anion which eliminates bromide ion, as in the Favorskii rearrangement, to give a cyclopropanone. This is opened by the cuprate reagent to give an α-alkyl-α′-enolate or α′-alkyl-α-enolate which can be methylated,[102,103] ethylated or isopropylated,[103] or protonated or deuteriated[102] to give the α,α′-disubstituted products. Some α,α-disubstituted product can arise, and only one t-butyl group can be introduced (from the cuprate reagent).[103]

Alkylation can be directed towards one α-methylene group of a ketone. For reviews, see Refs. 42 and 56. A formyl (*i.e.* hydroxymethylene) group is first introduced by a Claisen condensation: see Section 5.2.10.2 for the orientation. The resulting β-dicarbonyl compound is then alkylated using an alkyl halide and base — potassium carbonate in acetone is especially suitable — and the resulting α-alkyl-α-formyl ketone deformylated by dilute alkali. The method has been widely used in steroid syntheses[106] and in simpler systems, including cyclohex-2-enones (which undergo 6-alkylation),[108] but some *O*-alkylation also occurs. Similar results are given by α-ethoxalyl (*i.e.* ethoxyoxalyl) derivatives, formed by condensation of the ketone with ethyl oxalate,[57] or ethoxycarbonyl derivatives (from ethyl carbonate)[36] (see Section 5.2.10.2). Better results are given by converting the α-hydroxymethylene group into an α-n-butylthiomethylene group, by acid-catalysed reaction with n-butanethiol or by other methods.[109] This can be reduced with lithium or sodium in ammonia to the α-methyl enolate anion which can be alkylated (to the α-alkyl-α-methyl ketone), or quenched with water or deuterium oxide to give the α-methyl-α-protio-[109] or deuterio-ketone.[110] Direct reduction of the n-butylthiomethylene group with Raney nickel gives the α-methyl ketone.[109,111] Addition of lithium dimethylcuprate to the n-butylthiomethylene ketone gives an α-isopropyl enolate anion which can be alkylated by many alkyl halides, in dimethoxyethane, to give α-alkyl-α-isopropyl ketones in excellent yield.[112] The method is clearly best for constitutionally symmetrical, or α,α′,α′-trisubstituted ketones, which can give only one hydroxymethylene derivative. A related method of choice for the introduction of α-alkylidene or tertiary alkyl groups uses the reaction of lithium dimethylcuprate (Scheme 12) at −78 or 0 °C,



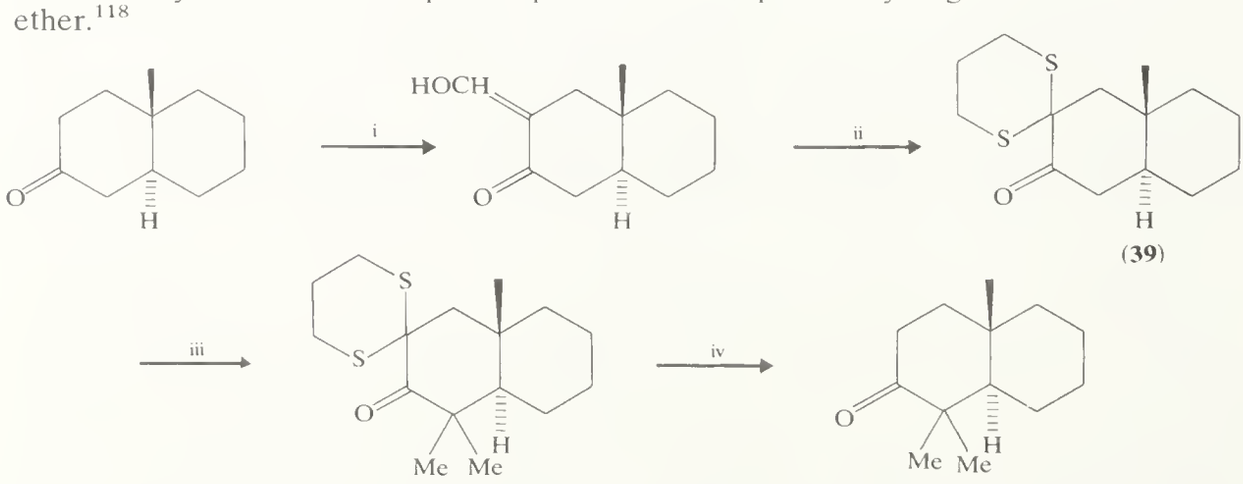
i, $LiMe_2Cu$, −78 °C; ii, $LiMe_2Cu$, 0 °C.

SCHEME 12

respectively, on α-ketoketen thioacetals (**38**). The latter are made by reaction of the ketone with carbon disulphide and a hindered base, followed by an alkyl halide.[113]

A new route of great promise for the clean alkylation of the less alkylated α-carbon atom uses the *N,N*-dimethylhydrazone (DMH) of a ketone (or aldehyde). Kinetically controlled anion formation, using lithium di-isopropylamide or sometimes butyl-lithium, occurs at the less heavily alkylated α-carbon atom, and clean α-alkylation follows. Mild periodate cleavage at pH 7 and 25°C gives the α-alkylated ketone.[114] Many other uses of the α-lithio DMH derivatives have been reported (see Sections 5.2.5.3, 5.2.7.1, 5.2.9, and 5.2.10.3). For the valuable alkylations of enamines, and of the anions of *N*-alkylimines derived from ketones, see Sections 6.2.1. and 8.1.2. The reaction of just over one mole of lithium diethylamide with the cyclohexylimines of aliphatic methyl ketones allows clean alkylation at the methyl group only; the use of two moles of base gives a 1,3-bislithio derivative from acetone cyclohexylimine, which is alkylated to constitutionally symmetrical dialkyl ketones.[65]

Alkylation can be directed to the more heavily substituted α-carbon of a ketone or the α-position which is not taken up by a hydroxymethylene group, in a variety of ways. Most usefully, the n-butylthiomethylene group is used to block one α-methylene position; it is stable enough for brief strong-base treatment then alkylation to introduce an α′-alkyl group, and is removed easily by acidic hydrolysis or aqueous alkali in refluxing diethylene glycol.[109] The α-hydroxymethylene ketone can be converted into its α,α′-dianion using potassamide in ammonia; monoalkylation takes place at the α′-carbon atom, and deformylation gives the clean α′-alkylated ketone.[115] More conveniently, the α-hydroxymethylene ketone is treated with trimethylene ditoluene-*p*-thiosulphonate (trimethylene dithiotosylate) to form (Scheme 13) the α-trimethylenedithio ketone (**39**). This is alkylated or dialkylated at the α′-carbon, using a tertiary alkoxide base and alkyl halide; Raney nickel removes the dithian group.[116] The α-position can also be blocked by aldol condensation with benzaldehyde or furfural, to give crystalline benzylidene or furfurylidene derivatives (see Section 5.2.7). Strong base gives the α′-enolate anion which is then alkylated. The method was used frequently in W. S. Johnson's steroid syntheses, but removal of the benzylidene group required several steps.[117] Recently the de-blocking has been achieved in a one-step retro-aldol hydrolysis by potassium hydroxide, catalysed by 4-aminobutyric acid in a dipolar aprotic solvent, preferably together with a crown ether.[118]



(**39**)

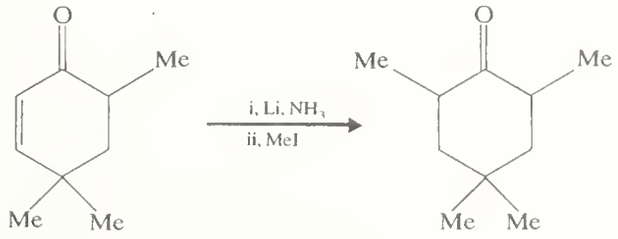
i, HCO_2Et, NaOEt; ii, $TosylS(CH_2)_3STosyl$; iii, $KOBu^t$, MeI; iv, Raney Ni.

SCHEME 13

5.2.5.2 Reductive alkylation at the α-carbon atom of α,β-unsaturated ketones

The enolate anion which is produced regiospecifically at the α-carbon when an α,β-unsaturated ketone is reduced with lithium in liquid ammonia can be methylated or

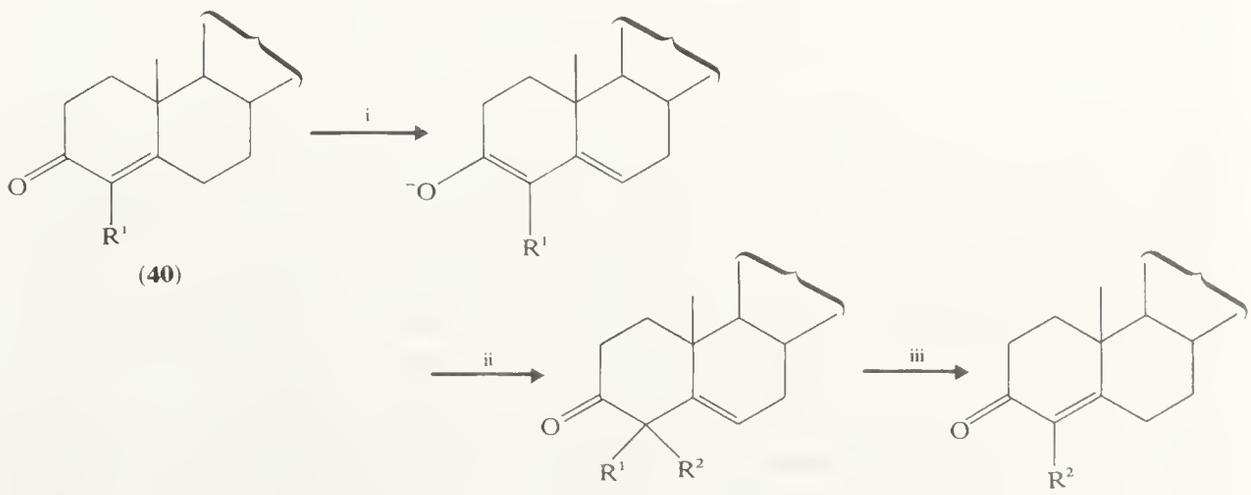
alkylated with reactive alkyl halides to give (equation 4) the α-alkylated saturated ketone (see Sections 5.2.9 and 5.2.14). A related reaction involves α-alkylation of the enolate produced by β-addition of an organocuprate reagent to an α,β-unsaturated ketone; this adds an α- and a β-alkyl group in one reaction (see Section 5.2.8). The epoxides of α,β-unsaturated ketones are easily prepared. Reduction with lithium in ammonia forms the β-oxido-α-enolate which is methylated to give the β-hydroxy-α-methyl ketone. Dehydration ($POCl_3$) forms the α-methylated α,β-unsaturated ketone or, if the original enone was α-substituted, the α-methyl-βγ-enone.[119]



(4)

5.2.5.3 Direct alkylation of α,β-unsaturated ketones

The treatment of α,β-unsaturated ketones bearing a γ-proton with bases such as potassium t-butoxide in t-butanol or potassium isopentoxide in benzene, which allow anion equilibration, gives mainly the 1(2),3(4)-dienolate anion by loss of the γ-proton. This is the case with steroidal Δ^4-3-ketones and their bicyclic analogues (**40**). Alkylation occurs (Scheme 14) at the α-carbon atom to give the α-alkyl-β,γ-enone. If this has an α-proton it is more acidic than the original ketone and is usually isomerized to the α-alkyl-α,β-enone, or suffers further alkylation to give the α,α-dialkyl-β,γ-enone.[120–123] Use of the lithio derivative of the ketone's *N*,*N*-dimethylhydrazone or cyclohexylimine, with a slight deficiency of base (see Section 5.2.5.1), allows similar anion equilibration, but gives clean monoalkylation; this seems a route of choice, particularly to α-methyl-α,β-enones.[124] The formation of spirocyclic rings at the α-carbon of β,γ-enones, by alkylation of the parent enones with α,ω-dihalides, has been studied.[122] The enolate anion formed under kinetic control from α,β-unsaturated ketones is normally the α′-enolate, which is alkylated — usually methylated — to form the α′-alkylated-α,β-enone. Thus, Δ^4-3-keto steroids and their bicyclic analogues give mainly the 2-alkylated product, and cyclohex-2-enones give 6-alkyl derivatives.[74] The method is claimed to be superior to the use of the kinetically controlled anions formed using an excess of base on *N*,*N*-dimethylhydrazones or metalloenamines.[124] Although triphenylmethyl-lithium has been used frequently to



i, $KOBu^t$, Bu^tOH; ii, R^2Hal; iii, when $R^1 = H$; base or acid.

SCHEME 14

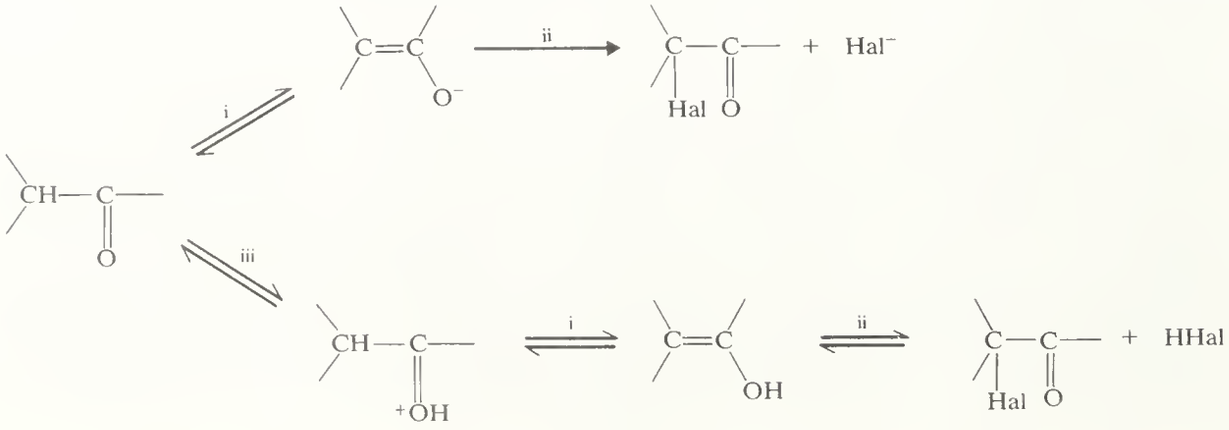
produce enolate anions, under kinetic control, from saturated ketones (see, *e.g.* Ref. 95), it gives predominantly the thermodynamically preferred γ-dienolate anion from some α,β-enones.[125]

5.2.6 HALOGENATION OF KETONES AND THEIR DERIVATIVES

This section is primarily devoted to the preparation of α-halo ketones by direct halogenation, followed by methods for regioselective and regiospecific halogenations of ketones and derivatives. Other routes to α-halo ketones are mentioned briefly. For further discussion, see Ref. 36. For halogenations of steroidal ketones, see Refs. 56 and 126; for halogenations of ketones by copper(II) bromide or chloride, see Ref. 127, and for a review on β-chloro-α,β-olefinic ketones, see Ref. 129. α-Halo ketones are frequently much more reactive towards bimolecular nucleophilic substitution than the corresponding alkyl halides. This appears to be due to an electrostatic attraction between the carbonyl carbon atom and the nucleophile, and the smallness of the carbonyl group adjacent to the α-carbon atom.[129a]

5.2.6.1 Direct halogenation of ketones

In classic halogenation the ketone is treated with molecular chlorine, bromine, or, occasionally, iodine, in alkaline or acidic solution. Despite claims to the contrary, it seems clear that the enolate anion of the ketone reacts under alkaline conditions,[130,131] and the enol under acidic conditions[132] (Scheme 15). Hydrogen halide is formed in acidic



i, base; ii, Hal_2; fast step; iii, H^+.

SCHEME 15

halogenations and only a trace of acid need be added to catalyse enolization and initiate reaction. Basicity studies on aliphatic α-halo ketones[133] and on 1- and 3-halogeno-*trans*-2-decalones[134] show that each extra halogen atom reduces the basicity of the ketone by 2–3 pK units. Thus the halo ketones are less extensively protonated than the parent ketones, and their rates of enolization are greatly reduced.[134] In most cases the enolization is towards the α-carbon atom which bears a chlorine or bromine atom, but away from a fluorine, although exceptions ascribed to steric effects on enolization do exist.[134] The use of acidic conditions should generally allow selective monohalogenation of ketones, and the mixture of α-halo ketones should reflect the composition of the mixture of enols (see Section 5.2.3). Dihalogeno ketones are nevertheless often formed in significant yield, even when a deficiency of halogenating agent is used. Recent work using substituted cyclohexanones showed that the α-halo ketone need not be the precursor of the (α,α′-) dihalo ketone.[135] In acidic conditions (acetic acid–acetate buffer) butan-2-one gives the 1- and

3-bromo ketones in equal yields initially, but further bromination and acetate substitution rapidly complicates the situation.[132] Bromination of butan-2-one in alkali involves rate-determining loss of the 1- and 3-protons at equal rates, giving an initial ratio of 1-bromo to 3-bromo ketone of 1.5 : 1. Further halogenation of the 1-bromo ketone (at C-1), like that of monochloroacetone, is 800–900 times faster. In contrast, the further bromination of 3-bromobutan-2-one is only as fast as the first, and is slower than hydrolysis.[130,131] The fact that the monohalo ketone usually forms an enolate much faster than does the parent ketone means that di- and multi-halogenation are frequent, and alkaline conditions should be avoided.

Direct halogenation of constitutionally unsymmetrical ketones is not generally a very clean or regiospecific reaction unless enolization or enolate formation in one direction is mandatory or strongly favoured. Despite this, the simplicity of the method has had attractions. Sodium or potassium chlorates are often added to oxidize hydrogen bromide back to bromine, which is economical and reduces the acidity. Bromination of neat butan-2-one, in the presence of chlorate, gives 32% of the 3-bromo and 9% of the 1-bromo ketone.[136] For direct brominations of many aliphatic ketones in diethyl ether, see Refs. 103 and 137. In carbon tetrachloride solution, bromination gives more attack at the more heavily substituted α-carbon atom than does chlorination, apparently because the free halogens affect the enolization reactions. The ratios of isomeric products in these brominations can vary with the amount of hydrogen bromide present, and thus with the extent of reaction.[138] The α- and α'-bromo ketone isomers are usually relatively unstable, and are frequently interconverted by hydrogen bromide which repeatedly reverses the normal bromination reaction (Scheme 15) and allows equilibration.[101,139,140] These effects do not seem to be important in chlorinations.[138] To complicate matters further, dilution of the reagents in carbon tetrachloride increases significantly the amount of bromination at the more substituted α-carbon (see later, also) but affects chlorination less, and in the opposite direction.[138]

5.2.6.2 Regioselective halogenation at the more heavily alkylated α-carbon atom of constitutionally unsymmetrical ketones

In strongly acidic solution (60–70% sulphuric acid), enolization is very fast and halogenation is rate-determining. This change of mechanism is reflected in changed product ratios. Butan-2-one gives the 3-chloro and 1-chloro ketones in a ratio *ca.* 9 : 1, and the 3-bromo and 1-bromo ketones in a ratio 11 : 1. Similarly, 2-methylcyclohexanone gives cleanly the 2-halo ketones.[141] Unreactive halogenating agents and those which generate very low concentrations of free halogen may be expected to give similar specificity. Phenyltrimethylammonium perbromide (PTT) is a stable, solid source of low concentrations of bromine, used in dry THF or tetrahydropyran, and has the desired regioselectivity. Its selectivity is enhanced by dilution, and the presence of traces of acid, and it can give different stereoselectivity from bromine in its reaction with steroid ketones; it does not attack activated benzenoid rings.[142,143] Pyridinium bromide perbromide has been used in the same way,[144] but is less stable.[143] Pyrrolidone hydrotribromide is more stable, has greater selectivity for ketones, and is quite unreactive towards olefinic groups and enol acetates.[145] Recently, 2-carboxyethyltriphenylphosphonium perbromide has been recommended; it does not react with conjugated olefinic bonds, or aromatic rings, or at the α-position of esters.[146] Sulphuryl chloride has been used for chlorinations of ketones — neat or in carbon tetrachloride — in the desired way. Its regiospecificity is not very high, and the major products from acetone and butan-2-one are 1,1-dichloroacetone, and 3,3- and 1,3-dichlorobutanones. It does not attack cyanides, esters, or nitro compounds under the same conditions. An ionic mechanism was suggested[147] but a radical process is possible, especially in the early stages of reaction when little acid is present. Radical paths are likely when reagents such as hypobromous

acid or *N*-bromosuccinimide are used in the presence of light irradiation or radical initiators, and more regioselective reaction is found: butan-2-one, for example, can give the 3- and 1-bromo ketones in a 25-40 : 1 ratio.[141]

5.2.6.3 Regioselective halogenation at the less-alkylated α-carbon atom of constitutionally unsymmetrical ketones

Clean halogenation of this type, and particularly at the methyl group of methyl ketones, is, perhaps surprisingly, quite common. Reaction of the dioxolan (ethylene acetal) derivative of the ketone with PTT in THF gives the required α-bromodioxolan, free of dibromination products. Remote hydroxy, acetate, and olefinic groups are untouched. The dioxolans of α,β-olefinic ketones (but not the ketones themselves) react rapidly and specifically at the α′-carbon, and may give the bromo ketone directly.[143] Free α,β-enones are brominated cleanly at the α′-carbon by 2,4,4,6-tetrabromocyclohexa-2,5-dienone in diethyl ether.[148] The dioxolans, dimethyl acetals, or 1,3-dioxans of constitutionally unsymmetrical ketones are brominated with high regioselectivity in diethyl ether or, less cleanly, in carbon tetrachloride;[140,149] the selectivity is increased by adding methanol or using it alone as solvent.[150] Direct bromination of methyl ketones in methanol-containing solutions gives highly specific attack at the methyl group.[150] Similar valuable results are found for chlorinations of the acetals or dioxans in carbon tetrachloride (methanol addition is inappropriate).[151] The 2-hydroxyethyl ketimines of methyl ketones, made by condensation of the ketones with 2-aminoethanol, are halogenated with useful regiospecificity using *N*-bromo- or *N*-chloro-succinimide in ether; gentle acidic hydrolysis releases the α-halo ketone from its derivative. It is assumed that the reaction occurs on a trace of the enamine tautomer of the ketimine.[152]

5.2.6.4 Regiospecific halogenation of ketone derivatives

The following methods allow the formation of a single halo ketone isomer, provided that the precursors are isomerically pure and isomerization is avoided during the isolation. The 2-hydroxymethylene derivatives of ketones containing the grouping CH_3CO— or —CH_2CO— (*i.e.* the 2-formyl ketones) are brominated cleanly at C-2, and easily deformylated by dilute alkali. The method has been used to make 2-bromo-Δ^4-3-keto steroids.[153] Enol acetates,[36,56,135,139,154,155] enol ethers,[56,149] and enol trimethylsilyl ethers[156,157] are halogenated with only slight, if any, loss of regiospecificity using the free halogens, *N*-halosuccinimides, or perchloryl fluoride (for fluorination).[56] Bromination of an enol ether in methanol gave the dimethyl acetal of the α-bromo ketone.[158] Enamines are halogenated, but not always satisfactorily.[101] A very flexible method uses enol borinates. Reaction of an α-diazo ketone with a trialkyl- or triaryl-borane gives an α-alkyl (or aryl) enol borinate which gives the α-alkyl (or aryl) α-halo ketone on treatment with *N*-halosuccinimides.[159] Addition of trialkylboranes to α,β-unsaturated ketones gives β-alkyl enol borinates which are similarly halogenated to β-alkyl-α-halo ketones.[159] A specific route to α-halomethyl ketones uses the reaction of anhydrous hydrogen chloride or hydrogen bromide on an α-diazomethyl ketone obtained from an acyl halide and diazomethane[129a] (equation 5). Lithium enolates, derived directly from ketones or from enol derivatives (Section 5.2.4), can be brominated, or fluorinated (using perchloryl fluoride)[62] with excellent yield and regiospecificity.[62,157]

$$RCOCl \xrightarrow{CH_2N_2} RCOCHN_2 \xrightarrow{HCl\ or\ HBr} RCOCH_2Hal \qquad (5)$$

5.2.6.5 Dihalogeno ketones

Both α,α- and α,α′-dihalo ketones are formed when ketones are treated with two equivalents of halogenating agents. The earlier discussion suggests that alkaline conditions

should give the α,α-product, but the method is preparatively poor due to hydrolysis and Favorskii rearrangements. Acidic conditions are much more satisfactory, and lead normally to α,α'-dihalo ketones, although the reaction is not always clean. Dibromo ketones can often be equilibrated by hydrogen bromide. For the α,α'-dihalogenation of aliphatic ketones, see Refs. 103 and 160; for alicyclic ketones, see Refs. 140 and 161. Dibromination of the dimethyl acetals of cycloalkanones gave the α,α'-dihalo acetals.[140] Many methyl ketones have been converted into 1,1-dichloromethyl ketones by reacting their cyclohexyl ketimines with two moles of *N*-chlorosuccinimide, followed by mild acid hydrolysis.[162] Acetylenes react with two moles of *N*-chlorosuccinimide or t-butyl hypochlorite in methanol to give α,α-dichloro dimethyl acetals which can be hydrolysed to the α,α-dichloro ketones; terminal acetylenes give 1,1-dichloromethyl ketones, but constitutionally unsymmetrical acetylenes give mixtures of products.[163]

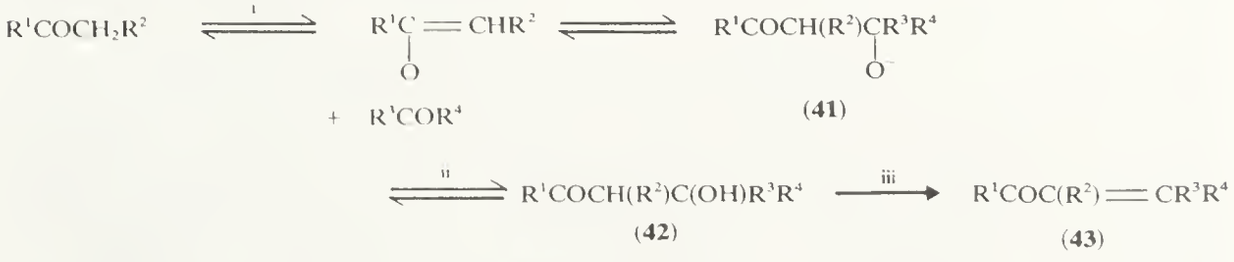
5.2.6.6 Trihalomethyl ketones

Methyl ketones, upon halogenation under alkaline conditions, give significant amounts of trihalomethyl ketones which are cleaved to the trihalomethane (haloform) and a carboxylic acid. The halogenation is not specific to the methyl group (see Sections 5.2.6.1 and 5.2.16) and does not represent a useful synthetic route. Trichloromethyl ketones have been made by adding sodium acetylides to chloral, followed by hydrogenation, and oxidation of the resulting trichloromethyl carbinol.[164] Acetoxymercuration of terminal acetylenes gives complexes which are chlorinated or brominated to trihalomethyl ketones.[164]

5.2.7 CONDENSATIONS AT THE α-METHYLENE GROUPS OF KETONES

5.2.7.1 Aldol condensations

In the base-catalysed aldol reaction, the enolate ion of the ketone attacks the carbonyl group of a second ketone or aldehyde molecule to give (Scheme 16) a β-hydroxy ketone (β-ketol) (**42**). This may be isolated, but often it dehydrates under basic conditions, and particularly in the presence of acid, to give the α,β-unsaturated ketone (**43**). Acid-catalysed aldol reactions also occur, in which the enol of the ketone attacks a second, protonated ketone or aldehyde carbonyl group; dehydration leads to the α,β-enone directly. Aldol reactions have been reviewed,[36,165] Ref. 165 having 402 pages and 2359 references! They also feature in annelation reactions (see Sections 5.2.9 and 5.2.11.2).



i, base; ii, H^+; iii, $-H_2O$.

SCHEME 16

The aldol reaction with formaldehyde gives α-hydroxymethyl ketones (**42**; R^3, $R^4 = H$) and thereby a good route to α-methylene ketones (**43**; R^3, $R^4 = H$). The examples given in Scheme 17 show that reaction occurs at the more heavily substituted α-carbon atom of the ketone, if the base concentration is kept low; acetaldehyde usually behaves similarly. If acidic conditions are used, other aldehydes normally react with alkyl methyl ketones at

C-3, *via* the predominant enol, but basic conditions lead to product mixtures whose compositions depend strongly upon the reactants and conditions.[169] Many aldehydes can form their own enolates which self-condense more readily than they react with ketones (see Section 5.1.5.2). Some useful 'crossed' reactions are the base-catalysed condensations of ketones with benzaldehyde and furfural, which introduce α-benzylidene or α-furfurylidene groups in excellent yield. For a discussion of their applications in blocking alkylation reactions, see Section 5.2.5. The rates of formation of benzylidene derivatives from 5α-3-keto steroids and related triterpenoids have been related to polar effects of substituents and to the transmission of conformational distortions from even remote substituents; attack is at C-2, *via* the more stable enolate.[170] Ketones self-condense, almost invariably at the less heavily substituted α-carbon, but the equilibria are not usually favourable to the β-ketol products unless constantly displaced, *e.g.* by dehydration. Mixed condensations of ketones are sometimes of value, but if both ketones can form enolate anions they usually lead to mixtures of products.

$$RCH_2COMe + CH_2O \xrightarrow{i} HOCH_2CH(R)COMe \xrightarrow{ii} CH_2{=}C(R)COMe$$

i, aq. NaOH; ii, H_3PO_4 or H_2SO_4 in $CHCl_3$, or I_2, formic acid, oxalic acid, or toluene-*p*-sulphonic acid; distil + hydroquinone. R = Me,[166–168] Et,[167] Pr^i.[167]

SCHEME 17

Recent improvements in the synthetic applicability of aldol reactions depend on the use of regiospecifically prepared, structurally stable, lithium enolates of the ketones (see also Section 5.2.4). The α-enolates produced by the conjugate addition to α,β-unsaturated ketones of lithium dialkylcuprates,[171] or of Grignard reagents catalysed by copper salts,[172,173] are trapped regiospecifically by formaldehyde to give β-alkyl-α-hydroxymethyl ketones,[171,172] or by other aldehydes followed by dehydration to give β-alkyl-α-alkylidene ketones.[173] The last application has great value in introducing both side chains of a prostaglandin into a cyclopentenone.[173] Lithium–ammonia reduction of α,β-unsaturated ketones also gives α-enolates which are trapped by formaldehyde, but special conditions are needed to avoid loss of positional integrity.[172] Many hindered aliphatic α-bromo ketones react with magnesium to form Grignard-type reagents which add to ketones and aldehydes and allow isolation of the β-hydroxy ketones.[137] Zinc reacts similarly with α-bromocycloalkanones and aliphatic aldehydes, although the products were dehydrated to enones.[98]

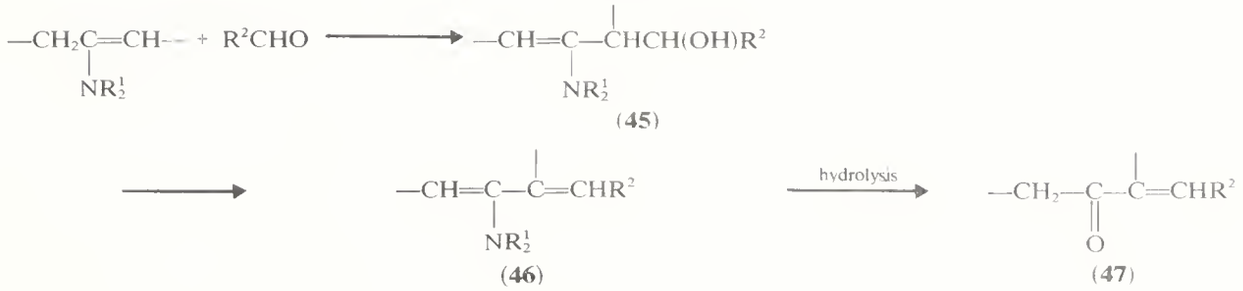
The lithium enolates derived from the reaction of trimethylsilyl enol ethers[172,174] or enol acetates[174] with methyl-lithium, or from lithium di-isopropylamide on ketones[68,174–176] (see Section 5.2.4) react regiospecifically, and in a stereoselcetive manner,[86,176] with aliphatic and aromatic aldehydes. The kinetic enolate from pent-3-en-2-one is formed at the acetyl group, and also adds in 1,2-fashion to the carbonyl group of crotonaldehyde[175] (see also Ref. 68). The addition of zinc or magnesium halides to these aldol reactions gives stronger chelation of the initially formed β-keto alkoxide ions (**41**) and allows particularly fast, clean reactions.[174] An excellent route uses the regiospecific attack of trimethylsilyl enol ethers on aldehydes or ketones, catalysed by titanium tetrachloride. The silyl ethers, derived from cyclopentanone, cyclohexanones, dialkyl ketones, and alkyl aryl ketones reacted with alkyl and aryl aldehydes, and dialkyl and diaryl ketones. Formaldehyde gave (Scheme 18) α-hydroxymethylene ketones, *e.g.* (**44**).[177] A related regiospecific reaction occurs (Scheme 19) between the morpholine enamines of cyclopentanones or of substituted cyclohexanones and aliphatic or aromatic

$$R^4COR^5 + R^1R^2C{=}C(R^3)OSiMe_3 \xrightarrow{i} R^4R^5C(OH)C(R^1R^2)COR^3$$

(**44**)

i, $TiCl_4$, then H_2O. $R^4 = R^5 = H$, alkyl, or aryl.

SCHEME 18

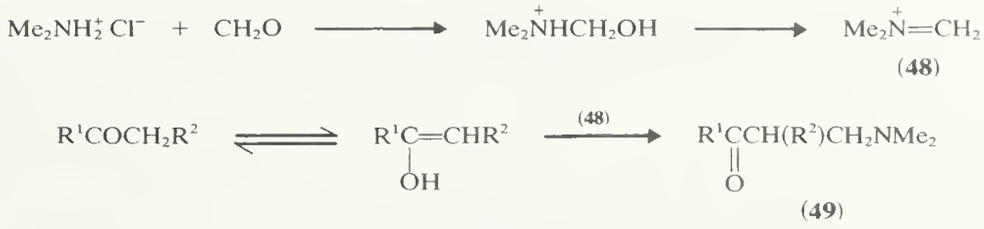


SCHEME 19

aldehydes. Water is lost from the intermediate (**45**) to form the dienamine (**46**), which gives the α-alkylidene or arylidene ketone (**47**) on hydrolysis.[178] Under carefully controlled acidic conditions an α-alkylidenecyclopentanone isomerized to the α-alkylcyclopentenone.[154] In a promising new route, the kinetically produced α-lithio derivative of the ketone's *N,N*-dimethylhydrazone (see Section 5.2.5.1) is added to aldehydes or ketones and the β-ketol released by mild periodate cleavage.[114,179] This variant of Wittig's directed aldol reaction[180] is important in allowing reaction with ketones, and in giving 1,2- (*i.e.* aldol) attack on α,β-enones in contrast to enolates, which usually give 1,4- (*i.e.* Michael) addition.

5.2.7.2 The Mannich reaction

In the Mannich reaction, a ketone (or other active methylene compound) reacts with formaldehyde and a secondary amine hydrochloride, with a trace of extra acid (see Scheme 20). The products are α-dialkylaminomethyl ketones (Mannich bases) (**49**). Primary amines or ammonia react in a similar way, but the products can react further. For reviews of the reaction, see Refs. 36 and 182. Constitutionally unsymmetrical ketones usually react *via* their more stable enol, which attacks the iminium salt (**48**) derived from the aldehyde and amine to introduce the aminomethyl group at the ketone's more highly substituted α-carbon atom. The early literature[182] is frequently unreliable on this point, but it has been confirmed for cyclic ketones[183] and a number of alkyl methyl ketones.[184,185] Undoubted exceptions do, however, exist and have been attributed to thermodynamic rather than kinetic control of the reaction.[36] It has been shown that some Mannich bases rearrange upon heating — for example, during distillation — although their methiodides seem to be more stable.[185] N.m.r. spectroscopy is preferred for analysing their isomer composition,[183–187] the spectra of their picrates or hydrochlorides being especially suitable.[186] Caution is advised before the structure of a Mannich base is assumed.



SCHEME 20

It is now becoming possible to direct Mannich base formation towards one or other α-carbon of a constitutionally unsymmetrical ketone, using preformed imonium ion reagents. Reaction with dimethyl(methylene)ammonium trifluoroacetate, prepared *in situ*, in the presence of trifluoroacetic acid allows selective attack on the more alkylated α-carbon. The more hindered de-isopropyl(methylene)ammonium salts react in an aprotic solvent (MeCN) specifically at the methyl group of alkyl methyl ketones.[187] Enol borinates, *e.g.* (**50**) and (**51**) in equations (6) and (7), react regiospecifically with

$$R^1_3B + R^2COCHN_2 \longrightarrow R^1_2BOC(R^2)=CHR^1 \xrightarrow[Me_2SO]{(52)} R^2COCH(R^1)CH_2NMe_2 \quad (6)$$

(50)

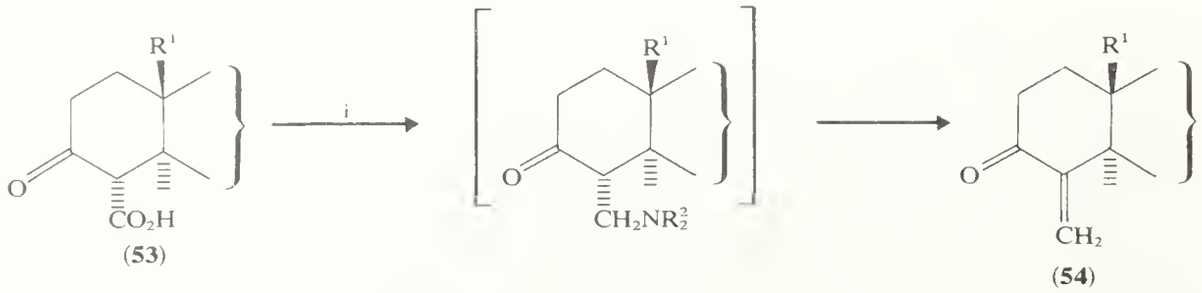
$$R^1_3B + R^2COC(R^3)=CH_2 \longrightarrow R^1_2BOC(R^2)=C(R^3)CH_2R^1 \xrightarrow[Me_2SO]{(52)} R^2COC(R^3)(CH_2R^1)CH_2NMe_2 \quad (7)$$

(51)

$Me_2\overset{+}{N}=CH_2\ I^-$

(52)

dimethyl(methylene)ammonium iodide (**52**) in DMSO; the method allows very versatile and efficient Mannich base formation from α-diazo ketones or α,β-unsaturated ketones or aldehydes.[188] The trimethylsilyl enol ethers of ketones (Section 5.2.4) react regiospecifically with the iodide (**52**) to give the silyl ethers of α-dimethylaminomethyl ketones; mild hydrolysis liberates the Mannich base.[189] The enolate anions of α-lactones react similarly,[189] so the lithium enolates of ketones should be equally suitable. An older route, due to Schopf, uses the reaction of a β-keto acid with formaldehyde and a dialkylamine: the acid is assumed to decarboxylate slowly to form the regiospecific enol of the ketone, which is aminomethylated and then eliminates the amine to give the α-methylene ketone. DMSO is an excellent solvent for this highly efficient process, *e.g.* (**53**)→(**54**)[190] in Scheme 21.



(53) (54)

i, aq. CH_2O + piperidine·HCl in Me_2SO.

SCHEME 21

5.2.7.3 Nitrosation of ketones

Ketones which have an α-methylene group (**55**) can be nitrosated using nitrous acid, nitrosyl chloride, nitrite esters, or nitrous fumes. Basic or acidic catalysts are used as appropriate, to form the reactive enolate anion or enol of the ketone. The α-nitroso compound (**56**) tautomerizes to the more stable α-oximino product (**57**) (equation 8). Ketones having an α-methine group (**58**) frequently suffer cleavage at the nitroso stage in order to form the α-oximino ketone (**59**) (equation 9). Similar reactions occur with a wide variety of compounds which bear carbanion-stabilizing groups; for a review, see Ref. 191. The position of nitrosation of constitutionally unsymmetrical ketones seems to correspond to the more stable enolate anion or enol, *i.e.* with attack at the more heavily alkylated α-carbon atom, followed by cleavage if necessary.[191] Thus methyl ketones (**55**; R^1 = Me, R^2 = alkyl) react under acidic catalysis to give the 3-oximino ketones.[192]

The α-oximino ketones can be converted into bis-oximes, *e.g.* the analytical reagent dimethylglyoxime, reduced (zinc–acetic acid or sodium dithionite) to α-amino ketones for use in the Knorr pyrrole synthesis, further reduced to α-amino alcohols, or hydrolysed to

$$R^1COCH_2R^2 \longrightarrow R^1COCH(R^2)NO \longrightarrow R^1COC(R^2)=NOH \quad (8)$$

(55) (56) (57)

$$R^1COCHR^3CO_2R^2 \longrightarrow R^1COC(R^3)(NO)CO_2R^2 \longrightarrow R^3C(=NOH)CO_2R^2 \quad (9)$$

(58) (59)

HO

α-diketones. For this last reaction, dilute mineral acid or nitrous acid suffice,[191] but more modern and selective methods of oxime hydrolysis should also be suitable (see Section 5.2.15).

Nitrosation of β-diketones is useful in giving the oximes of 1,2,3-triketones.

5.2.7.4 Diazonium coupling of ketones

The reaction of arenediazonium ions with α-methylene ketones (**55**) is very similar to the nitrosation discussed above, with tautomerism producing the phenylhydrazone (**60**) of an α-dicarbonyl compound (see Scheme 22). For a review, see Ref. 193. Applications to aliphatic and alicyclic ketones are few: β-diketones and β-keto aldehydes give the phenylhydrazones of 1,2,3-tricarbonyl compounds.[193]

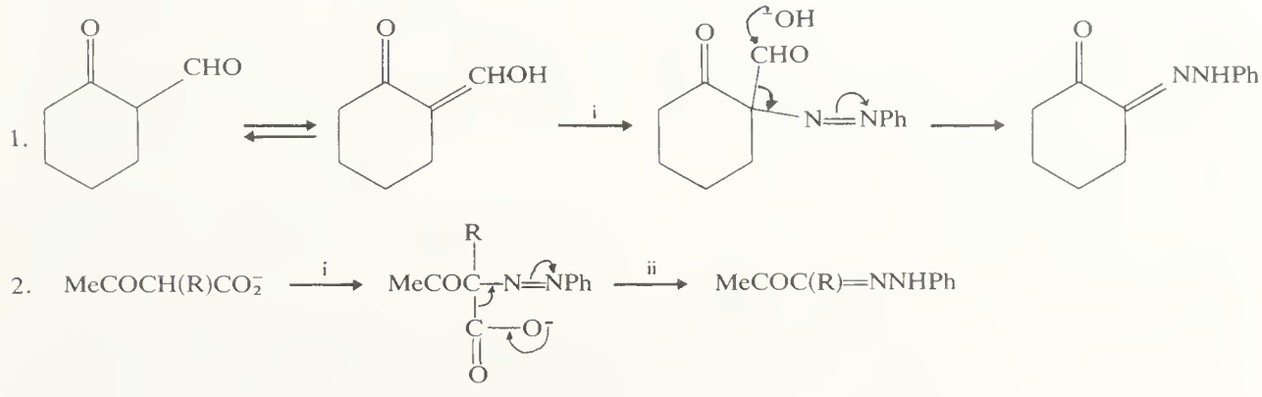
$$R^1COCH_2R^2 \longrightarrow R^1CO\bar{C}HR^2 \xrightarrow{i} R^1COCH(R^2)N{=}NPh \underset{}{\overset{ii}{\rightleftharpoons}} R^1COC(R^2){=}NNHPh$$

(**60**)

i, PhN_2^+ near neutral pH; ii, acid or base.

SCHEME 22

In the Japp–Klingemann reaction (for a review, see Ref. 194) the diazonium coupling is followed by cleavage analogous to that discussed earlier. The reaction is thus applied (see Scheme 23) normally to β-dicarbonyl compounds, and especially to β-keto acids which suffer decarboxylation.



i, PhN_2^+; ii, $-CO_2$.

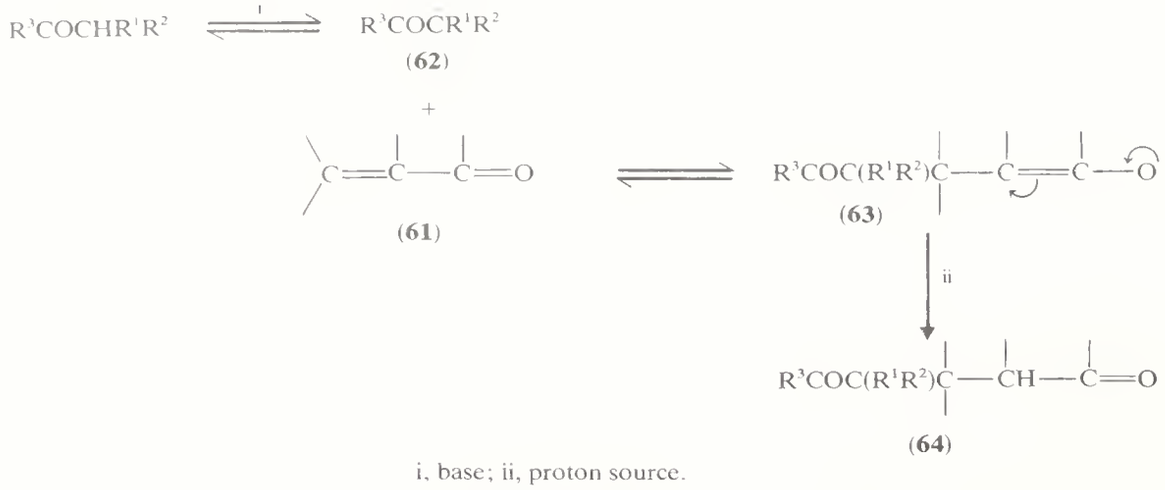
SCHEME 23

5.2.8 THE MICHAEL REACTION, AND ADDITIONS OF ORGANOMETALLIC REAGENTS AND YLIDES TO KETONES

5.2.8.1 The Michael reaction

The Michael reaction as shown in Scheme 24 was originally the 1,4-addition of a 'donor' containing an α-proton in the system —CHCO to the olefinic group of an α,β-unsaturated carbonyl compound (**61**). The reaction is performed typically in the presence of a base and then involves the addition of the 'donor's' enolate anion (**62**) to the 'acceptor' (**61**). The anionic product (**63**) is stabilized by delocalization whereas the product (**65**) of a direct 1,2-addition of the enolate (**62**) to the carbonyl group of (**61**) is not.

The scope of the reaction has been greatly broadened to include the conjugate (1,4-) addition of many anions or nucleophiles, as donors, to many α,β-olefinic or acetylenic ketones, aldehydes, esters, cyanides, nitro compounds, sulphones, *etc.*, in which the anion

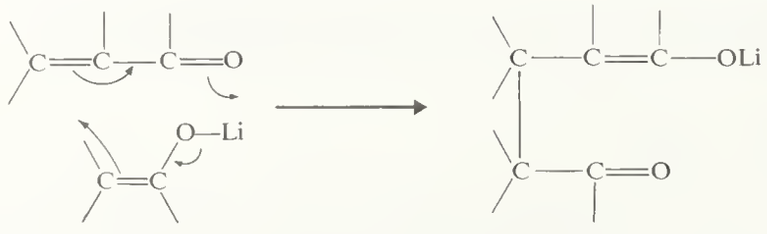


i, base; ii, proton source.

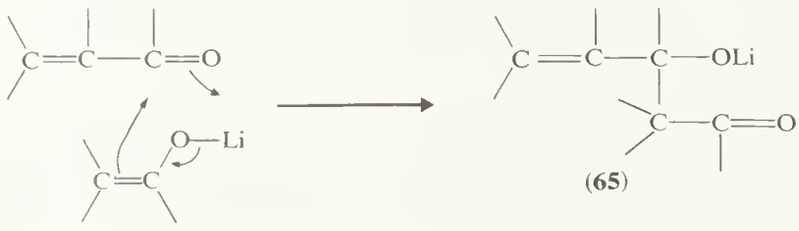
SCHEME 24

analogous to (**63**) can be similarly stabilized. For reviews, see Refs. 36 and 195. The related additions of organometallic compounds to α,β-unsaturated ketones are discussed in Section 5.2.8.2. Many alkyl- or aryl-lithiums, as opposed to enolate anions, give only 1,2-addition.

The ability of nucleophiles to add in either 1,2- or 1,4-fashion to α,β-enones is of great importance since modification of the reagents or conditions can influence the reaction to follow more of one pathway or the other. Stork and Maldonado[196] have discussed the spectrum of 1,2- *versus* 1,4-additions of α-lithiated cyanohydrin ethers in terms which are directly applicable here also — see equations (10) and (11). Increasing the size of the substituents at the α-carbon of enolate (**62**) or on the carbonyl group of the enone (**61**) should sterically increase 1,4- relative to 1,2-addition. This correlates with the fact that most Michael additions involve rather large donors such as β-diketones, β-keto esters, or many analogous difunctional compounds. Moreover, if the additions can be made reversible, by increasing the stability of the enolate (**62**) relative to that of (**63**) or (**65**), the thermodynamically favoured 1,4-addition will predominate. This can be achieved by further delocalizing the charge on (**62**), as is the case when the donor is a β-diketone, β-keto ester, *etc.* A related and valuable explanation of the spectrum of 1,2- *versus* 1,4-addition of organometallics to conjugated ketones uses the hard and soft acid–base (HSAB) theory, and can be extended to Michael additions.[197] The additions of ester enolates to cyclohex-2-enones further bear out these arguments. Kinetically controlled (Reformatsky-type) addition at −78 °C gives a 1,2-adduct of type (**65**), but ready reversal at 25 °C allowed thermodynamically controlled 1,4-addition.[198]



(10)



(11)

(i) Michael additions of saturated ketones to unsaturated ketones

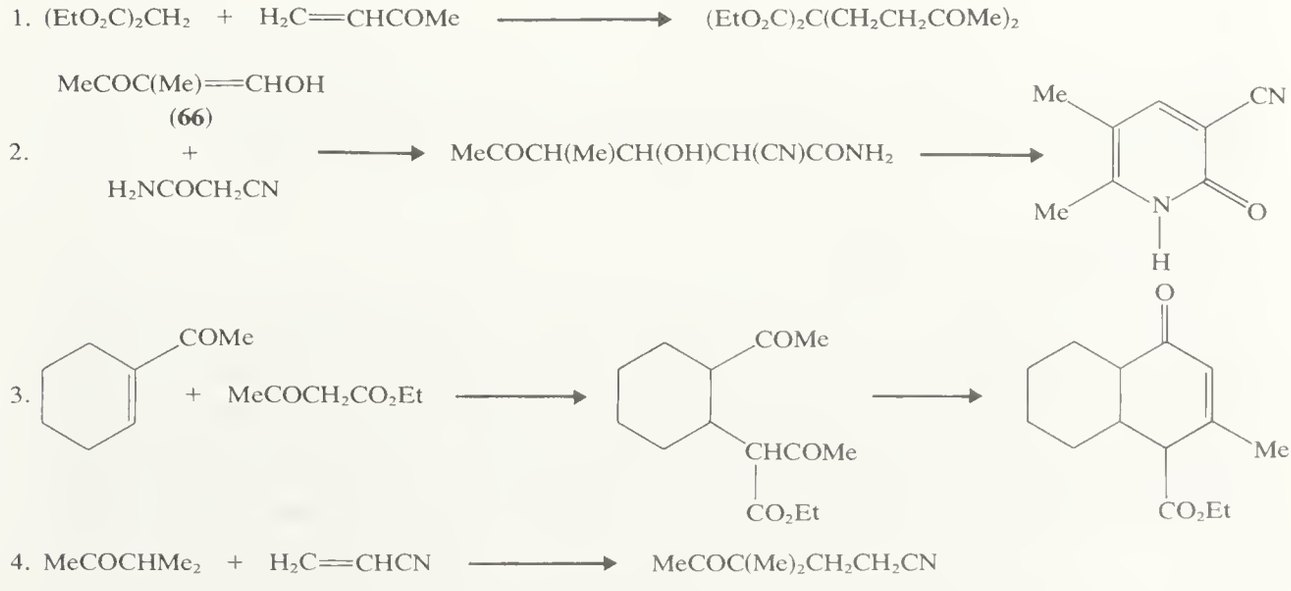
These additions give 1,5-dicarbonyl products of type (**64**), the saturated ketone acting as the donor, and the enone as acceptor. Because the products can react further by intramolecular aldol reaction, to form cyclohexenones, the additions are treated in Section 5.2.9.

(ii) Additions to α,β-unsaturated ketones

Many relatively acidic active methylene compounds have been used as Michael donors. They include malonate esters, β-keto esters, malononitrile, cyanoacetate esters, β-diketones, nitroalkanes, cyanoacetamide, and sulphones. The addition products frequently cyclize to make available a wide variety of six-membered ring products, which may be alicyclic or heterocyclic (see Ref. 195). Instead of the free α,β-unsaturated ketones one can use precursors which liberate them slowly under the Michael reaction conditions; for examples, see Section 5.2.9 and Refs. 36 and 195. If the unsaturated ketone has an enolizable proton, it can potentially act as a donor and an acceptor, leading to polymerization. To reduce this and other side reactions the conditions used for the addition should be kept as mild as possible. The bases used, and the amounts needed, vary with the reagents employed. If the anionic product (**63**) is more basic than the enolate (**62**) it can regenerate the base by deprotonating a protic reaction solvent. A small amount of base, which is frequently an amine or alkali metal hydroxide or alkoxide, or benzyltrimethylammonium hydroxide (Triton B), in an alcohol or an alcohol–ether mixture, may then suffice. Stronger bases, such as alkali metal alkoxides, sodium hydride or sodamide, are used to produce the enolate or analogous anion from weakly acidic donors, and especially from ketones. The enol forms of β-diketones and β-keto aldehydes (*i.e.* α-hydroxymethylene ketones) can act as Michael acceptors: see Ref. 195 and (**66**).

(iii) Ketones as donors in Michael additions

Monoketones are among the less acidic compounds whose anions are stabilized by resonance. They are slightly stronger acids than the analogous sulphones, cyanides, and carboxylate esters, but much weaker than the analogous nitroalkanes, β-keto esters, and malonate esters. They add readily to the more reactive Michael acceptors such as

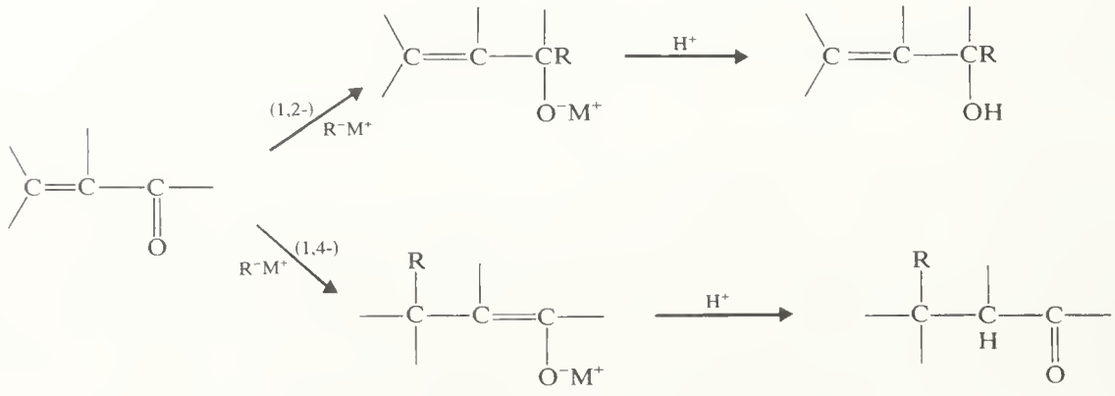


SCHEME 25[195]

acrylonitrile (cyanoethene), but less readily to other unsaturated systems such as α,β-enones and α,β-unsaturated carboxylate esters. The use of stronger bases and higher reaction temperatures may not increase the yield of adduct, owing to the increase in side reactions or cyclization of the products. Constitutionally unsymmetrical alkyl ketones and cyclic ketones normally react preferentially (see Scheme 25) at their more highly substituted α-position, *via* the more stable enolate anion. The reasons for this are, however, neither simple nor entirely clear.[36] When α,β-unsaturated ketones act as donors they may react *via* the enolate formed at the α'-position or, occasionally, *via* the more polarizable γ-enolate which leads to a more stable product.[36,195]

5.2.8.2 Additions of organometallic reagents and ylides to ketones

The addition of Grignard reagents and organolithium compounds to ketones, to give tertiary alcohols, is well known (see Sections 15.1.1 and 15.2.2). Many other organometallic reagents and ylides add in the same way. Additions to α,β-unsaturated ketones are more complex, because 1,2- or 1,4- (conjugate) addition, or both, may occur (see Scheme 26). In this section the reagents will be divided into those giving 1,2- and those giving 1,4-addition to α,β-enones. In general, organolithiums[199] and other reagents derived from unstable carbanions and alkali metals are highly reactive and give 1,2-addition whereas more stable anions, such as enolates and particularly organocopper(I) reagents, give 1,4-, *i.e.* Michael, addition. Grignard reagents tend to give either mode of reaction, as do the organozinc or magnesium derivatives of α-halocarboxylic esters in the Reformatsky reaction (see Section 9.3.3 and Ref. 200).



SCHEME 26

Steric hindrance or additional conjugation of the carbonyl group diminishes the importance of 1,2- relative to 1,4-addition. Large groups attached to the carbanion centre of the organometallic, or delocalization of the charge, have the same effect.

(*i*) *Reagents giving* 1,2-*addition*

Alkali metal acetylides add to ketones to give 3-hydroxyalkynes (after acidification):[201] see Section 2.3.10.4. The lithium derivative of 1,3-bis(methylthio)propene adds to give (**67**), which is hydrolysed by aqueous mercuric salts, dehydrates, and tautomerizes to give γ-hydroxy-α,β-unsaturated aldehydes (2-formylethenyl carbinols) (equation 12). The reagent thus acts as a masked $\bar{C}H$=CH—CHO group.[202] The lithio derivative of dibromomethane, formed *in situ* using either lithium dicyclohexylamide or lithium 2,2,6,6-tetramethylpiperidide as hindered bases, adds to ketones to give dibromomethyl carbinols.

$$\underset{\textbf{(67)}}{R_2C(OH)CH(SMe)CH{=}CHSMe} \longrightarrow R_2C(OH)CH{=}CHCHO \qquad (12)$$

Treatment with butyl-lithium gives a β-oxidocarbenoid which rearranges (by C—C insertion into the O=C—C bond) to homologated ketones. The method can be used to expand the rings of cyclic ketones and can be highly regioselective.[203] The 1-lithio derivative of methoxyethene adds to the carbonyl group of ketones or α,β-enones to give adducts which, upon mild acidic hydrolysis of the enol ether function, give 3-hydroxyalkan-2-ones (*i.e.* α-ketols), the products of a formal acetyl anion (CH_3CO^-) addition.[204] The 1-lithio derivatives of other monosubstituted enol ethers act similarly, that from 1-methoxypropene being equivalent to propionyl anion, and that from 1-methoxybuta-1,3-diene to the crotonyl anion.[204] References to other approaches to acyl anion equivalents are given in Refs. 17 and 205. The 2-lithio-2-alkyl-1,3-dithians serve similarly, the dithian–carbinol adducts[206] being hydrolysed by buffered aqueous mercuric salt solutions to the free α-ketols.[18] The dithian adducts obtained from α,β-enones can be isomerized by dilute acid to protected γ-hydroxy-α,β-enones, which are readily oxidized to protected 2-ene-1,4-diones; hydrolysis with mercuric ion gives the enediones.[207]

Many ylides add to the carbonyl group of ketones (and aldehydes) and αβ-enones. The Wittig reaction of phosphonium ylides and related additions of phosphonate and phosphinoxy carbanions (to form alkenes) are discussed in Chapter 10.6, and the addition of alkylidene- and methylene-sulphuranes (sulphonium ylides) (to form oxirans) in Chapter 11.15. Provided the carbonyl group is not exceptionally hindered the addition is of the 1,2-type.[208] The bulkier and less reactive sulphoxonium ylides add to the olefinic bond to give cyclopropyl ketones (Chapter 11.15 and Ref. 208). A new method for converting a ketone carbonyl into a methylene ($>C=CH_2$) group uses the 1,2-addition of phenylthiomethyl-lithium, $PhSCH_2Li$, followed by acylation of the carbinol. Reduction by lithium in ammonia removes the phenylthio group and expels the acyloxy anion, giving the olefin, even from hindered ketones and other substrates with which the Wittig reaction fails.[209]

(*ii*) *Reagents giving 1,4-addition to α,β-unsaturated ketones*

It has recently become possible to introduce β-alkyl groups into α,β-unsaturated ketones (and aldehydes) with high positional (*i.e.* constitutional) specificity. The reagents most often used are lithium dialkylcuprates or lithium diarylcuprates, LiR_2Cu, 'mixed' analogues LiR^1R^2Cu or LiRXCu or, less often, organocopper(I) compounds, RCu, in the presence of lithium halides. For reviews, see Ref. 210. The LiR_2Cu reagents are made by addition of two equivalents of an organolithium RLi to one of purified cuprous iodide — or the bromide or chloride — in diethyl ether or THF, or by addition of organolithium RLi to an organocopper RCu.[211,212] The latter method allows the preparation of a reagent free of lithium halide. The mixed reagents are made by successive additions of R^1Li and R^2Li to the cuprous halide, or from the organolithium and pre-formed organocopper(I) compound, RCu or CuX.[213] All operations require strictly anhydrous conditions and inert atmospheres. Depending upon their stabilities, the reagents are made at 25 °C down to −78 °C; they contain no detectable amount of free organolithium.[211] It is sometimes desirable to add a complexing ligand such as tri-n-butylphosphine, trimethyl phosphite, tri-n-butyl phosphite, dimethyl sulphide, di-isopropyl sulphide, or others listed in the central papers published by House and his co-workers.[212,214] Trimethyl phosphite and dimethyl sulphide are most easily removed in the work-up, but the complexation is usually an unnecessary complication.

Groups R which have been transferred to the β-position of α,β-enones[210] include methyl, ethyl, n-propyl, 2-propenyl, allyl, isopropyl, n-butyl, s-butyl, t-butyl, n-pentyl, n-heptyl, cyclopentyl, benzyl, vinyl (with tri-n-butylphosphine present),[215] phenyl, substituted phenyl, and benzyl. The lithium dialkylcuprates derived from 1-lithio-1-ethoxy-[216] or 1-lithio-1-methoxy-ethylene[217] transfer the 1-alkoxyvinyl group which is easily hydrolysed to acetyl, and thus act as masked acetyl anions, or can be ozonized to methoxycarbonyl groups;[217] the yields from β,β-dialkyl-α,β-enones are poor.[217,218]

A Grignard reagent or, less frequently, an organomagnesium compound R_2Mg can also be used, with a catalytic amount of cuprous or cupric chloride, bromide, iodide, acetate,

or cyanide, to effect conjugate addition. The Grignard reagent reduces cupric ions to cuprous, and then seems to produce small amounts of the much more reactive[211] organocopper(I) reagent *in situ*: this is continuously regenerated during the reaction. In most cases the reactions of the preformed and the catalytically produced reagents are the same. However, additions to β,β-disubstituted α,β-enones frequently fail when the catalysed Grignard reagent is used, but may succeed with the preformed cuprate reagents.[218] The copper-catalysed reaction of allylmagnesium bromide with a steroidal 1-acetylcyclopentene gives only carbonyl addition, whereas many other alkyl and aryl groups were added at the β-carbon.[219] Lithium diallylcuprate adds 1,4- to cyclohex-2-enone but only to the carbonyl group of 3,5,5-trimethylcyclohex-2-enone, whose olefinic group is more hindered.[220] Lists of conjugate additions effected by the two types of reagent (up to 1971) are given by Posner.[210] In the absence of copper salts, the Grignard reaction normally gives much more 1,2-addition.[211,214]

The lithium organocuprates are much less basic and nucleophilic than the corresponding organolithiums and are relatively unreactive towards saturated ketones, esters, carboxylic acids, alcohols, and tetrahydropyranyloxy groups.[211] Selective, very rapid, conjugate addition can be achieved, but prolonged contact with an excess of the reagent allows 1,2-attack on ketones,[211] carboxylate esters rarely,[221,222] and anhydrides.

The yield and stereochemistry of 1,4-addition vary with the bulk of the transferred group R, and of the existing groups, particularly those at C-4 and C-5 in cyclohex-2-enones. The new group enters predominantly axially and *trans* to sterically interacting groups.[168,214,219] The reduction of yield caused by the presence of large groups at the β-position has been alluded to, and sometimes the reaction fails altogether with β,β-dialkyl enones.[216]

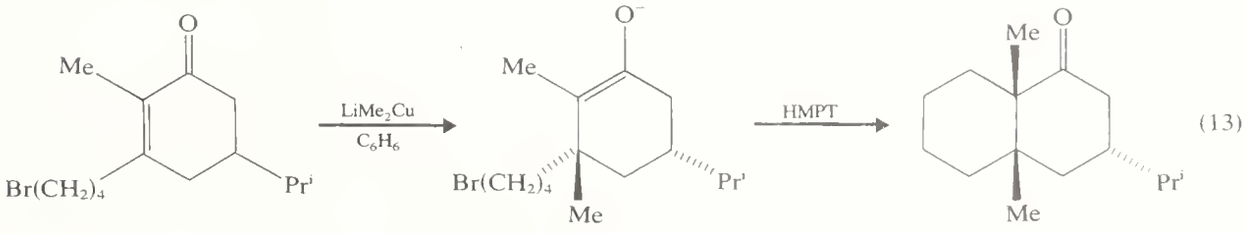
The reagents LiR_2Cu transfer only one group R to the substrate, which is wasteful if LiR is valuable, and secondary and tertiary alkyl groups tend to give unstable reagents which need to be used in large excess. 'Mixed' cuprate reagents, LiR^1R^2Cu or LiR^1XCu can often transfer the R^1 group with high selectivity. The favoured retained groups X are alkoxy, and particularly t-butoxy,[213,223] phenoxy, t-butylthio, phenylthio, or diethylamino.[223] Retained groups (R^2) are usually acetylenic, particularly the pent-1-ynyl group when R^1 is n-alkyl, t-butyl, or vinyl.[213,224] The specificity of transfer of alkyl groups R^1 rather than R^2 from LiR^1R^2Cu has been studied; a s- or n-butyl group R^1 is cleanly transferred whilst a t-butyl group R^2 is retained.[213] The conditions used can alter the results: lithium methyl vinylcuprate transfers the vinyl group when THF is used as reaction solvent, but transfers methyl and vinyl equally in diethyl ether, and methyl in its reactions with oxirans and acyl chlorides.[225] It is not possible to transfer an ethynyl group directly to the β-carbon, because of strong acetylene–copper bonding, but the same result has been achieved indirectly.[226]

The structures of the lithium dialkylcuprates have been discussed at length, the latest suggestion being a cyclic dimeric structure.[227] An electron-transfer reaction mechanism seems to fit all the available data,[214,228,229] but has been questioned.[230] The mode of reaction has been related to the polarographic reduction potentials of the α,β-unsaturated carbonyl compounds. If the reduction potential of the ketone is too low, there is no reaction with LiR_2Cu; if one electron can be transferred within the correct range of potential, alkylation occurs; if a second electron can be accepted readily by the ketone, it is reduced, *via* its radical anion, to a dihydro derivative.[228] Empirical rules have been deduced which relate the half-wave reduction potential of ketones to their structures.[229]

(*iii*) *Other synthetic applications of 1,4-additions*

The enol acetates,[222] enol ethers, or enol thioethers[231] of β-dicarbonyl compounds, or the related β-halo-α,β-enones,[232] react with LiR_2Cu by a stereoselective β-addition, then elimination, to give a β-substituted α,β-enone; reaction with further reagent yields the β,β-disubstituted compound.[231] Similar β-alkylation of the enol acetate of ethyl acetoacetate affected only the enol ester function.[222] The additions involve the

formation of a lithium enolate[87] which can be captured by standard reagents and converted into enol acetates,[87,123,211] and enol silyl ethers.[46] The enolate can be trapped using formaldehyde[171] or aliphatic aldehydes[173] to introduce a hydroxymethyl or α-hydroxyalkyl group (as in the aldol reaction), and alkylated by reactive alkyl halides, to introduce both an α- and a β-group in a regiospecific manner.[219,233] The method is particularly valuable for cyclopentanones and in the prostaglandin[173,225,234] series. Intramolecular alkylative cyclization, as of (**68**) in equation (13), can be achieved, and



(13)

(**68**)

introduces a valuable *cis* ring junction.[225] The enolates are relatively unreactive, and it is usually necessary to replace the solvent with HMPA or DME to accelerate alkylation and avoid loss of specificity; many alkyl halides (methyl, ethyl, isopropyl, isobutyl, allyl, and but-3-enyl) can then be used.[112] For further applications, see Sections 5.2.5 and 5.2.9.

The β-alkylation of α,β-enones can be achieved using trialkylboranes as alternatives to organocopper reagents, and is better for easily polymerized enones such as methyl vinyl ketone. α-Methylenecycloalkanones, prepared *in situ* from the Mannich bases, with R_3B give the ketone bearing an α-CH_2R group; R may be primary or secondary, alkyl or cycloalkyl.[235] The mechanism involves a radical chain, and enones having a single β-alkyl substituent react well when a supply of radicals is assured.[236] Many alkenyl and alkynyl groups, but not vinyl, can be transferred to unalkylated or monosubstituted β-carbons of α,β-enones — provided the carbonyl and olefinic bonds can adopt a *cisoid* conformation — by *B*-alkenyl- or *B*-alkynyl-9-borabicyclo[3,3,1]nonanes.[237] All the reactions proceed *via* an enol borinate intermediate.

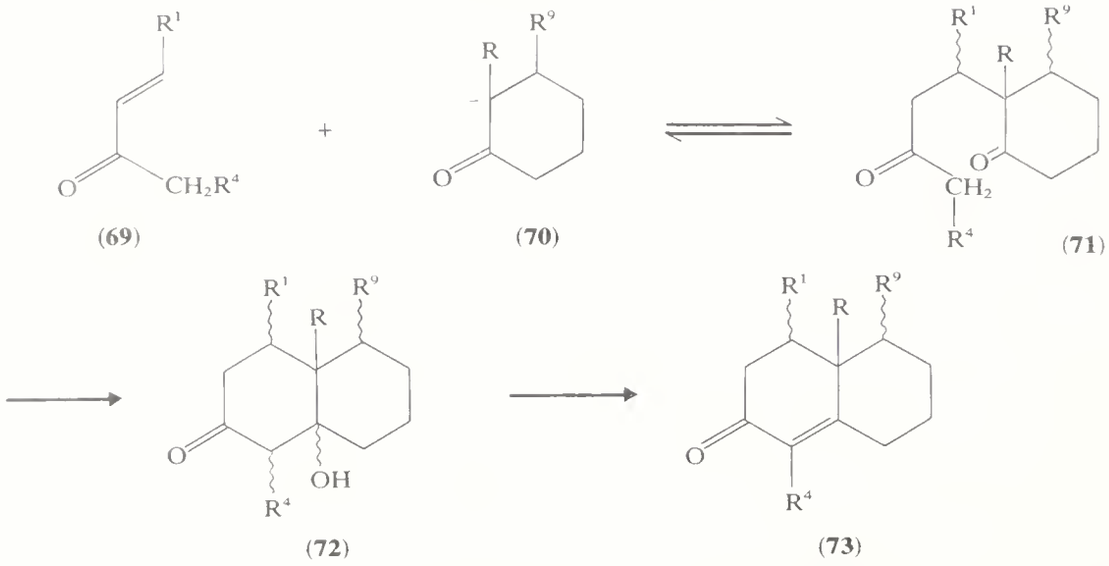
5.2.9 RING-FORMING REACTIONS AND ANNELATIONS

Annelation is the building of a ring on to an existing system. Usually a six-membered or five-membered ring is built on to a ketone, a process of immense value in the synthesis of steroids and many terpenoids. We will also discuss the analogous syntheses of monocyclic cyclohexenones. For reviews, see Refs. 36, 238, and 239.

5.2.9.1 Robinson annelation

This is a ring extension by condensation of a cycloalkanone derivative with a methylene vinyl ketone or its equivalent, a reaction pioneered by Sir Robert Robinson. At its simplest a cyclic 1,3-diketone, 2-alkoxycarbonylcycloalkanone, 2-cyano-, or 2-alkylcycloalkanone is converted into its anion which undergoes Michael addition to an α,β-unsaturated ketone such as methyl vinyl ketone, to give a 1,5-diketone. This cyclizes, *via* an aldol addition, to a 3-keto alcohol which can dehydrate to a new cyclohexenone ring, *e.g.* (**69**)–(**73**) in equation (14).

Many annelations are performed using sodium alkoxides or trialkylamines as bases, and allow the full sequence (**69**)–(**73**), but conditions can be chosen to allow each intermediate compound to be isolated. In one well-developed procedure a trace of hydroxide ion in methanol is used to effect the Michael addition, then pyrrolidine or pyrrolidine/acetic acid catalyses the aldol reaction. The dehydration is catalysed by acids or bases.[240,241] Examples include the Wieland–Miescher ketone (**73**; R = Me, R^9 = =O, $R^1 = R^4$ = H),[240] (**73**; R = OCOMe, R^9 = =O, $R^1 = R^4$ = H),[241] (**73**; R = Me, R^9 = =O, R^1 = H, R^4 = Me)[242] and



(14)

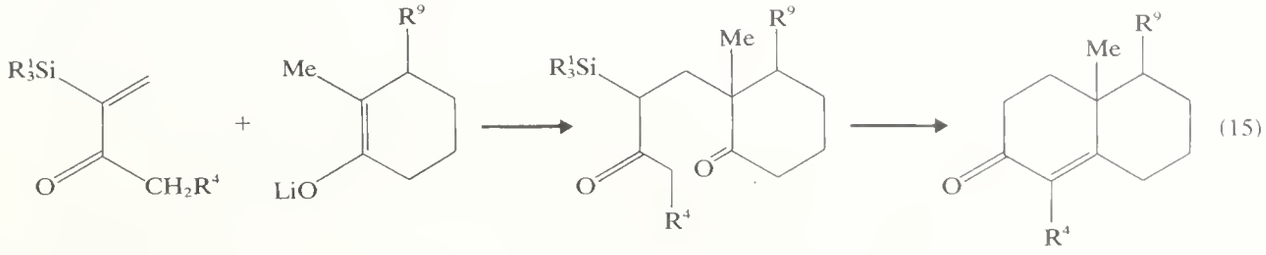
and another using ethyl vinyl ketone (**69**; $R^1 = H$, $R^4 = Me$).[243] Uncatalysed Michael additions of 2-alkylcyclopentane- and 2-alkylcyclohexane-1,3-diones to methyl vinyl ketone are reported; the use of an optically active amine or amino acid as base in the cyclization step gives high yields of products with very high optical purity.[190,244] Examples of the use of the single-step procedure to prepare compounds (**73**) include reactions of (i) pent-3-en-2-one (**69**; $R^1 = Me$, $R^4 = H$) with cyclic keto esters (**70**; $R = CO_2Alkyl$) or cyclohexanones (R = alkyl) having a variety of alkyl or alkenyl substituents,[245] of (ii) ethyl vinyl ketone to attach the B ring and 10-methyl group to the C/D rings of a steroid,[190] and of (iii) methyl vinyl ketone with many compounds (**70**).[246] The annulation of 2-methylcyclohexanone with methyl vinyl ketone, to give (**73**; R = Me, $R^1 = R^4 = R^9 = H$) has been studied in detail; a trace of sodium ethoxide is used to make the ketol (**72**) (up to 55%) which is separately dehydrated. Cyclohexanone and 2,6-dimethylcyclohexanone give poorer results.[247] The Michael addition of 2-alkylcyclohexanones occurs primarily at C-2, for reasons which are not entirely clear, but which seem general.[36] The stereochemistry of the annulation steps is investigated in Refs. 241, 245, and 247. In the cases studied the aldol cyclization is highly stereoselective, kinetically controlled, and not reversed under the dehydration conditions.[247]

The use of strong bases with vinyl ketones frequently causes polymerization; moreover, constitutionally unsymmetrical cycloalkanones can give two isomeric enolate anions. In order to achieve greater regioselectivity, and to allow the Michael addition to occur under very mild conditions, the cyclic ketone or 1,3-diketone (**70**) is frequently converted into its enamine (usually the pyrrolidine enamine). Reaction with the enone (**69**) under carefully defined conditions can give greatly improved yields.[248] The mechanism of the route[249] and the stereochemistry of the cyclization have been studied.[248,249] Compounds prepared include (**73**; R = Me, $R^9 = =O$, $R^1 = R^4 = H$),[249] its analogues with R = Et and Pr^i,[250] and with $R = R^1 = Me$,[248] and many octalones (**73**) having R = H.[251] The latter reactions using morpholine enamines allow isolation of the 1,5-diketone, which is cyclized separately, whereas the pyrrolidine enamines lead directly by cyclization to the enamine of the bicyclic ketones (**73**).[251] Because the enamines from 2-alkylcycloalkanones have the 6-alkyl-1-dialkylaminocycloalkene structure, they lead to annulation products having a 6-alkyl group and a hydrogen atom at C-10 (steroid numbering) which are in equilibrium with the $\Delta^{5(10)}$-isomers.[251]

Annulations can use materials which act as *in situ* sources of α,β-unsaturated ketones (**69**). Robinson introduced the use of β-dialkylamino ketones (Mannich bases) or their methiodides, and β-chloro ketones, which slowly produce the enones in a basic reaction medium. Yields can be much improved by this technique, and in some cases may improve still further now that isomerically pure Mannich bases can be made from constitutionally unsymmetrical ketones (Section 5.2.7.2). Examples are given in Ref. 252. Acidic catalysis

can also be used, either with β-chloro ketones or with the unsaturated ketones, and can give excellent results.[242,253] Unsaturated ketones containing other functional groups have been used, including 1,4-dimethoxybutan-2-one as a source of 1-methoxybut-3-enone,[254] ethyl 5-ethoxy-3-oxopentanoic acid as a source of ethyl 3-oxopent-4-enoate, the methyl ester of this olefinic keto acid,[255] and ethyl 4-oxopent-2-enoate.[251] The use of but-3-yn-2-one allows the annulation of a cyclohexadienone ring, but yields are poor.[256]

Despite much attention to experimental conditions, the annelations described previously can be inefficient, and the use of enamines cannot direct the Michael addition towards C-2 of a 2-substituted cycloalkanone. A major improvement uses α-silylated enones (**74**) which react under aprotic conditions with the regiospecifically prepared lithium enolates of cyclic ketones (equation 15). The Michael adduct (**75**) forms very readily, without polymerization of the enone; dilute alkali effects cyclization, dehydration,

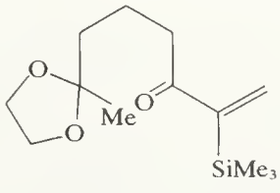


(15)

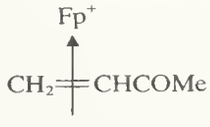
(**74**) (**75**)

and cleavage of the carbon–silicon bond. The more substituted enolate of 2-methylcyclohexanone was conveniently made using a trace of potassium t-butoxide, but the trimethylsilyl enol ether–methyl-lithium method was also used to produce this and the alternative enolate.[257]

Cyclohex-2-enones were also converted into isomerically stable enolates by conjugate addition of lithium dialkylcuprates, giving a 9-alkylated product, or by lithium–ammonia reduction; both give annelation at the carbonyl group and C-2.[258] Extension to more complex α-silylated vinyl ketones, *e.g.* (**76**), allows annelations which add on two rings; the acetal is hydrolysed to release the second 1,5-diketone, which then cyclizes.[258] Two other promising methods are available. Methyl vinyl ketone can be complexed with cyclopentadiene iron dicarbonyl (**77**) (made from methyl vinyl ketone epoxide) to enhance

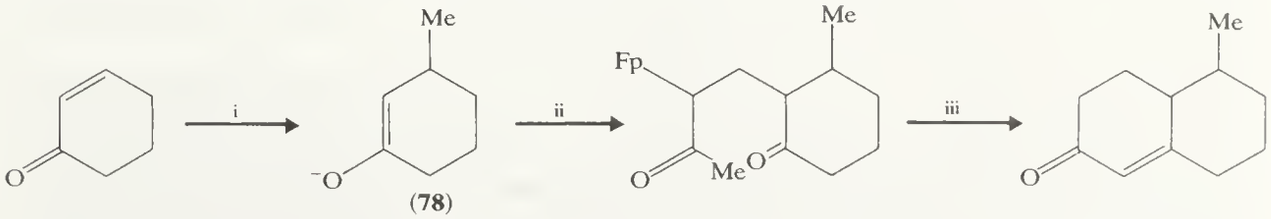


(**76**)



(**77**) where Fp$^+$ is η^5-$C_5H_5Fe(CO)_2$

its Michael acceptor properties. Regiospecific attack occurs rapidly with enamines, the enol silyl ether, or the lithium enolate of cyclohexanone, the more substituted silyl enol ether of 2-methylcyclohexanone, and the enolate (**78**)[259] (Scheme 27). In the second



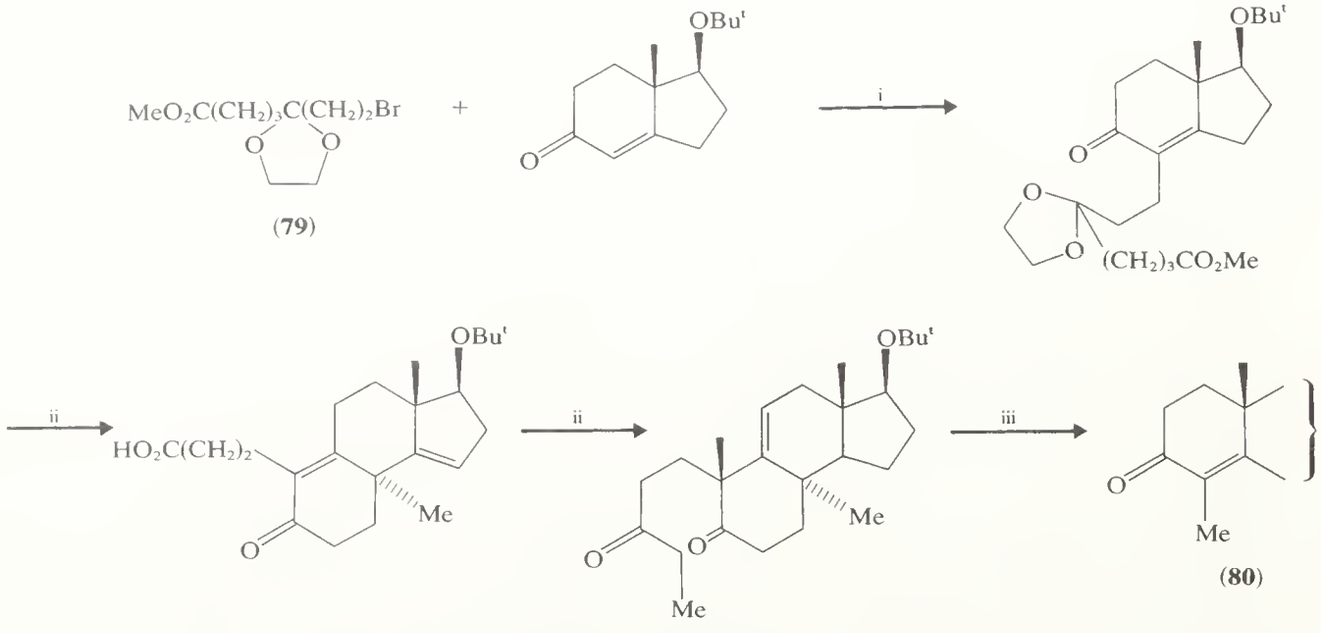
i, $LiMe_2Cu$; ii, reagent (**77**) in MeCN, −78 °C;
iii, 2% KOH–MeOH.

SCHEME 27[259]

method, the 6-lithio derivative of 2-methylcyclohexanone-*N*,*N*-dimethylhydrazone (see Section 5.2.5) is converted into a lithium diorganocuprate complex which gives an excellent Michael addition to methyl vinyl ketone. Removal of the dimethylhydrazone group releases the 1,5-diketone, which is cyclized in the usual way.[179]

5.2.9.2 Other annelation methods

Annelation methods exist which employ an alkylation reaction, rather than Michael addition, to introduce a 3-ketoalkyl group at the α-carbon of a ketone. A free[260] or protected β-chloro ketone may be used: the example (**79**) → (**80**) shown in Scheme 28

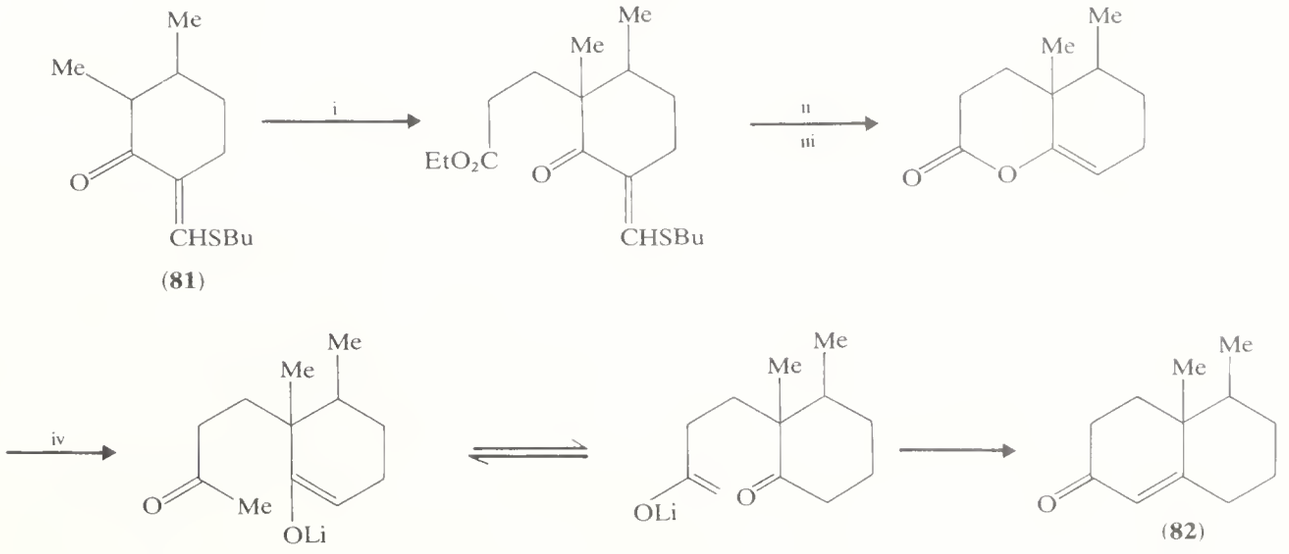


i, NaH, Me_2SO; ii, various steps; iii, base (Triton B).

SCHEME 28[261]

allows two rings to be introduced.[261] The use of an α-chloro ketone introduces a cyclopentenone ring.[260] In the Wichterle reaction the enolate of the cyclic ketone is alkylated with 1,3-dichloro-*cis*-but-2-ene (as a methyl vinyl ketone equivalent). Hydrolysis of the vinylic chloride by sulphuric acid gives the 1,5-diketone which cyclizes. An important side reaction in this step, and sometimes the sole reaction, is cyclization of the side-chain carbonyl group with the α'-methylene of the cyclic ketone, giving a bridged ring system.[261a] Although this can be circumvented,[262] it offers an important route to bicyclo[3,3,1]nonan-9-ones, *e.g.* in the synthesis of helminthosporal.[263] A related method, as in (**81**) → (**82**) in Scheme 29, is alkylation of the cyclic ketone by a β-halo ester.[264] The 5-keto ester product is converted into an enol lactone, which is treated with a Grignard reagent or alkyl-lithium to give an enolate of a 1,5-diketone and then the cyclohexenone — often in better yield than direct Robinson annelations. For reviews of this route, see Refs. 238 and 265.

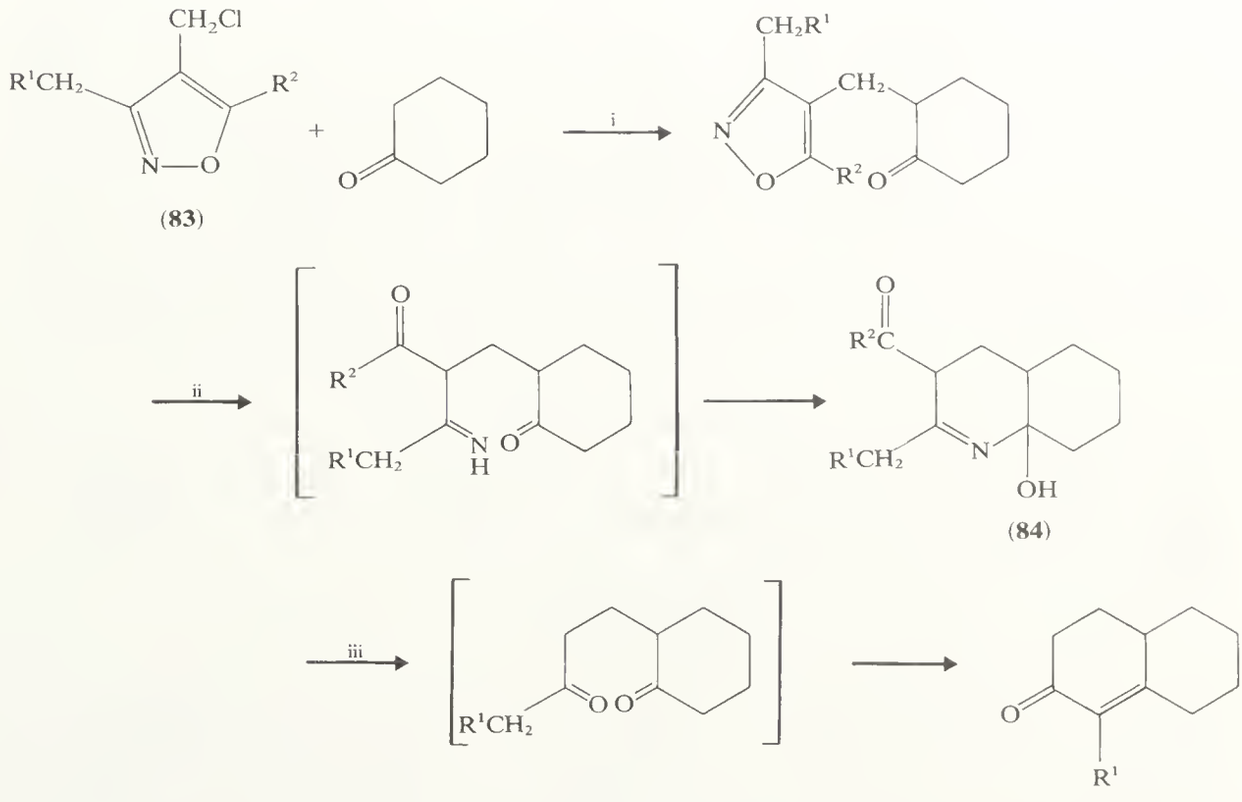
An important alkylation route (see Scheme 30) uses 3,5-dialkyl-4-halomethylisoxazoles (**83**) to alkylate ketones in the conventional ways (Section 5.2.5). The isoxazole ring is then converted into a 3-oxoalkyl group, most satisfactorily by hydrogenolysis *via* a carbinolamide (**84**), the alkyl group next to the isoxazole nitrogen being incorporated into the cyclohexenone ring.[266] If the initial alkylation is at the α-carbon of an α,β-cyclohexenone, the olefinic group can be reduced stereoselectively before cleavage of the isoxazole ring.[266a] A bis-annelating agent (**85**) was used in the syntheses of (±)-D-homotestosterone and (±)-progesterone.[266b]



(**81**)

i, base + $BrCH_2CH_2CO_2Et$; ii, OH^- to remove =CHSBu group and to saponify ester; iii, Ac_2O; iv, MeLi.

SCHEME 29[264]



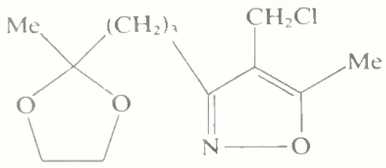
(**83**)

(**84**)

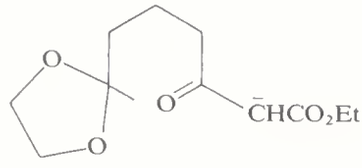
i, NaH, glyme; ii, H_2, Pd/C; iii, 10% KOH

SCHEME 30

Annelations can be performed in a manner 'complementary' to some already mentioned. The 1,5-dicarbonyl compound can be built up by the Michael addition of an enolate anion — usually of a β-keto ester — to an α-methylenecycloalkanone, or by alkylation of an enolate with an α-halomethylcycloalkanone (or a related compound).[190] The former method gives an equatorial 3-oxoalkyl group in a steroid synthesis, and can be used in bis-annelations,[190] *e.g.* (**86**) → (**87**) in Scheme 31. For a related reaction which uses a Michael addition to a 1-formylcyclohexene, see Ref. 267.

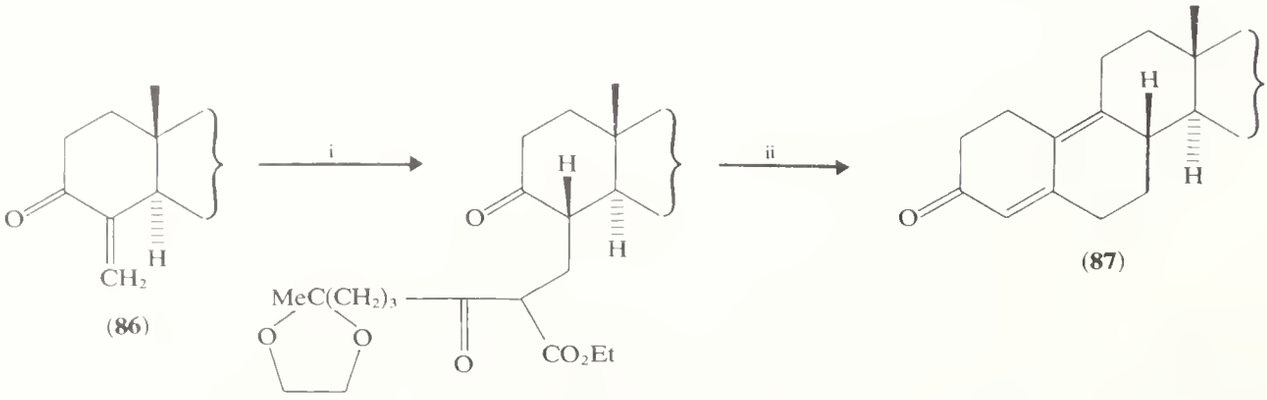


(**85**)



(**88**)

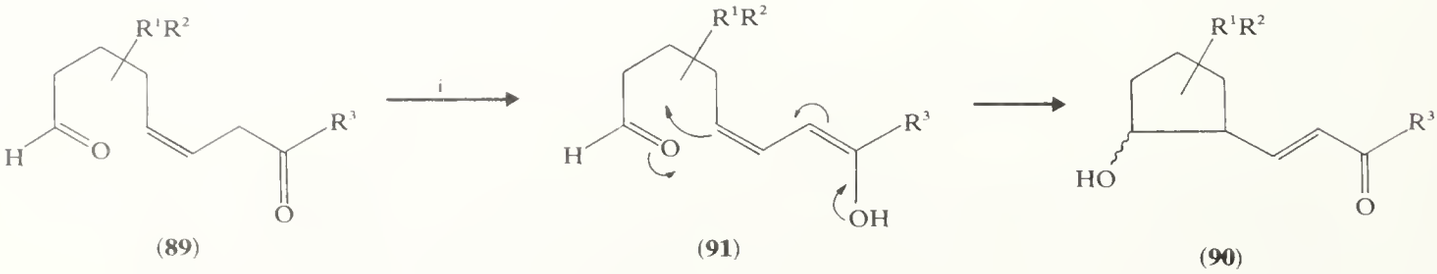
Some aldol reactions of conjugated enols have been used in forming five- and six-membered rings. The Δ^5-8-keto aldehyde (**89**), produced *in situ* from its bis-ethylene acetal, cyclizes to form the prostaglandin precursor (**90**) (see Scheme 32). The phenylthio analogue of (**91**) (SPh in place of OH) cyclizes similarly.[268] The 4-(3-oxoalkyl)cyclohexenones (**92**) condense, presumably *via* the enols, and dehydrate to form the bicyclics (**93**) as shown in Scheme 33. The synthesis ensures that R^1 and R^2 are *cis*.[269]



(**86**) (**87**)

i, (**88**); ii, cyclization, hydrolysis, $-CO_2$, deacetalize, cyclize.

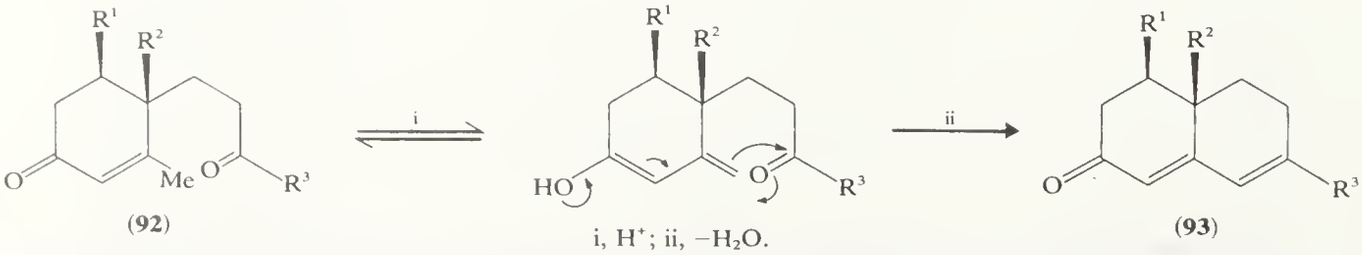
SCHEME 31[190]



(**89**) (**91**) (**90**)

i, $SnCl_4$ or *p*-TsOH.

SCHEME 32[268]



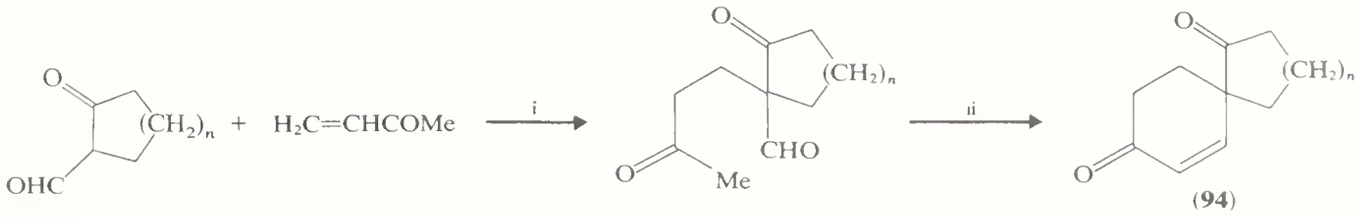
(**92**) (**93**)

i, H^+; ii, $-H_2O$.

SCHEME 33[269]

5.2.9.3 Spiroannelations

When an α-hydroxymethylene (*i.e.* α-formyl) cycloalkanone is used as the Michael donor in a Robinson annelation, the 5-keto aldehyde cyclizes more readily than the



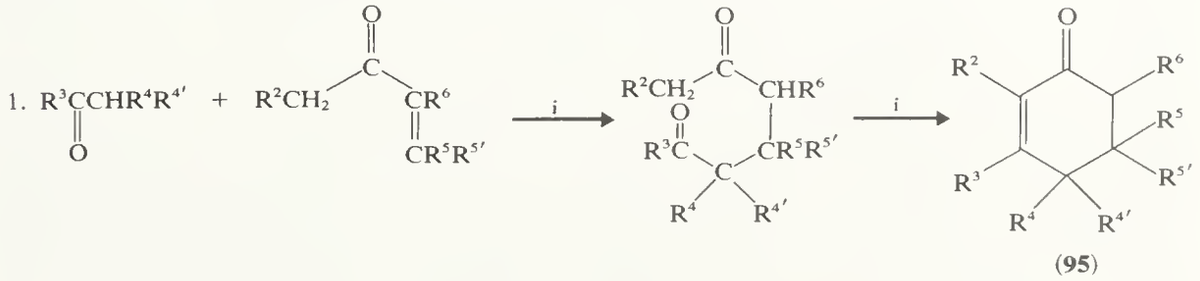
i, base; ii, base or acid.

SCHEME 34[270]

1,5-diketone system to give a spiro-annulated cyclohexenone (**94**) as the major product[270] (Scheme 34). Relatively weakly activated formylcycloalkanes react similarly if 1,5-diazabicyclo[5,4,0]undec-5-ene is used to catalyse the Michael addition.[271] For other spiroannelations, see Section 11.15.3, and Refs. 238 and 239.

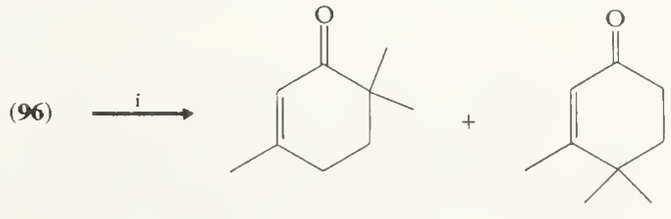
5.2.9.4 Formation of cyclohexenones

Many monocyclic cyclohexenones have been made by successive Michael and aldol reactions, as in the Robinson annulation. The addition of alkyl methyl ketones to acraldehyde and crotonaldehyde gives 5-keto aldehydes, and involves the more substituted α-position of the ketone.[272] More vigorous alkali treatment gives aldol attack by the acetyl's methyl group on the aldehyde carbonyl group to form cyclohex-2-enones.[273] Similar reaction occurs between aldehydes or ketones which have an α-CH group and α,β-unsaturated ketones,[108,121] as shown in Scheme 35. The cyclohexenones (**95**) which are formed are shown with their precursors. A number of ambiguities are possible in these reactions. For example, isopropyl methyl ketone can give two enolate anions. In fact, the more substituted enolate adds to methyl vinyl ketone (as is generally found in Michael additions). The 1,5-diketone (**96**) which is formed initially can give three enolates, of which the two terminal isomers can cyclize to cyclohexenones. The major product forms by enolate attack on the less-hindered carbonyl group.[121,273,274] The Michael donor



2. $MeCOCHMe_2$ + $H_2C{=}CHCOMe$ —i→ $MeCOC(Me)_2CH_2CH_2COMe$

(**96**)



i, 2–3.5M NaOMe or KOMe in MeOH.

SCHEME 35

component in these syntheses can advantageously be replaced by the enamine of the aldehyde or ketone,[251,275] and the use of enamines derived from esters or amides of L-proline allows asymmetric syntheses.[276]

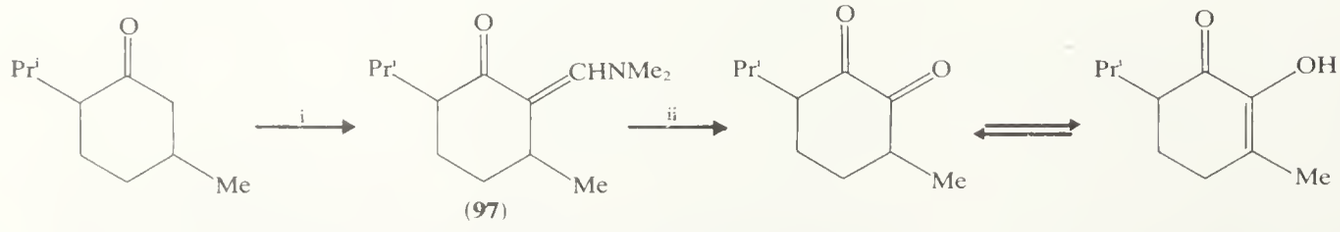
Diels–Alder addition of 2-chloroacryloyl chloride to dienes gives 1-chlorocyclo-hex-3-ene-1-carbonyl chlorides which are transformed into cyclohex-3-enones under very mild conditions. Similar addition of 2-chloroacrylonitrile[277] or 2-acetoxyacrylonitrile, and hydrolysis gives the 3-enones[278] which are isomerized to cyclohex-2-enones if they have a 2-proton. Intramolecular acylation of olefinic carboxylic acids by heating with strong acids gives cyclopent-2-enones or cyclohex-2-enones, but the use of low temperatures allows isolation of 2-alkylidenecycloalkanones.[279]

5.2.10 DIKETONES

5.2.10.1 1,2-Diketones (α-diketones)

Many cyclic and acyclic aliphatic α-diketones are available by oxidation of α-hydroxy ketones (Section 5.2.11.1), usually with cupric acetate,[280] or less often with chromium(III) oxide,[280] or bismuth trioxide.[281] A simple route from non-terminal acyclic olefins or from cyclic olefins uses their oxidation by permanganate in acetic anhydride; the diketone must not have its carbonyl groups constrained *cis*. Thus, cyclo-octene is the smallest cycloalkene to be oxidized satisfactorily (in 25% yield). An α-acetoxy ketone is often also formed, but can be hydrolysed to the α-hydroxy ketone and oxidized to the diketone.[282] Cyclic α-bromo ketones and aryl α-bromoalkyl ketones are readily oxidized to α-diketones by treatment with DMSO, using iodide ion catalysis.[283] The nitrate esters of α-ketols are available from α-bromo ketones and silver nitrate and decompose easily *in situ*, in DMSO with acetate ion catalysis, to α-diketones and nitrite ion.[284] The method can succeed with hindered α-bromo ketones for which the preceding method fails.[283] The bistrimethylsilyl ethers of enediols, which are produced in the modern variant of the acyloin condensation (Section 5.2.11.1) are oxidized directly to the corresponding (constitutionally symmetrical) α-diketones by bromine in aprotic solvents. This method avoids the need to isolate the α-ketol (acyloin), and is best for preparing non-enolizable diketones.[285] An excellent new route from cyclic and acyclic methylene ketones uses their reaction with t-butoxybis(dimethylamino)methane to form an α-enamino ketone (**97**), which is cleanly cleaved by photosensitized (singlet oxygen) oxidation to give the α-diketone, as shown in Scheme 36. The enamine formation should follow the direction of Mannich base formation (see Section 5.2.7); thus a 5α-H 3-keto steroid forms the enamine and then ketone function at C-2.[286] Non-terminal acetylenes[287] and 1,2-diols[288] are oxidized to α-diketones by ruthenium tetroxide, which can be prepared *in situ*.[287] Selenium dioxide has been used classically to oxidize ketones to α-diketones, and methyl ketones to α-keto aldehydes, but the yields are often poor; other reactions are possible and it is often difficult to purify the products; see Section 5.2.13.1.

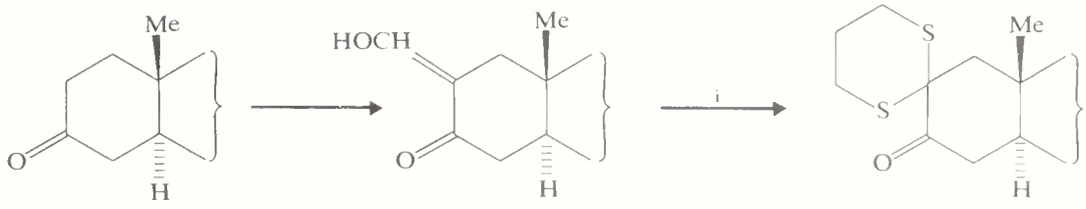
Partially protected α-diketones have great value in synthesis, and are now easily available. The α-trimethylenedithio ketones (2-ketodithians) (**98a**) and (**98b**) are made (see Scheme 37) by reaction of α-hydroxymethylene ketones,[116,289] or enamines derived



i, $(Me_2N)_2CHOBu^t$; ii, singlet O_2.

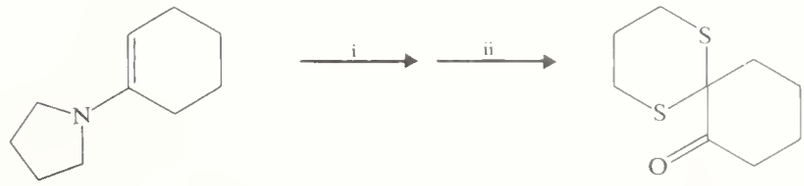
SCHEME 36[286]

1.



(**98a**)

2.

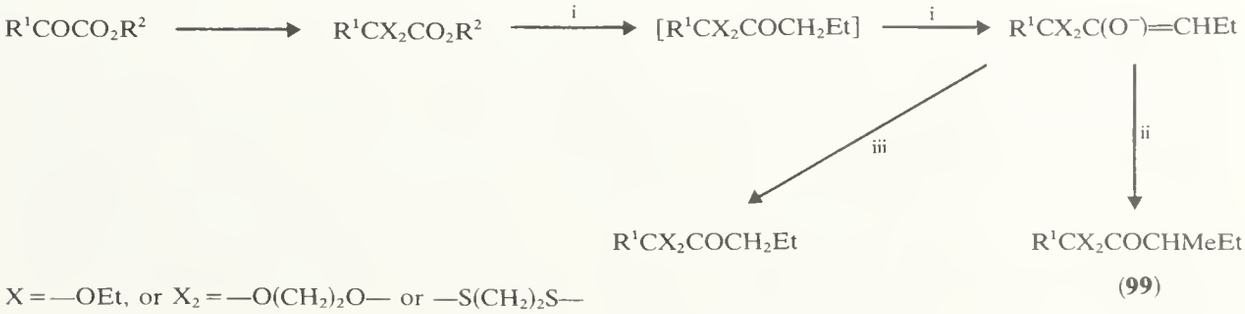


(**98b**)

i, $TsS(CH_2)_3STs$ + NEt_3 or $MeCO_2K$; ii, aq. HCl.

SCHEME 37

from ketones, or α-acetoxymethylene- or α-dialkylaminomethylene-ketones[290] with trimethylenedithiotosylate and a base. The enamine products have to be hydrolyzed. Acylic 2-acyl-1,3-dithians are available by acylation of 2-lithio-2-alkyldithians using acyl chlorides or carboxylate esters (see Section 5.2.2).[18,19] The dithian group is easily converted into a carbonyl group in these systems by oxidative cleavage using *N*-bromo- or *N*-chloro-succinimide, especially in the presence of silver ions,[18] or by methylation in aqueous organic solvents.[290] These routes therefore also represent syntheses of α-diketones. The acetals, ethylene acetals, or thioacetals of α-ketocarboxylate esters react with excess of many Grignard reagents to form the acetals of α-diketones; this method also allows an alkylation step to give further ramification, as in (**99**)[291] in Scheme 38. A similar ester to methyl ketone transformation used lithium dimethylcuprate to convert the diethyl acetal of ethyl 2-ketobutanoate into 3,3-diethoxypentan-2-one.[221]



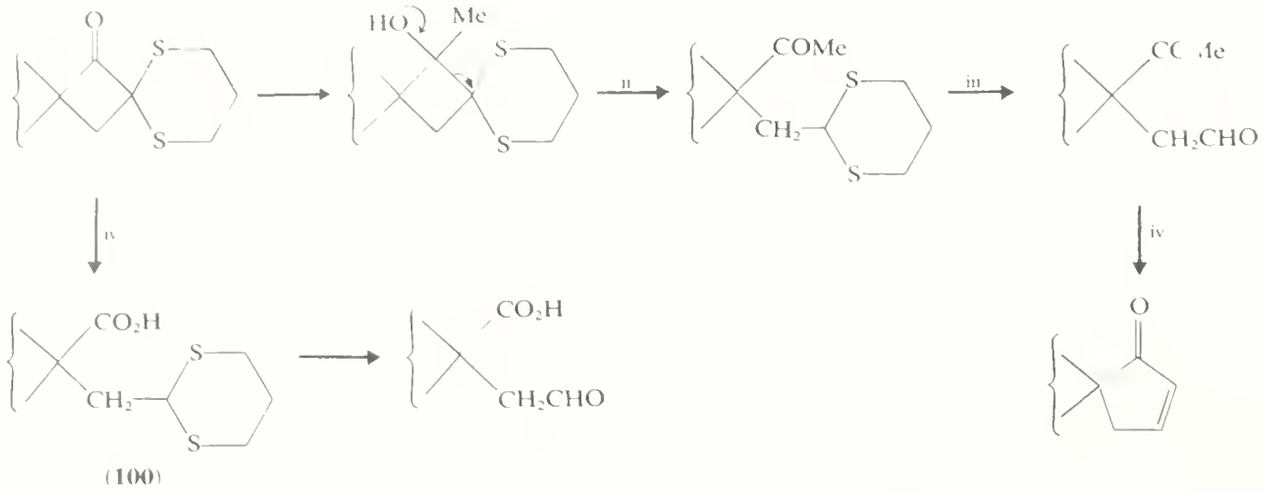
(**99**)

i, Pr^nMgCl; ii, MeI; iii, H_2O.

SCHEME 38

(*i*) *Reactions of 1,2-diketones*

α-Diketones are useful as precursors of acyclic and cyclic alkynes; their bishydrazones are oxidized by mercuric oxide[280] or lead tetra-acetate, or in the presence of oxygen catalysed by copper(I) chloride in pyridine,[292] and loss of nitrogen gas follows. They also react with *o*-phenylenediamines to form quinazolines. A major application is in ring cleavages, especially in the periodate or hydrogen peroxide oxidation of cyclohexane-1,2-diones to hexane-1,6-dioic acids which can be converted into cyclopentanones, for example in the syntheses of a steroid ring D.[117] An equivalent route is the ring opening by hydroxide ion of 2,2-trimethyleneditioncycloalkanones — see (**100**) in Scheme 39 — to ω-trimethylenedithioalkanoic acids. The latter are converted into ω-aldehydo acids.[289,290] Other related valuable transformations are possible.[290]



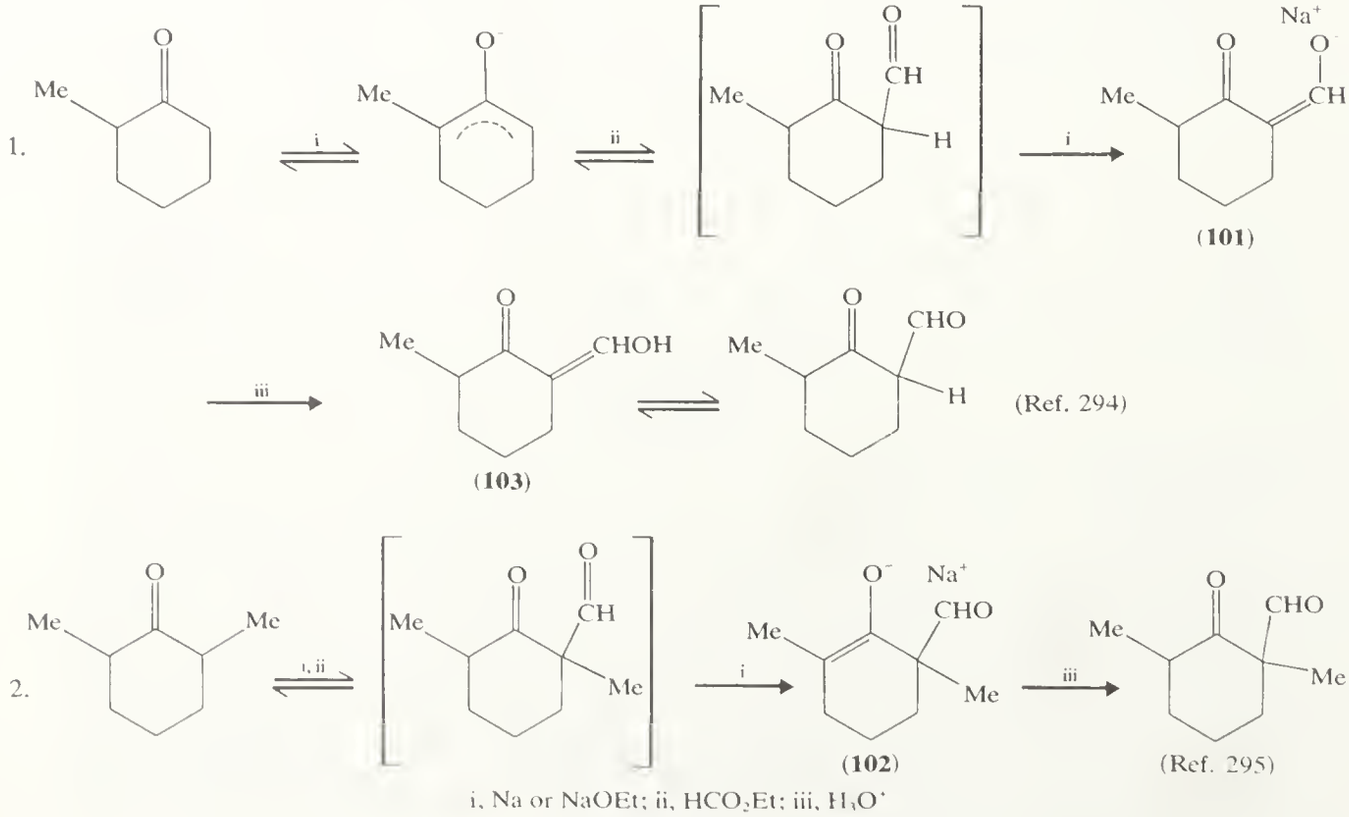
(**100**)

i, MeLi; ii, MeO^-; iii, MeI, aq. MeCN; iv, OH^-.

SCHEME 39

5.2.10.2 1,3-Diketones (β-diketones)

The Claisen condensation is widely used to prepare β-diketones from enolizable ketones and carboxylate esters. In the presence of a basic condensing agent (*e.g.* Na, NaOEt, NaH, $NaNH_2$) the enolate anion of the ketone is acylated, and the sequence of equilibria shown in Scheme 40 is displaced by formation of the anion of the β-diketone, or by distilling off ethanol. For reviews, see Refs. 36 and 293; the latter lists many examples. The related acylation of preformed enolates using acid chlorides or anhydrides is discussed in Section 5.2.4. Acylation occurs readily at α-methyl or methylene groups, but only rarely at methine, presumably because of the greater stability of enolates of the type (**101**) compared with (**102**) and the reversibility of the reaction.



(**101**)

(**103**)

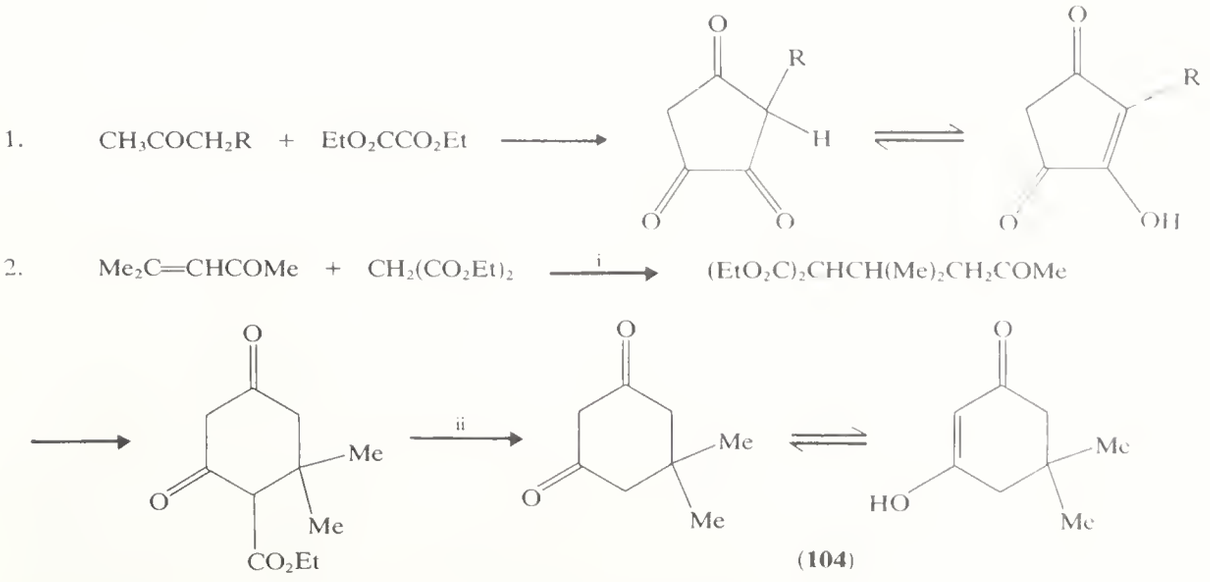
(Ref. 294)

(**102**)

(Ref. 295)

i, Na or NaOEt; ii, HCO_2Et; iii, H_3O^+

SCHEME 40

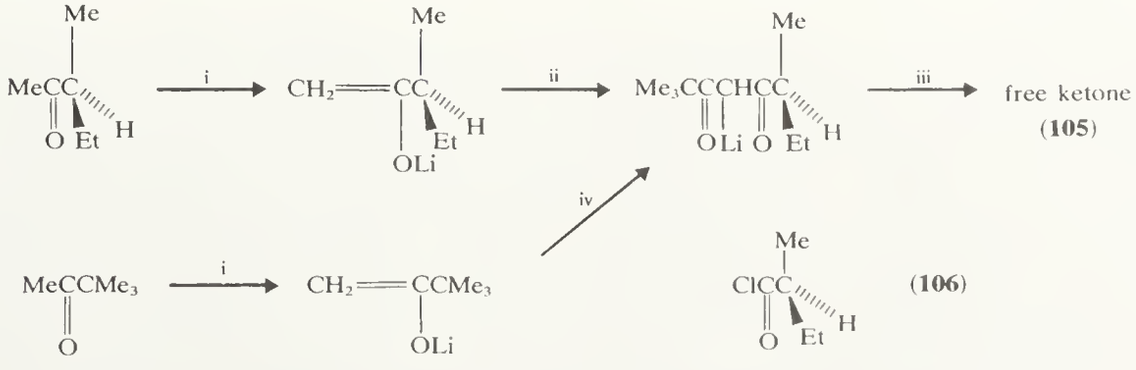


i, base; ii, hydrolysis; $-CO_2$.

SCHEME 41

Methyl alkyl ketones are aeylated predominantly or exelusively at the α-methyl group, but formate esters reaet preferentially with the methyl group of some ketones and the methylene of others. The produets from formates are β-keto aldehydes which exist predominantly in their enolic, α-hydroxymethylene forms, *e.g.* (**103**). These, and the α-alkoxyoxalyl ketones obtained by eondensation with dialkyl oxalates, are used in directing α-alkylation — or, indirectly, α'-alkylation — of ketones (Section 5.2.5). Diethyl carbonate introduees an α-ethoxyearbonyl group, to form a β-keto ester. Reaetions with oxalate esters can involve a 2 : 1, 1 : 2, or 1 : 1 ratio of ketone to ester; the monoaeylation products can cyclize (see Scheme 41) to form (enolie) cyclopentane-1,2,4-triones.[293,296] Both 5α- and 5β-3-keto steroids and Δ^4-3-keto steroids, and their bieyelie analogues, react with formate and oxalate esters to form the 2-acyl ketones. These are the thermodynamically controlled products whieh lack the sterie interferenee with the 6- or 4-positions suffered by the 4- or 6-acyl ketones.[36,56] Intramoleeular eyclizations of 4-, 5-, 6-, and 7-keto esters give, respectively, eyelopentane-1,3-diones, eyclohexane-1,3-diones, 2-aeylcyclopentanones, and 2-acylcyclohexanones. The 5-keto esters are easily obtained by Michael addition of β-diearbonyl eompounds to α,β-unsaturated esters[293] or of malonie esters (for example) to α,β-unsaturated ketones,[250] and eyelization follows (see Scheme 41) under alkaline eonditions, *e.g.* to dimedone (**104**).

Pre-formed stable lithium enolates have been made from ehiral ketones and lithium di-isopropylamide at low temperatures, as shown in Seheme 42. Acylation with half an



i, $LiNPr^i_2$, toluene, THF; ii, 0.5 equiv. Me_3CCOCl;
iii, H_3O^+; iv, 0.5 equiv. compound (**106**).

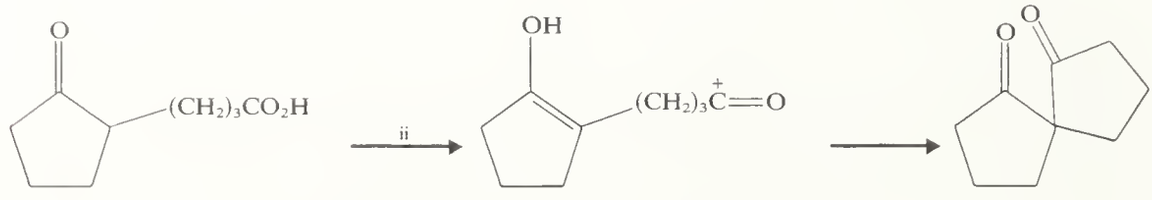
SCHEME 42

equivalent of an acid chloride gives the chiral β-diketones (**105**), as their lithium salts, with excellent optical purity and no detectable *O*- or *C*-acylation.[61] Enol esters can be converted by treatment with acids or bases, or by heating or u.v. irradiation, into their β-dicarbonyl isomers.[36,297] Enamines are acylated efficiently and regiospecifically by acyl chlorides and anhydrides, preferably in the presence of a tertiary amine.[36,251]

Acid-catalysed analogues of the Claisen condensation are common and valuable. The ketone and an acid anhydride react in the presence of a proton or Lewis acid, usually boron trifluoride. A complex of the enol form of the ketone, or an enol ester, is assumed to be acylated to give a difluoroboron complex of the β-diketone, which is released by treatment with aqueous sodium acetate. Methyl, methylene, and, less commonly, methine groups can be acylated. Methyl alkyl ketones acylate at either α-carbon, depending on the particular ketone and the reaction conditions. If toluene-*p*-sulphonic acid is added as an enolization catalyst, and the boron trifluoride is introduced slowly, the methylene group, *i.e.* the more stable enol, can be acylated with good selectivity in many cases; see (**107**) → (**108**) in Scheme 43. Because the 'wrong' isomer can usually be extracted out into alkali, this offers a good route to different β-diketone isomers from those formed under basic conditions.[36,293] The example of the dispiro-β-diketone (**109**) in Scheme 43 is of interest because it involves condensation at a methine group and uses very convenient reagents.[298]

1. $MeCOCH_2Bu^n + (MeCO)_2O \xrightarrow{i} MeCOCH(Bu^n)COMe$

(**107**) (**108**)

2. 

(**109**)

i, $BF_3 + H^+$; ii, polyphosphoric acid + CH_3CO_2H.

SCHEME 43

The boron trifluoride catalysed *C*-acetylations of a number of steroidal ketones, α,β-unsaturated ketones, and 2-methylcyclohexanone and their enol acetates have been studied in detail.[297] Cyclohexane-1,3-dione is formed by hydrogenation of resorcinol in aqueous alkali.[299,300] For a reliable route to 2-alkylcyclopentane-1,3-diones and -1,3,4-triones, see Ref. 301.

(*i*) *Reactions*

The major reaction of β-diketones is their mono- or di-alkylation at C_α *via* the enolate ion.[36] Alkyl halides are usually employed and, because the normal order of reactivity is followed, iodides are preferred to bromides. Dialkyl sulphates can be used for methylation and ethylation, and alkyl toluene-*p*-sulphonates for alkylation with higher alkyl groups; the more reactive trialkyloxonium fluoroborates have also been used. Alcohols are often used as solvents, but dipolar aprotic solvents, especially DMSO, allow very fast reactions.[36,302] Clean α-alkylation of many β-diketones is achieved using methyl or other reactive iodides, with potassium carbonate as the base and acetone as the solvent. Alkali metal alkoxides or hydroxides are the usual alternative bases.[250,299,303] If one, or more than one, equivalent of base is used, some dialkylation can occur, and the use of excess of potassium carbonate and alkyl halide gives excellent yields of α,α-dialkyl products. Two different groups can be introduced in sequential reactions.[304] The alkylation of cyclohexane-1,3-dione has been particularly closely studied, and the influence of the many relevant factors has been summarized.[300]

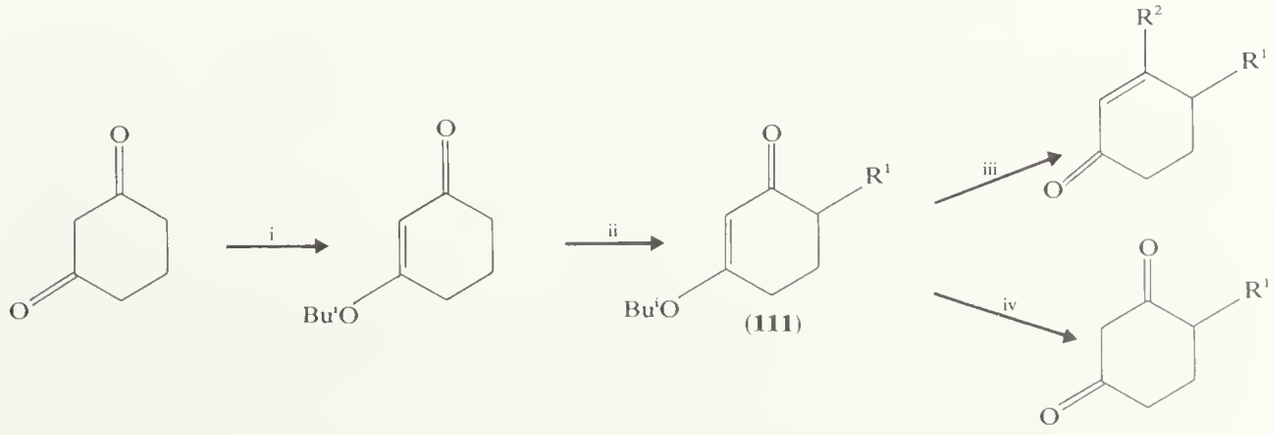
Alkylation can occur at an oxygen atom, to form a monoenol ether, the ratio of *C*- to *O*-alkylation products varying with the size and nature of the alkyl group, with the halide or other leaving group, with the metal cation associated with the enolate, and with the solvent polarity.[36] The enol ethers can often be removed by acid hydrolysis at room temperature, but the separation of unalkylated from mono- and di-alkylated diketones can be difficult. Clean, almost quantitative monoalkylation or, by repetition of the process, dialkylation of *acyclic* β-diketones is achieved by heating their easily prepared monothallium(I) salts in the neat alkyl iodide or bromide.[305] However, similar reaction of the thallium(I) salts of cyclopentane-1,3-dione and cyclohexane-1,3-diones gives almost entirely *O*-alkylation,[306] and 2-hydroxymethylenecyclohexanone, *i.e.* 2-formylcyclohexanone, gives a mixture of *C*- and *O*-ethylation.[307] Acylation can be directed specifically to give the mono enol acetate (using acetyl chloride at −78 °C) or the α-acetyl product, a triacylmethane (using acetyl fluoride at room temperature).[305] Tertiary alkyl groups cannot be introduced under basic conditions, because the tertiary halides or sulphonates suffer elimination. Acid-induced alkylation does succeed, using an olefin (isobutene) and perchloric acid to form a tertiary carbenium ion which attacks the enol of acetylacetone to give 3-t-butylpentane-2,4-dione.[308]

Alkylation at the γ-carbon atom of β-dicarbonyl compounds is achieved *via* the α,γ-dienolate, which is traditionally made using two or more equivalents of potassamide in liquid ammonia.[115,309] This dianion attacks electrophiles specifically at its highly basic and nucleophilic γ-carbon, allowing alkylation, carboxylation, acylation, aldol additions, and Michael additions at this centre. Dianion formation from constitutionally unsymmetrical β-diketones occurs preferentially under kinetic control at the α- and the less alkylated γ-carbon; sodium enolates are less prone to isomerization than the potassium counterparts.[115,309] The dianions also react with dihlaides, ranging from iodine, dibromomethane, and 1,2-dibromoethane to longer-chain α,ω-dihaloalkanes, with copper(I) salt catalysis, to form coupled tetraketones (**110**)[310] (equation 16). The trianions of

$$2RCOCH(Na)COCH_2Li + Hal(CH_2)_nHal \xrightarrow{i} \xrightarrow{ii} \underset{(\mathbf{110})}{RCOCH_2COCH_2(CH_2)_nCH_2COCH_2COR} \quad (16)$$

i, Cu(I) chloride; ii, H_3O^+.

2,4,6-triketones are accessible when lithium di-isopropylamide is used as base in THF; carboxylation allows the preparation of 3,5,7-triketo acids which are of interest in the biosynthesis of phenolic natural products.[309] The monoenol ethers of cyclohexane-1,3-diones are ionized by lithium di-isopropylamide, and alkylated to form the synthetically valuable compounds (**111**); this is a formal synthesis of the 4-alkyl-1,3-diketones[79] and is outlined in Scheme 44.

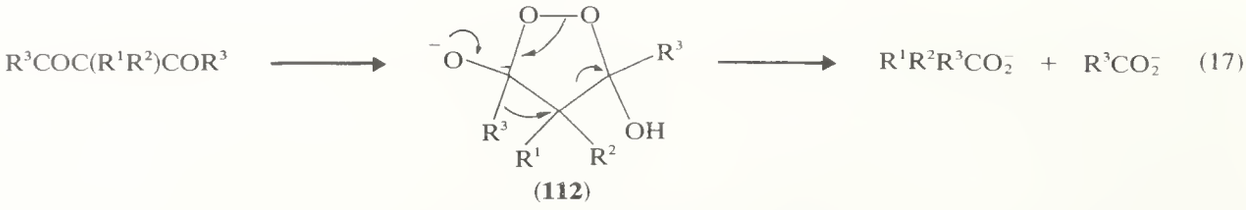


i, $Bu^tOH + TsOH$; ii, $LiNPr^i_2$, then R^1I + HMPT: iii, see Section 5.2.5; iv, H_3O^+.
R = allyl, Pr^n, Pr^i.

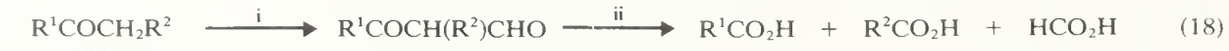
SCHEME 44[79]

(ii) Cleavage of β-diketones

Aqueous periodate[311] or alkaline hydrogen peroxide[303] cleaves 1,3-diketones which are unsubstituted at C-2 to give formic acid from C-2 and carboxylic acids which incorporate C-1 and C-3. The 2-alkyl diketones give the C-2 alkanoic acid instead of formic acid. Alkaline peroxides give an oxidative rearrangement of acyclic 2,2-dialkyl-1,3-diketones, *via* the intermediate (**112**) in equation (17). 2-Alkyl analogues give some rearrangement of this type.[303] Periodate cleavage of α-hydroxymethylene ketones (β-keto aldehydes) is similar, and allows a route for regiospecific cleavage of monoketones; see (**113**)[312] in equation (18). Base-induced cleavages are well known. The α,α-disubstituted β-diketones cannot form a stabilizing α-enolate and readily undergo a retro-Claisen reaction upon treatment with metal alkoxides, alcohols, or aqueous alkali, to form an acid or ester and a ketone. Constitutionally unsymmetrical diketones form the ketone which has the more stable enolate anion. Cleavage of α-monoalkyl diketones requires prolonged treatment with hydroxide or alkoxide bases, but potassium carbonate in ethanol can suffice.[313] The cleavage of 2-substituted cyclohexane-1,3-diones offers a valuable route to 6-substituted 5-ketohexanoic acids, and has been reviewed.[300] The alkylation of acetylacetone, followed by alkaline cleavage, represents a synthetic route to alkylated acetones equivalent to the acetoacetic ester route, but free of competing cleavage to alkylacetic acids.[313]



(**112**)

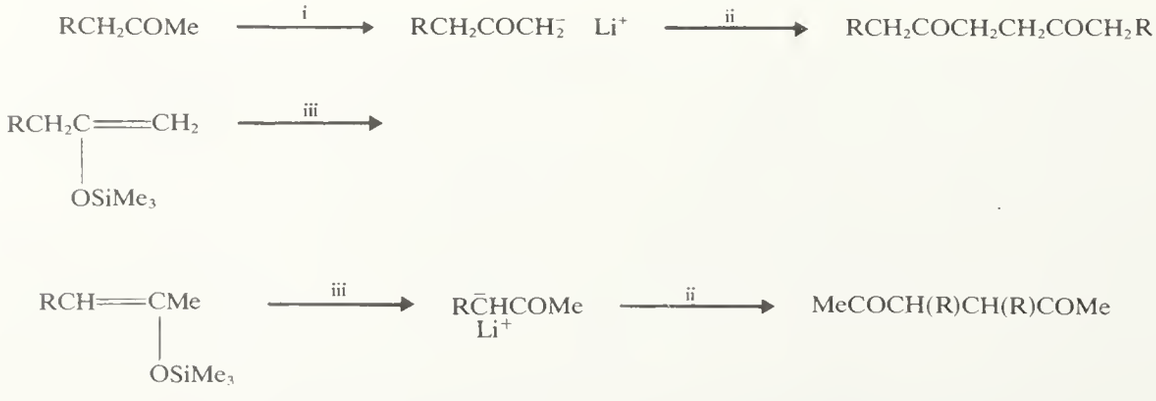


(**113**)

i, HCO_2Me, MeO^-; ii, $NaIO_4$, aq. MeOH.[312]

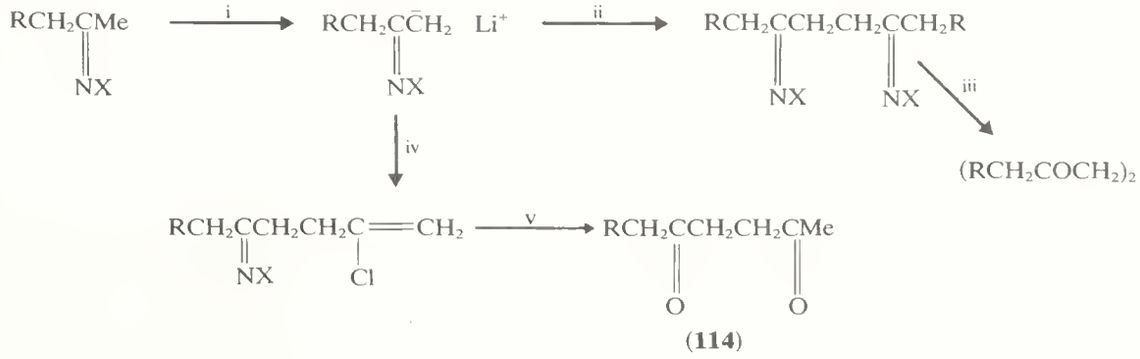
5.2.10.3 1,4-Diketones (γ-diketones)

A number of preparations of constitutionally symmetrical 1,4-diketones are based on the dimerization of monoketones through their α-carbon atoms. A series of alkyl isopropyl ketones, $RCOCHMe_2$ (R = Me, Pr^i, Bu^t) dimerize upon treatment with acetyl peroxide to give $RCOC(Me)_2C(Me)_2COR$, *via* the α-radicals.[314] More generally, the lithium enolates of ketones are coupled using cupric chloride; see Scheme 45. The 1-enolates of alkan-2-ones, made using lithium di-isopropylamide, or the regiospecifically generated enolates produced from trimethylsilyl enol ethers and methyl-lithium, have



i, $LiNPr^i_2$, THF, −78 °C; ii, Cu_2Cl_2, DMF; iii, MeLi.[315]

SCHEME 45

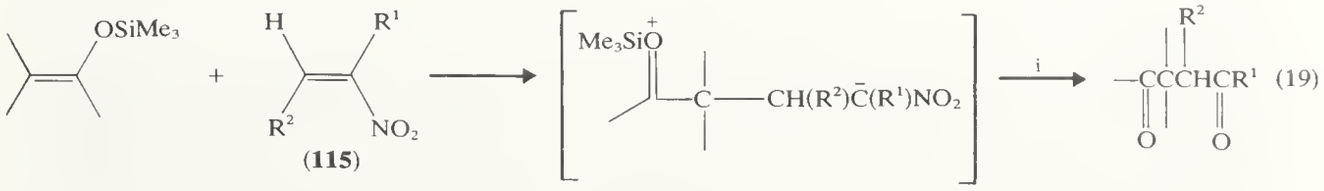


i, Bu^nLi or Et_2NLi; ii, I_2; iii, aq. $NaIO_4$ for $X = NMe_2$;[179] iv, $CH_2{=}C(Cl)CH_2Cl$; v, aq. H_2SO_4 for X = cyclohexyl.[65]

SCHEME 46

been used.[315] The α-lithio-*N*,*N*-dimethylhydrazones of ketones, acting as enolate equivalents (see Section 5.2.7.1), are coupled using iodine, and the 1,4-diketones are released by periodate,[179] as shown in Scheme 46. The closely related terminal lithio derivatives of the *N*-cyclohexylimines of alkyl methyl ketones react with 2,3-dichloropropene under iodide ion catalysis to form, after hydrolysis, alkyl 3-halobut-3-enyl ketones. Sulphuric acid hydrolysis of the vinylic chloride function liberates the constitutionally unsymmetrical 1,4-diketone (**114**).[65]

Conjugate addition to α,β-unsaturated ketones of the lithium diorganocuprate reagents derived from 1-lithio-1-alkoxyalkenes gives adducts which, upon acid hydrolysis of their enol ether function, yield β-acyl ketones, *i.e.* 1,4-diketones; see Section 5.2.8.[216,217] The anions of nitroalkanes, $R\bar{C}HNO_2$ can act as masked acyl anions, RCO^-. Michael addition of such anions to methyl vinyl ketone gives 4-nitro ketones, $RCH(NO_2)CH_2CH_2COCH_3$, which are cleanly reduced — presumably to imines — and hydrolysed by aqueous titanium(III) chloride to the 1,4-diketones, $RCOCH_2CH_2COCH_3$.[316] In a complementary process outlined in equation (19), a nitroalkene (**115**) reacts with a trimethylsilyl ether

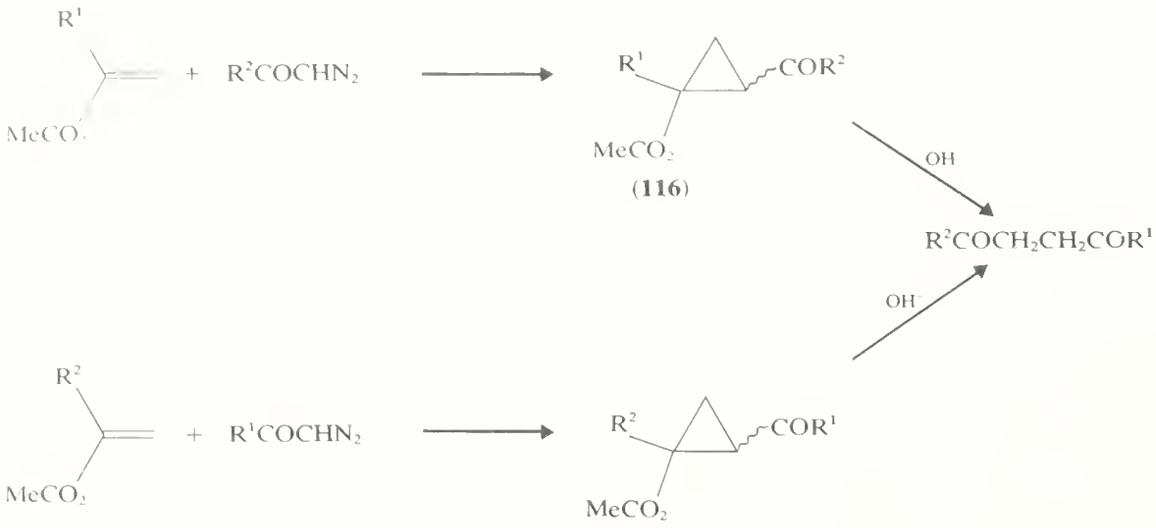


(19)

i, aq. $TiCl_3$.[317]

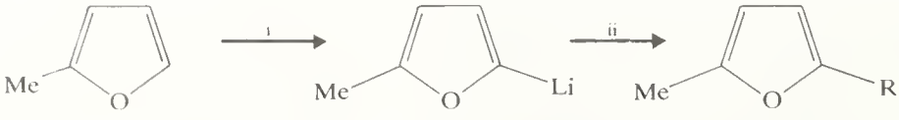
under Lewis acid catalysis to give a 4-nitro ketone derivative which is converted into the diketone by boiling with water.[317] Aliphatic and alicyclic ketones can have an acetonyl, *i.e.* 2-ketopropyl, group introduced at an α-CH centre by reaction with isopropenyl acetate and manganese(III) acetate. Constitutionally unsymmetrical ketones react more readily, but not exclusively, at the less-substituted α-carbon. Although yields are only moderate (20–35%), the method is very simple.[318]

A further class of preparation uses the hydrolysis and retro-aldol cleavage of 1-acyl-2-acyloxycyclopropanes (**116**), as shown in Scheme 47. These precursors are available from the addition of α-ketocarbenes (from α-diazo ketones) to the olefinic group of enol acetates, with copper acetylacetonate as the best catalyst. Under the alkaline conditions used, the diketone cyclized to a cyclopentenone.[319] Similar addition of α-ketocarbenes to trimethylsilyl enol ethers is assumed to give analogous 1-acyl-2-trimethylsilyloxycyclopropanes which open and hydrolyse to give the 1,4-diketones.[66] Many 1,4-diketones are available from mild acidic hydrolysis of furans (equation 20). Simple furans are readily lithiated and then alkylated at C-2, and can be converted directly into the diketones[320,321]



SCHEME 47

or their bisethylene acetals.[321] Oxidation of 4-hydroxy ketones allows versatile syntheses; chromic acid (Jones' reagent) can be used,[322] but pyridinium chlorochromate is particularly recommended.[179] A wide range of 4,6-disubstituted pentane-2,5-diones is available from standard reactions of α-chloro ketones with sodio ethylacetoacetate.[323] For a specific route to 2-hydroxy-1,4-diketones, by aldol coupling of α-keto aldehydes with sodium acetoacetate, see Ref. 324; for other routes, see Ref. 325.

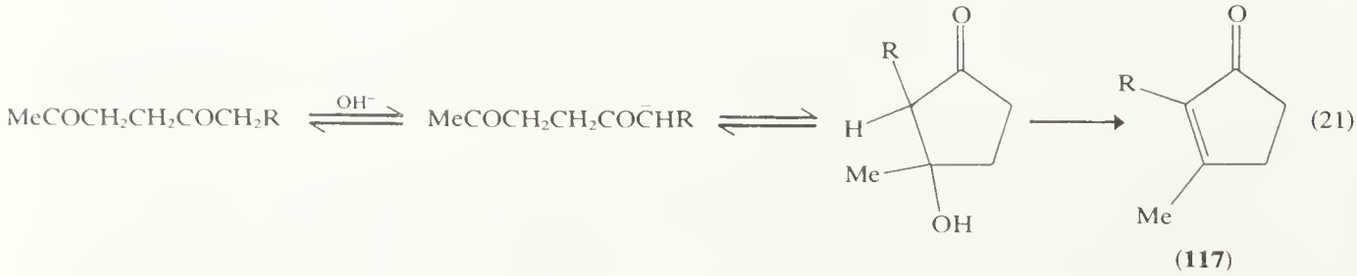


(20)

i, BuLi, THF; ii, RBr; iii, dil. H_3O^+.

(*i*) *Reactions*

The main reaction of 1,4-diketones is their cyclization to cyclopentenones (*via* aldol condensation and dehydration) under mild basic conditions. The more alkylated methylene group at C-5 attacks the less-hindered carbonyl group at C-1 to form a 2-alkylcyclopent-2-enone; C-2 and C-3 of the diketone can be mono- or di-substituted.[326] Many of these reactions have been used (equation 21) to make *cis*-jasmone (**117**; R = $CH_2CH{=}CHEt$)[316,319,320] and its side-chain dehydro[316,319] and dihydro[65,318] analogues.



(21)

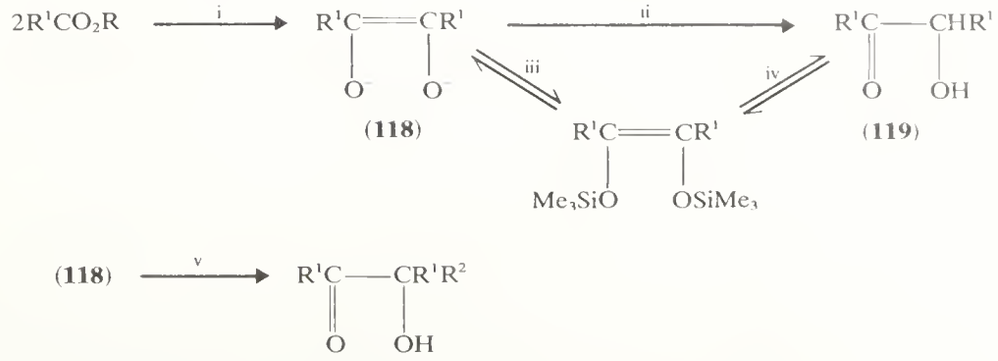
(**117**)

The cyclopentenone function is central in prostaglandin[268] and pyrethrenoid[324,327] syntheses. Reaction of 1,4-diketones with hydrogen sulphide gives 2,5-disubstituted thiophens,[323] ammonia derivatives give pyrroles, and direct dehydration gives furans by the Paal–Knorr reactions. Excellent results in the furan synthesis are given by slow distillation from a sulphonic acid ion-exchange resin.[328] For other reactions, see Ref. 325.

5.2.11 HYDROXY KETONES

5.2.11.1 2-Hydroxy ketones (α-hydroxy ketones; α-ketols)

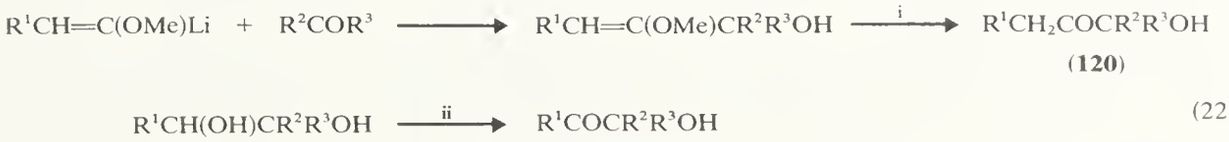
The most used route to symmetrical α-ketols, which can be cyclic or acyclic, is the acyloin condensation;[329] see Scheme 48. Two moles of a carboxylate ester, or one of a dicarboxylate ester, are reduced, usually by sodium or sodium–potassium alloys, to give an ene-diolate (**118**). Protonation gives the acyloin (α-ketol) (**119**). In a highly advantageous variant, trimethylchlorosilane is added during the reduction, to form the easily separated and purified bistrimethysilyl ether of the enediol. Aqueous acid or, preferably, oxygen-free ethanol, frees the ketol.



i, Na or K; ii, H_3O^+; iii, Me_3SiCl; iv, MeOH or H_3O^+; v, R^2Hal, then H_3O^+.

SCHEME 48

The reaction has been applied to aliphatic groups R^1 from methyl to C_{22}, and to α,ω-diesters to form 4–26-membered rings. Mixed condensations, to form constitutionally unsymmetrical ketols, are unsatisfactory.[329] Treatment of the bis-silyl ether with methyl-lithium re-forms the bisenolate (**118**), which can be alkylated in high yield to produce α-keto tertiary alcohols. These were reduced to α-diols and cleaved to the ketones R^1COR^2, thus using the acyloin as a masked acyl anion.[330] The addition of 2-alkyl-2-lithio-1,3-dithians to the carbonyl group of aldehydes and ketones (including α,β-unsaturated ketones) gives the dithians of α-ketols (for a review, see Ref. 17). Cleavage of the dithian ring by mercuric chloride and calcium carbonate, or by *N*-halosuccinimides in aqueous buffers, frees the ketols.[18,19,330a] The monothioacetals of α-diketones (Section 5.2.10.1) are reduced by lithium aluminium hydride to those of the α-ketols.[331] α-Methoxyvinyl-lithium adds to the carbonyl groups of aldehydes and ketones (equation 22)

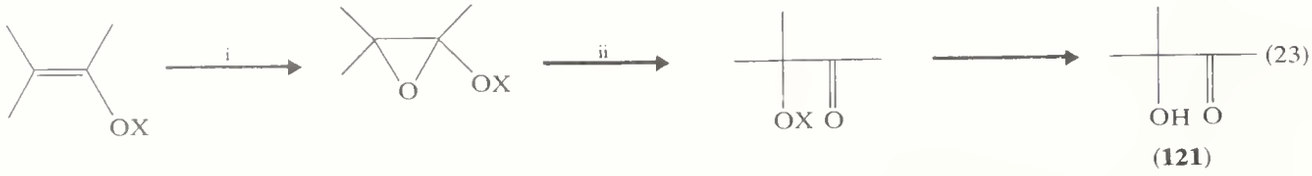


i, H_3O^+;[204] ii, see Ref. 333. (22)

including enones, giving adducts which are readily hydrolysed to α-ketols (**120**). Reaction with carboxylate esters, $R^2CO_2R^3$ leads to the 3-hydroxy-3-R^2-pentane-2,4-diones. Analogous transfers of masked propionyl and crotonyl anions can be effected,[204] and the method allows a dihydroxyacetone group to introduced at C-17 in steroids.[332]

Most oxidizing agents cleave 1,2-diols, but many secondary-tertiary diols can be oxidized by Corey's complexes of methyl alkyl sulphides or dimethyl sulphoxide with chlorine or *N*-chlorosuccinimide.[333] Enol trimethylsilyl ethers derived from cyclic or acyclic ketones (Section 5.2.4) are epoxidized by peroxy acid; aqueous acid or alkali gives a rearrangement and hydrolysis to the α-ketol, in a regiospecific manner; see (**121**)[334] in equation (23). A similar rearrangement occurs on pyrolysis of the epoxides of enol acetates, to form α-ketol acetates.[123,335,336] The formation of ketol acetates by acetate ion

attack on steroidal α-bromo ketones has been studied closely, and much older work corrected.[335] An α-halo ketone can often lead to an α′-acetoxy ketone, probably *via* an S_N2' displacement on the α′-enol.[56,337] Electrochemical reduction of branched α,α′-dibromo ketones in acetic acid can give α-ketol acetates.[338] This class of product can also often be obtained by direct reaction of ketones (*via* their enols) with lead tetra-acetate[339] or, in some cases, with thallium(III) acetate.[341,342] Better yields are obtained by treating the latter with an enamine derived from the ketone.[341] Dialkylacetylenes are oxidized to α-ketols in good yield by aqueous thallium(III) nitrate, further oxidation (to α-diketones) being relatively slow.[343] For a valuable new route from ketones, *via* their α-lithio-*N*,*N*-dimethylhydrazones, to α-methoxy or α-methoxy-α-methyl ketones, see Ref. 344.



(23)

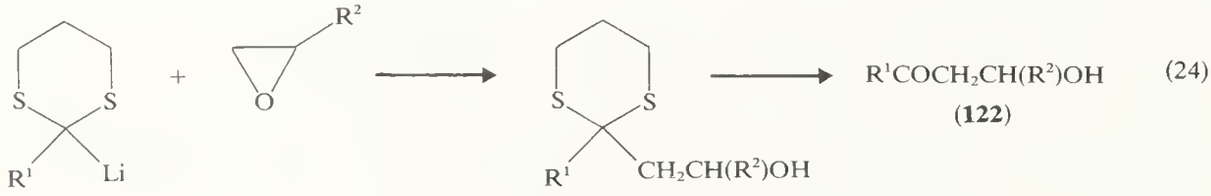
(121)

i, *m*-chloroperbenzoic acid; ii, for X = $SiMe_3$, H_3O^+ or $OH^- \rightarrow$ (**121**); for X = COMe, 160 °C.

α-Hydroperoxy ketones are formed by reaction with oxygen gas of α,α-dialkyl ketones in the presence of a tertiary alkoxide base in t-butanol solution, preferably with added DMF or other solvents. The hydroperoxide, derived from the α-enolate, can be reduced to an α-ketol by triethyl phosphite or zinc in acetic acid.[345] The α-ketols $MeCOC(R^1R^2)OH$ are formed by hydration of the adducts $HC{\equiv}CC(R^1R^2)Oh$ of lithium acetylide to R^1COR^2.[330a]

5.2.11.2 3-Hydroxy ketones (β-hydroxy ketones; β-ketols)

Very many β-ketols, and/or the olefinic ketones derived from them by facile acid- or base-catalysed dehydration, are made by aldol condensations (Section 5.2.7), and in annelation reactions (Section 5.2.9). Other routes of special value include the reaction of masked acyl anions 'RCO^-' with oxirans (epoxides); see (**122**)[19,207] in equation (24) and a review.[199]

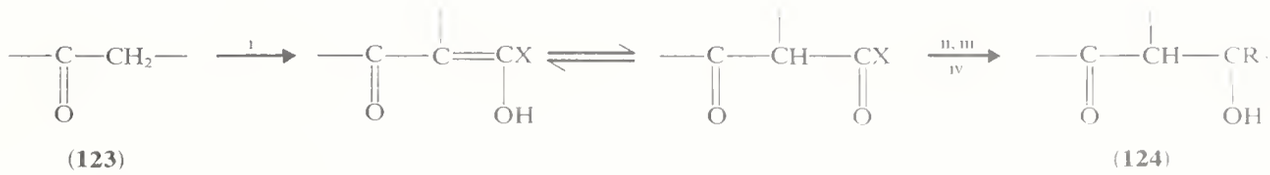


(24)

(122)

R = H, primary or secondary alkyl, allyl, benzyl.

The transformations (**123**) to (**124**) in Scheme 49 have been achieved by converting the ketone to a β-keto ester or α-hydroxymethylene derivative, followed by protection of the ketone function by enolate formation, and reaction with methyl-lithium[243] (to form a β-dimethyl ketol) or aluminium hydride (to form an α-hydroxymethyl ketone).[346] Constitutionally symmetrical secondary 1,3-diols are cleanly oxidized by Fetizon's silver carbonate on Celite reagent to the β-hydroxy ketones, but cyclohexane-1,3-diol gives some cyclohexenone as well. Primary-secondary 1,3-diols are oxidized preferentially at the secondary group, to form (terminal) β-hydroxy ketones, not hydroxy aldehydes. In a similar way, 1,2-diols lead to α-hydroxy ketones, and 1,4-diols give γ-hydroxy ketones; other diols were also studied.[347] Base-catalysed addition of alcohols to α,β-olefinic ketones, analogous to the Michael addition, sets up an equilibrium with the 3-alkoxy ketones. Cyclopent-2-enone does not add methanol; cyclohept-2-enone, cyclo-octenone



(123) (124)

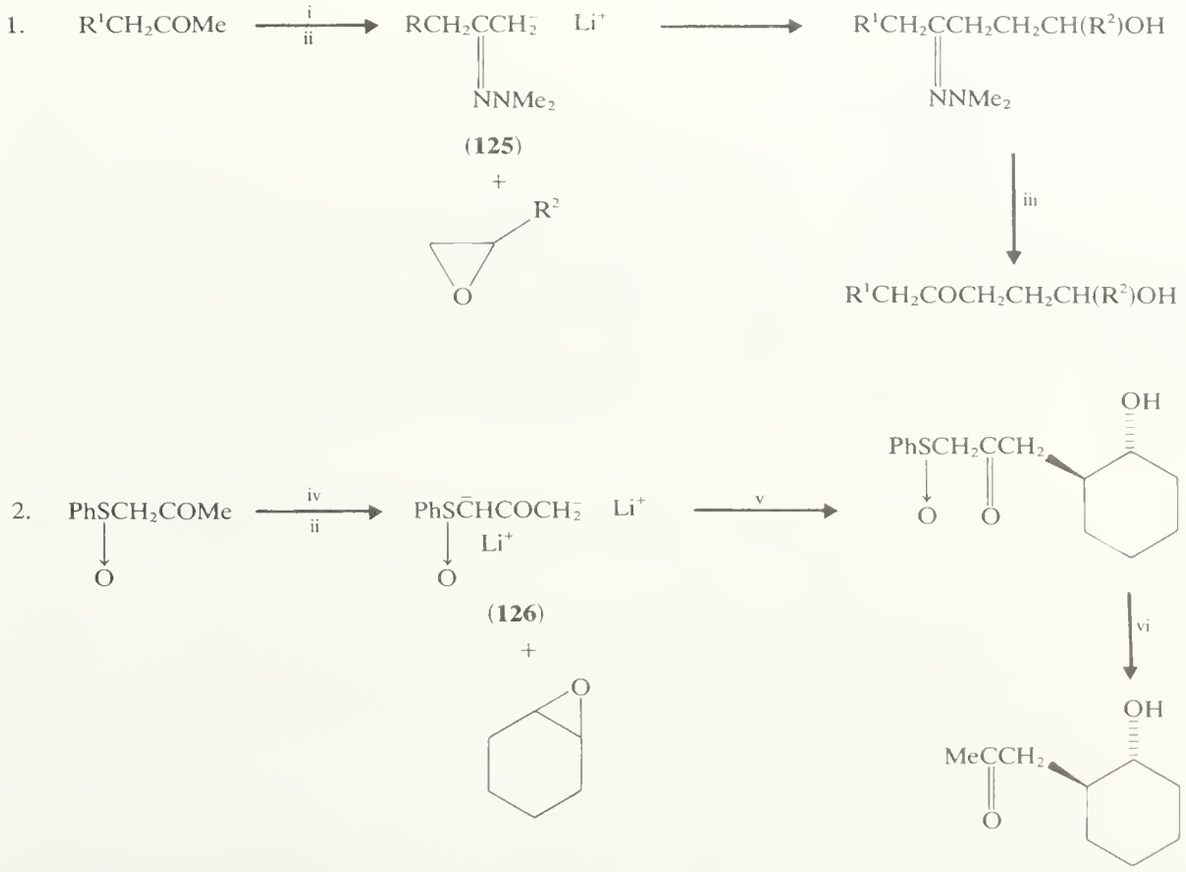
i, for X = OEt, $(EtO)_2CO$ + NaH; for X = H, HCO_2Et + NaH; ii, NaH; iii, for R = H, AlH_3; for R = Me, MeLi; iv, H_3O^+.[243,346]

SCHEME 49

and cyclononenone give predominantly the 3-methoxy ketones, and cyclohex-2-enone and 3-methoxycyclohexanone are in a ratio close to unity.[348] For studies of the kinetics of these additions to cyclic enones, see Refs. 348 and 349, and for acyclic enones, see Ref. 350.

5.2.11.3 4-Hydroxy ketones (γ-hydroxy ketones; γ-ketols)

Masked forms of enolate anions react with oxirans (epoxides) to form masked γ-ketols. Recent examples include the use of α-lithio-*N*,*N*-dimethylhydrazone derivatives of ketones (**125**),[179] and the dianions of β-keto sulphoxides (**126**),[322] as indicated in Scheme 50. In a related reaction, masked acyl anions react with oxetans to give masked γ-ketols, but there have been few examples so far.[19] See Ref. 347 for the oxidation of 1,4-diols to γ-ketols.



i, H_2NNMe_2; ii, Bu^nLi; iii, aq. $NaIO_4$; iv, NaH; v, add, then H_2O; vi, Al/Hg in aq. THF.[179,322]

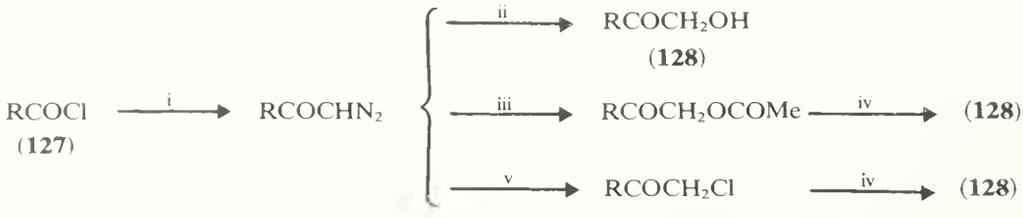
SCHEME 50

5.2.11.4 Polyhydroxy ketones

The aliphatic polyhydroxy ketones are represented by ketose carbohydrates, the simplest member being dihydroxyacetone (1,3-dihydroxypropan-2-one). The standard nomenclature uses the suffix '-ulose', $HOCH_2COCH(OH)CH_2OH$ being a 'threulose' or 'erythrulose'. The chemistry of ketoses (keto sugars) is discussed in the carbohydrate literature, *e.g.* Ref. 351. Many 2-ketoses are made by standard α-ketol syntheses; see, for example, (**127**) → (**128**) in Scheme 51. The α-ketol rearrangement (Lobry de Bruyn–Alberda van Ekenstein reaction) interconverts aldoses and ketoses,

$$HC(=O)—CH(OH)— \rightleftharpoons HOCH_2C(=O)—,$$

under alkaline or, less readily, acidic conditions. Examples of its use in synthesizing ketoses are given in Ref. 351. Many ketoses are available by aldol addition of the carbanion of dihydroxyacetone to aldehydes or aldoses.



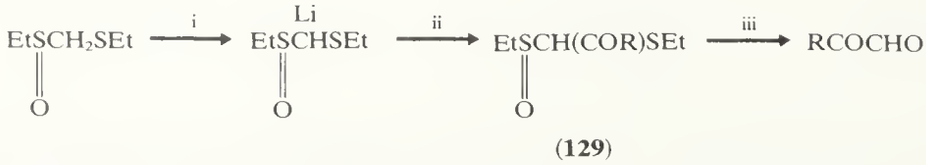
i, CH_2N_2; ii, H_3O^+; iii, HOAc + $Cu(OAc)_2$ catalyst; iv, hydrolysis; v, HCl gas.

SCHEME 51

5.2.12 KETO ALDEHYDES

5.2.12.1 2-Keto aldehydes (α-keto aldehydes)

Some preparations of α-keto aldehydes are similar to those of α-diketones (Section 5.2.10.1). These include the Kornblum reaction of α-halomethyl ketones, $RCOCH_2Hal \rightarrow RCOCHO$,[284] the (non-specific) oxidation of methyl ketones with selenium dioxide (Section 5.2.13.1), and standard methods such as ozonolysis or equivalent cleavage of the olefinic group of enones RCOCH=C<, and hydration of α,β-acetylenic aldehydes (Section 5.2.2). The monoxide of di(ethylthio)methane can be acylated to form the dithioacetal derivative (**129**), which is hydrolysed to an α-keto aldehyde[352] (equation 25).



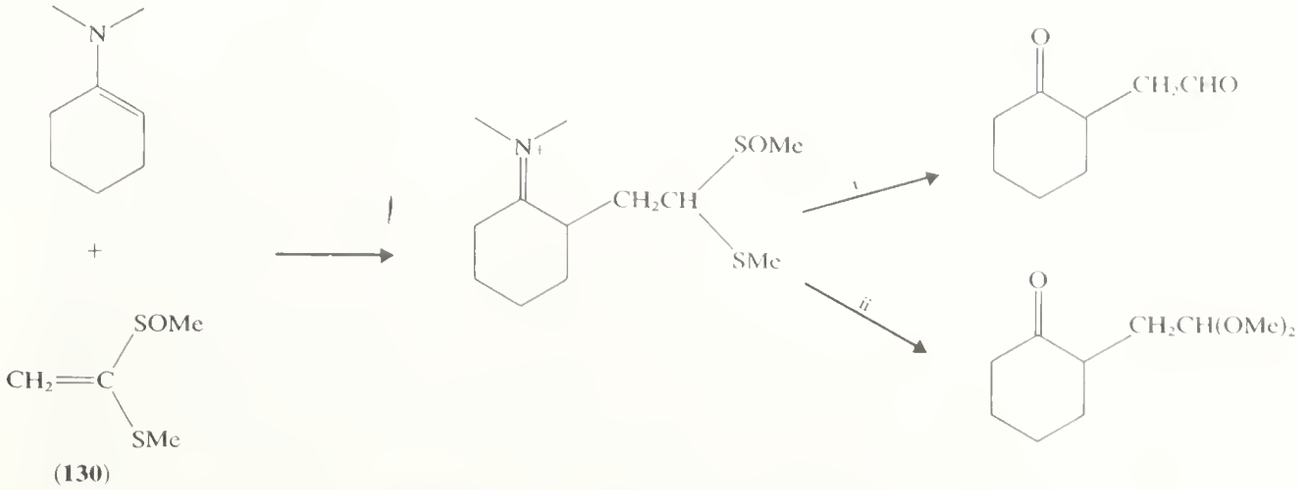
i, Bu^nLi in THF; ii, 0.5 equiv. RCOCl, or RCO_2Et; iii, hydrolysis.

5.2.12.2 3-Keto aldehydes (β-keto aldehydes)

The general route to β-keto aldehydes (α-hydroxymethylene ketones) uses the Claisen condensation of ketones with formate esters (Section 5.2.10.2). Acetoacetaldehyde (formylacetone), CH_3COCH_2CHO, is unstable and trimerizes to 1,3,5-triacetylbenzene; its chemistry and that of its acetals and other related compounds have been reviewed.[353] The β-keto aldehydes are strongly enolic, relatively acidic, and form stable, insoluble copper salts.

5.2.12.3 4-Keto aldehydes (γ-keto aldehydes)

Many γ-keto aldehydes can be made by cleavage of the olefinic group of appropriate γ-olefinic ketones, or by mild acid hydrolysis of 2-substituted furans (compare Section 5.2.10.3). A new route shown in Scheme 52 uses the reaction of an enamine with the monoxide of keten dimethylthioacetal (**130**);[354] presumably, enolate anions would serve also.



i, trace $HClO_4$ in aq. MeCN; ii, $(MeO)_3CH$ + MeOH + trace $HClO_4$.

SCHEME 52

5.2.12.4 5- and 6-keto aldehydes

These are commonly made by ozonolysis or equivalent cleavage of 1-substituted cyclopentenes or cyclohexenes, respectively. The 5-keto aldehydes are also available by Michael addition of ketones to α,β-olefinic aldehydes: alkali converts them into cyclohex-2-enones which bear a hydrogen atom at C-3 (see Section 5.2.9). With alkali, the 6-keto aldehydes cyclize to 2-acylcyclopentanols or the derived 1-acylcyclopentenes,[268,355] or to 2-alkyl-1-formylcyclopentenes,[263] which are important in syntheses of prostaglandins and of terpenoids. Many 5-keto aldehydes are made by acid hydrolysis of 2-alkoxy-2-alkyl-3,4-dihydropyrans, which are available from cycloaddition of α,β-olefinic aldehydes (acting as 4π-electron components) to vinyl ethers (acting as 2π-electron components). Other cycloadditions of this type have been reviewed.[356]

5.2.13 UNSATURATED KETONES

5.2.13.1 General preparations

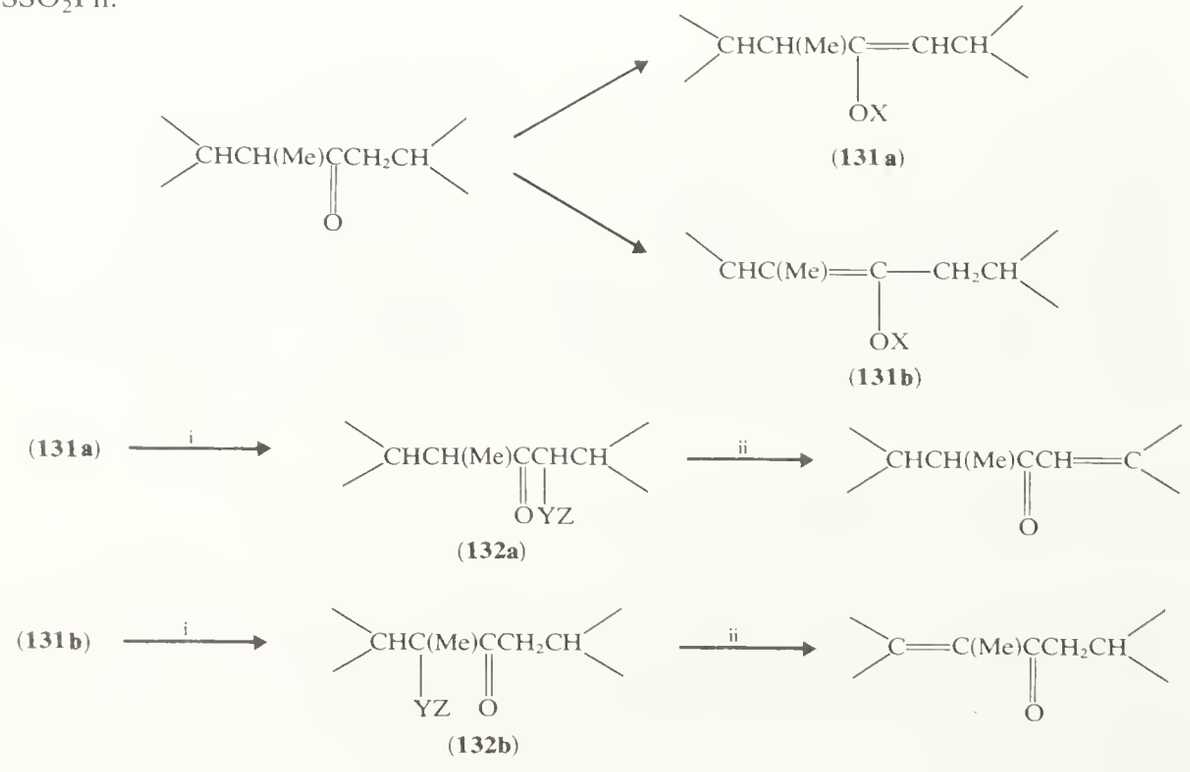
The types of preparation available for olefinic ketones are (i) the introduction of a double bond into an existing ketone, (ii) the building up of the ketone skeleton from smaller molecules, with the double bond or a precursor being formed in the process, and (iii) the conversion of another functional group in an olefinic molecule into a carbonyl group. The classes (ii) and (iii) are also satisfactory for preparations of acetylenic ketones.[357]

(i) *Introduction of a double bond into a ketone molecule*

Many α-halogeno ketones (see Section 5.2.6) have been dehydrohalogenated to form α,β-unsaturated ketones.[36,358] Hydroxide and alkoxide bases, and tertiary amines (pyridine, collidine, quinoline), were formerly used, but often lead to rearrangement or

other reactions and give poor yields. Much better results follow treatment with lithium chloride, magnesium chloride, lithium carbonate, or calcium carbonate[168] in boiling DMF or dimethylacetamide. Alternatively, heating the α-halo ketone with 2,4-dinitrophenylhydrazine and sodium acetate in acetic acid gives the dinitrophenylhydrazone of the α,β-enone.[358] Pyruvic acid frees the enone, but more recent methods (Section 5.2.15) should allow better results. Acetals of α-bromo ketones are converted into α,β-unsaturated acetals by heating with alkali metal alkoxides in DMSO; mild acid hydrolysis liberates the enones, particularly cycloalkenones and α,α′,β,β′-cycloalkadienones.[140]

A number of valuable new routes depend on oxidative eliminations from α-thio or α-seleno ketones; similar reactions apply to aldehydes and carboxylate esters. The lithium enolates of cyclic and acyclic ketones react regiospecifically with phenylselenenyl bromide, PhSeBr, or PhSeCl in aprotic solvents to give the α-phenylseleno ketones (**132**),[359,360] as shown in Scheme 53. The enol acetates of cyclopentanone and cyclohexanone react similarly with PhSeBr and silver trifluoroacetate at 0 °C.[361] Periodate oxidation[359,361] or, preferably, treatment with hydrogen peroxide in dichloromethane,[360] gives the selenoxides which decompose at, or slightly above, room temperature to afford excellent yields of the α,β-enones. Some cyclic ketones form with difficulty the cyclic transition state necessary for elimination; acetalization of the α-phenylseleno ketone, followed by oxidation and elimination, gives good yields of the unsaturated acetals.[360] Ketones react with PhSeCl in ethyl acetate at 25 °C, presumably *via* the enol; thus, cholestan-3-one gives mainly the 2-phenylseleno ketone, and then the $\Delta^{1,2}$-enone.[362] A closely related route uses dimethyl sulphide or (better) diphenyl sulphide, which reacts with lithium enolates of ketones to form α-thiomethyl or α-thiophenyl ketones. These are oxidized to the sulphoxides, then warmed to form high yields of the enones. The regiospecificity is quite high, and is increased further by using the more reactive enolate-trapping reagent $PhSSO_2Ph$.[363]



X = Li or COMe; YZ = SMe, SPh, or SePh

i, PhSeCl or PhSeBr or Me_2S_2 or Ph_2S_2, when X = Li;
PhSeCl or PhSeBr + $AgOCOCF_3$, when X = COMe;
ii, $NaIO_4$ or H_2O_2.

SCHEME 53

Selenium dioxide, usually used in tertiary alcohols, oxidizes many ketones, but the products vary. For reviews, see Refs. 36, 364, and 365. Sometimes an α-methylene group is oxidized to give an α-dicarbonyl compound, often in only moderate yield. Some cyclic ketones are oxidized instead to their α,β-olefinic derivatives, steroidal examples being common. Cholestan-3-one gives the 2,3-diketone, but many 5α-H 3-ketones give their 1,2-dehydro compounds, and 5β-H diastereoisomers give the 4,5-dehydro ketones, by attack on the enol form.[366] Further oxidation leads to 1,4-dien-3-ones.[367] For discussion of these and other selenium dioxide oxidations, see Refs. 365 and 368.

(*ii*) *The building up of a ketone skeleton from smaller molecules, with the double bond or a precursor being formed in the process*

An α-methyl or α-methylene ketone can be converted into a Mannich base (β-dialkylaminomethyl ketone) by the Mannich reaction or variants of it (Section 5.2.7.2). Thermal decomposition,[186,369] quaternization, and treatment with base,[370] or conversion into the hydrochloride and pyrolysis,[184] give the α,β-olefinic ketone with a terminal methylene group (**133**) (equation 26). The method has been used widely in making α-methylenecycloalkanones[369] and alkyl vinyl ketones for use in Robinson annelation reactions (Section 5.2.9). The Mannich bases have also been made by reacting dialkylamines with β-chloro ketones, than which they are more satisfactorily stored.[184]

$$—COCH_2R^1 \longrightarrow —COCH(R^1)CH_2NR_2^2 \longrightarrow —COC(R^1)=CH_2 \quad (26)$$

(**133**)

Many β-hydroxy ketones (β-ketols; Section 5.2.11.2), formed by aldol and related reactions, have been dehydrated to the α,β-enones under acidic (usually phosphoric, sulphuric or toluene-*p*-sulphonic) or basic catalysis. Examples include 3-methyl-[371] and other 3-alkyl-but-3-en-2-ones,[167] 3-isopropylbut-3-en-2-one,[186] many branched acyclic and cyclic α,β-enones,[137] α-alkylidenecyclopentanones,[154,173] and many linear dienones.[68] See also Sections 5.2.7 and 5.2.9.

Many α-hydroxymethylene (α-formyl) derivatives of cyclic ketones react with Grignard reagents or alkyl-lithiums to form α-alkylidene ketones *via* a process analogous to the lithium aluminium hydride reduction of β-diketones (Section 5.2.14.7). The α-alkoxymethylene analogues, and the crystalline difluoroboron complexes, react in the same way.[372]

Dehydrohalogenation of β-chloro ketones by the usual bases forms α,β-enones. Although some chloro ketones are made from β-hydroxy ketones, for example by using hydrogen chloride as catalyst in the aldol condensation,[373] the usual route uses Friedel–Crafts acylation of alkenes. For a review, see Ref. 374. Many alkyl vinyl ketones (**134**) were made from ethylene and acyl halides[375] (equation 27); propene and acetyl chloride

$$R^1COCl + CH_2=CHR^2 \xrightarrow{i} R^1COCH_2CH(Cl)R^2 \xrightarrow{ii} R^1COCH=CHR^2 \quad (27)$$

(**134**)

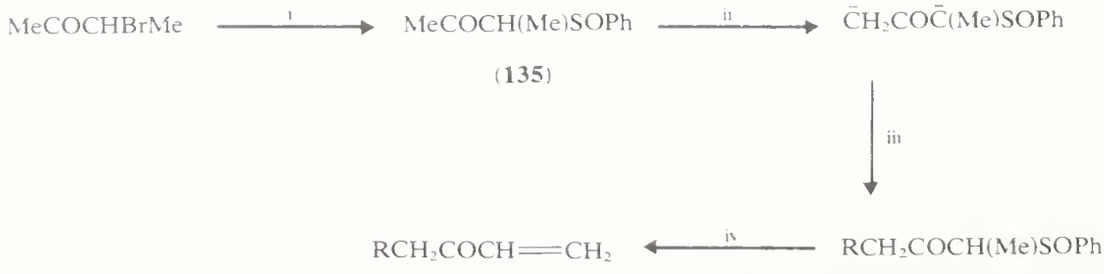
$R^2 = H$, $R^1 = Et$, Pr^n, Pr^i, Bu^t, Ph[375]

i, $AlCl_3$, $CHCl_3$; ii, Na benzoate or $PhNEt_2$ or quinoline.

form 4-chloropropan-2-one, which gives *trans*-pent-3-en-2-one. Upon distillation this ketone is partly isomerized to the lower-boiling β,γ-enone, which is reconverted to the stable α,β-unsaturated isomer by heating with a trace of acid.[376] Acylation can be effected by carboxylic acid anhydrides, and may give the enones directly. Either of the α,β- or β,γ-unsaturated isomers can be formed, irrespective of their relative stabilities.[374] Divinylic ketones, $RCH=CHCOCH=CH_2$ and $RCH=CHCOCH=CHR$, can be obtained from the β,β′-dichloro ketone products of the addition of β-chloroacid chlorides to olefins.[377] Many α,β- and non-conjugated olefinic ketones have been made by reaction of

the corresponding unsaturated carboxylic acids with an excess of methyl-lithium[378] (see Section 5.2.2), or from vinyl-lithium with carboxylic acids in 1,2-dimethoxyethane.[379] A related route to α,β-acetylenic ketones uses the reaction of acyl chlorides with copper acetylides, which may be preformed or made *in situ* from a cuprous halide and lithium or other acetylides. The acyl chloride can be varied widely.[380]

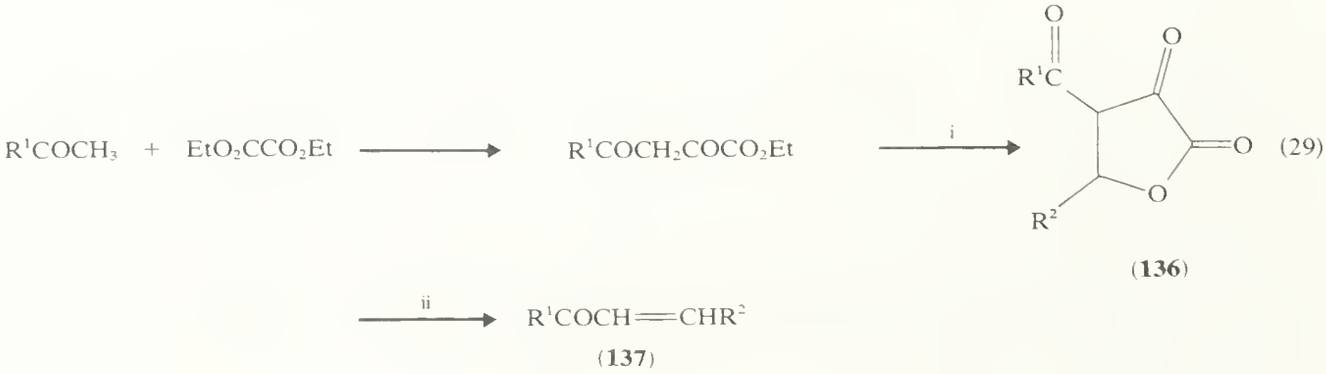
A general route to alkyl vinyl ketones, $RCH_2COCH{=}CH_2$, uses the clean γ-alkylation of the α,γ-dianion of the β-keto sulphoxide (**135**), prepared as shown in equation (28).



(135) (28)

i, PhSNa, then $NaIO_4$; ii, NaH, then Bu^nLi, in THF + HMPA; iii, RHal, then H_2O; iv, 70–75 °C.

See also Section 11.7.4. Gentle heating produces the enone in excellent yield.[381] A further promising route uses the base-catalysed condensation of aldehydes with α-ethoxalyl ketones (see Section 5.2.10.2) to form diketo lactones (**136**) which, upon flow-pyrolysis, decarboxylate and decarbonylate to the α,β-enones (**137**) in good yield[382] (equation 29).



(136) (29)

(137)

i, R^2CHO, base; ii, Δ.

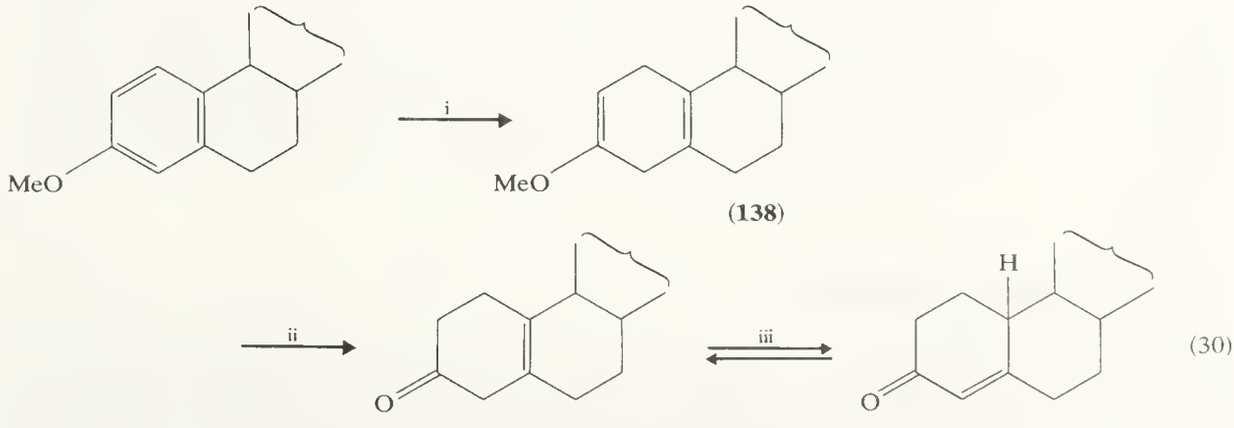
A reliable, although somewhat expensive, route to α,β-enones uses a Wittig reaction of an aldehyde with the phosphorane derived from an α-chloro ketone.[211] Allylic and acetylenic secondary alcohols, which are readily made by 1,2-addition of alkyl-lithiums or Grignard reagents to α,β-unsaturated aldehydes, or of vinylmagnesium bromide or lithium acetylides to aldehydes, are oxidized by Jones' chromic acid reagent or, preferably, other two-phase variants of it,[67] to the α,β-enones or α,β-acetylenic ketones;[201,383] incomplete oxidation may be a problem.[376] Similar results are obtained by oxidizing the olefinic or acetylenic alcohols with activated manganese dioxide in neutral solution. Although the reagent is somewhat variable, it oxidizes α,β-unsaturated alcohols selectively; for reviews, see Ref. 67. Jones' oxidation and its variants can be used to oxidize β,γ-olefinic and β,γ-acetylenic secondary alcohols to the β,γ-unsaturated ketones in good yield.[90,384] Normally isomerization is not a problem.[67,385] Oxidation with DMSO–dicyclohexylcarbodi-imide (Moffat oxidation)[67,386] is also very satisfactory. Many ketones which are not α,β- or β,γ-unsaturated are available by standard alkylations of acetoacetic esters or β-diketones with allylic or other alkenyl and alkynyl (non-vinylic) halides.[313,324,378,387] Remote acetylenic ketones, $RCO(CH_2)_nC{\equiv}CH$ with $n>2$ have been made from the cyanoacetylenes $NC(CH_2)_nC{\equiv}CH$ and Grignard reagents or alkyl-lithiums.[23]

(iii) The introduction of a carbonyl group into an olefinic molecule

Direct allylic oxidation of $-\overset{|}{C}=\overset{|}{C}CH_2-$ to $-\overset{|}{C}=\overset{|}{C}CO-$ is frequently effected using t-butyl chromate[388] or sodium chromate or chromic acid in acetic acid–acetic anhydride.[336] Fused cyclohexenes are converted into cyclohexenones,[388] and cyclopentenes to cyclopentenones.[388a] The chromic oxide–(pyridine)$_2$ complex is claimed to be superior, and oxidizes many monocyclic and steroidal cyclohexenes to cyclohexenones, under much milder conditions.[389] Similar oxidations of non-terminal alkynes give α,β-acetylenic ketones; although sodium chromate gives lower yields than chromic oxide–pyridine complex, it is more convenient.[390] The terminal methyl groups of alk-2-ynes and allylic methyl groups are not readily oxidized. The selectivity of attack has been discussed in terms of the conversion of the allylic system $R^1CH_2CH{=}CHR^2$ to an allylic radical or cation $R^1\overset{*}{C}HCH{=}CHR^2 \leftrightarrow R^1CH{=}CH{-}\overset{*}{C}HR^2$ which is oxidized at either terminus; stereochemical and stereoelectronic factors are then important.[389] Selenium dioxide oxidizes many olefins at the allylic positions. The products can be allylic alcohols or α,β-unsaturated ketones,[391] or both.[173,365] For discussions of the mechanism, stereochemistry, and regioselectivity of attack on constitutionally unsymmetrical olefins, see Ref. 365. See Section 4.3.6.2 for the Claisen rearrangement of allyl vinyl ethers to γ,δ-unsaturated aldehydes and ketones.

5.2.13.2 Cyclohexenones

Many cyclohexenones are prepared by ring-forming reactions (see Section 5.2.9). Many others are available by the reduction of phenol ethers by alkali metals in liquid ammonia (Birch reduction). For reviews, see Refs. 36, 392, and 393. The Birch reduction gives (equation 30) 2,5-dihydro aromatic compounds (**138**) in which the added protons avoid substituents in the order OMe > alkyl > H. Careful acidic hydrolysis liberates a cyclohex-3-enone. Lithium has advantages over sodium and potassium as the reducing metal, and is compatible with co-solvents (*e.g.* diethyl ether or dioxan) which may be necessary with sparingly soluble substrates. An acidic additive, usually methanol, ethanol, or ammonium chloride, is added to avoid the accumulation of amide ion which would isomerize the unconjugated 2,5-dihydro aromatic to a conjugated diene. The latter system can be reduced further by excess of the metal. Many modifications, including the use of carefully distilled ammonia with the inexpensive sodium or potassium metals, and examples of applications to steroidal molecules are given in Ref. 393.



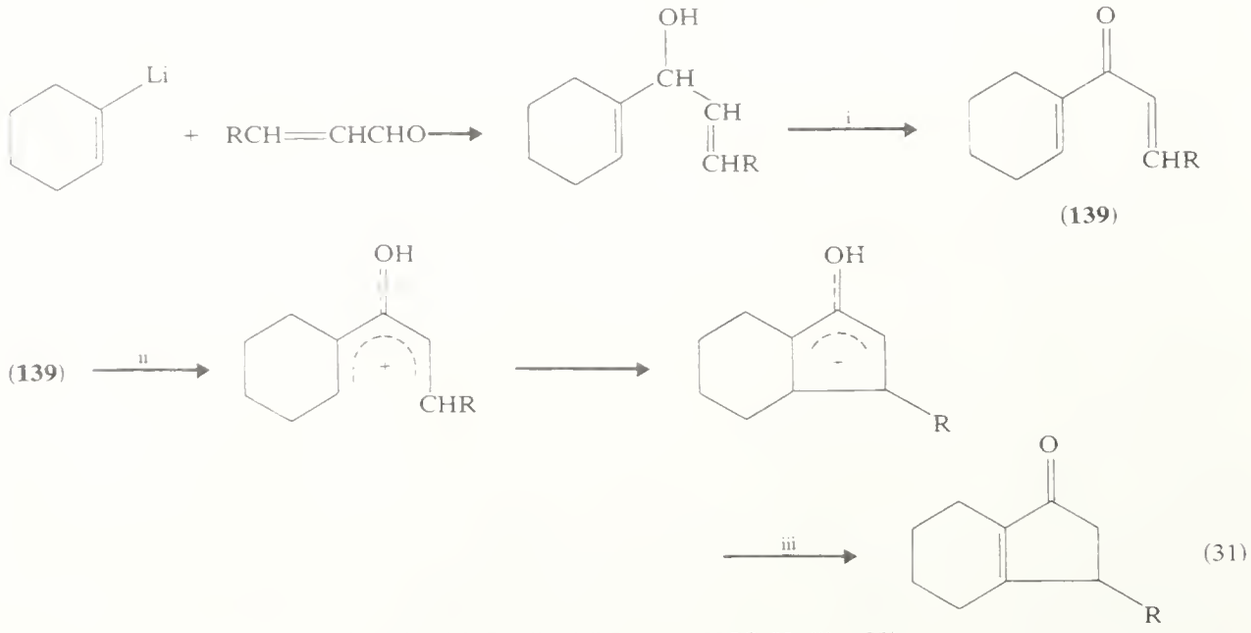
(30)

i, Na, K, or Li in NH_3; ii, mild H_3O^+; iii, stronger H_3O^+ or base.

5.2.13.3 Cyclopentenones

Many cyclopent-2-enones have been made by cyclization of 1,4-diketones and of 4-keto aldehydes (Sections 5.2.11 and 5.2.12). Applications to syntheses of jasmone and its

derivatives, prostaglandins, and pyrethrin-type compounds are numerous. Another important route is the Nazarov cyclization under acidic conditions of divinylic ketones,[377,394] which are frequently made by manganese dioxide oxidation of bisallylic alcohols; see (**139**) in equation (31). Related reactions are the acylation of cyclohexene with but-2-enoic acid, and the convenient reaction of esters of α,β-olefinic acids, both induced by polyphosphoric acid.[395] Another approach introduces the ketone and alkyl functions into the cyclopentene ring of dicyclopentadiene, and then liberates the cyclopentenone and cyclopentadiene by a thermal reverse Diels–Alder reaction.[173,234] Cycloaddition of enamines to the zwitterions $R\overset{+}{C}HCO\overline{C}HR$ obtained from α,α'-dibromo ketones and iron carbonyls leads to 2,5-dialkylcyclopent-2-enones.[396]



(31)

i, active MnO_2; ii, H_3PO_4 + HCO_2H; iii, $-H^+$.

5.2.14 REDUCTION OF KETONES

In most reductions of ketones, two electrons and two protons are formally added to produce a secondary alcohol. The main classes of reagents used are hydrogen with a catalyst, complex metal hydrides, dissolving metals, and hydrogen transfer reagents. Deoxygenation reactions convert ketones into alkanes or alkenes. One-electron reductions allow the formation of radical-anions, dimerization of which gives pinacols (1,2-diols) (see Section 4.1.2.3). When the carbonyl group is conjugated with an olefinic double bond it is possible for one or the other or both groups to be reduced. Electronegative leaving groups α to the ketone function are frequently replaced by hydrogen during reductions.

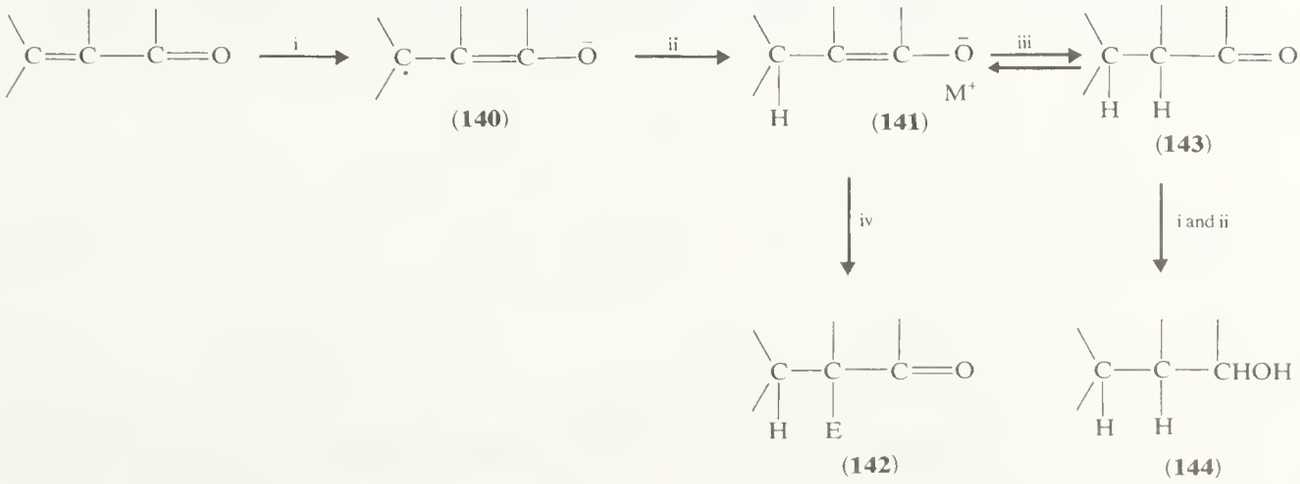
5.2.14.1 Catalytic hydrogenation

For reviews, see Refs. 36 and 397. Saturated ketones are not normally reduced by hydrogenation over palladium catalysts, but are reduced over other catalysts, *e.g.* platinum, Raney nickel, and ruthenium. Ketone groups are hydrogenated much more slowly than olefinic bonds, more slowly than aldehydes, but faster than esters, nitriles, and benzene rings. A useful list of reactivity is given in Ref. 36. The rate of reduction and stereochemistry of the secondary alcohol products have been widely studied, and vary considerably with the catalyst, solvent, and acidity or basicity of the reduction medium. The order of reactivity of carbonyl groups at the various positions in steroids has been determined.[397] As a general rule, basic catalysts (Raney nickel, and platinum oxide used

in alcoholic solution) or platinum catalysts in basic media lead to the more stable epimeric alcohol; in the cyclohexane series this is usually the equatorial isomer. Hydrogenation in acidic media gives the axial, or less stable, alcohol in greater proportions, or almost exclusively. Hydrogenation of α,β-unsaturated ketones to saturated ketones is particularly easy; palladium catalysts are often preferred, but platinum oxide is frequently perfectly satisfactory. In neutral, and particularly in basic, media the conjugated olefinic group can usually be saturated without reduction of isolated olefinic groups. The selectivity of reduction of steroidal α,β-enones is discussed by Augustine.[397] Steroidal 4-en-3-ones having a methyl or hydrogen atom at C-10, and their bicyclic analogues, give mixtures of *cis*- and *trans*-fused ring products in which the *cis*-isomer can greatly predominate. This is in contrast to the results of metal–ammonia reductions. However, the stereochemical results can vary dramatically with the conditions used. The general rule[36,398] is that the major product arises by *cis* addition of hydrogen from the less-hindered side of the molecule, when palladium catalysts are used in neutral or weakly acidic media. Other catalysts seem to give lower stereoselectivity, in the order platinum oxide > Raney nickel > rhodium > ruthenium > iridium, but other experimental conditions also play an important role.[398] Most readily cleaved groups are removed by reduction, before the carbonyl group is hydrogenated, but α-ketols can be reduced satisfactorily to 1,2-diols.[280]

5.2.14.2 Reduction by alkali and alkaline earth metals in liquid ammonia

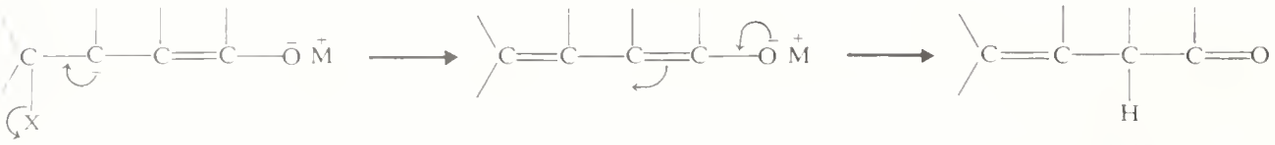
These reductions have been widely applied to ketones and to aldehydes. For general reviews, see Refs. 36 and 399–401. Their main application, as shown in Scheme 54, is to α,β-unsaturated ketones which are reduced *via* (**140**) to form an enolate (**141**). This is usually stable in the absence of acids (proton donors) which are stronger than ammonia, and can be quenched regiospecifically using many electrophilic reagents, to form the α-substituted ketones (**142**).[399] Water gives the saturated ketone (E = H),[108,402] deuterium oxide gives the α-deuterio ketone (E = D),[402] reactive alkyl halides give α-alkyl ketones[108,402] (see Section 5.2.5), carbon dioxide gives β-keto acids,[402] pentyl nitrite forms α-nitro ketones, and cyanogen chloride yields α-cyano ketones. Acyl halides give *O*-acylation, to form enol esters[399] (see Section 5.2.4). The isomeric integrity of the enolates is maintained with lithium as the cation, but is lost if sodium or potassium are used, or if the lithium enolate is transferred to a dissociating solvent, such as DMSO.[402] The enolate (**141**) can undergo other reactions in complex ketones.



i, metal–NH_3; 1 electron reduction; ii, 1 electron + H^+; iii, proton donor, HA; iv, electrophile, E^+.

SCHEME 54

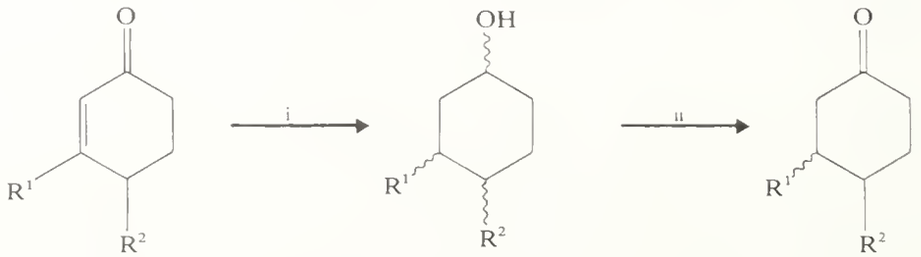
Intramolecular alkylations by the radical anion (**140**) or the corresponding dianion are possible.[399,402] Leaving groups at the γ-carbon atom are eliminated, to form the β,γ-unsaturated ketone (**145**) by kinetic protonation, or to allow equilibration with the α,β-unsaturated isomer in the presence of acid or base (equation 32). Leaving groups at the β-carbon atom may be reductively eliminated from the enolate (**141**) to form the parent α,β-enone which is reduced further to the saturated ketone. The existence or absence of this reaction can often be controlled by variations in the reaction conditions;[402] it is usually avoided in catalytic hydrogenations.



(32)

(**145**)

In the presence of excess of metal and of proton donors of comparable acidity to itself, the saturated ketone (**143**) is further reduced to the alcohol (**144**), and unconjugated carbonyl groups elsewhere in the molecule are reduced (Scheme 54). If this must be avoided, the other groups should be protected as their acetals, enol ethers, or enol acetates. Usually, however, the alcohol can be oxidized back to the ketone using chromic oxide, provided this is compatible with other functions[403] (equation 33). The proton

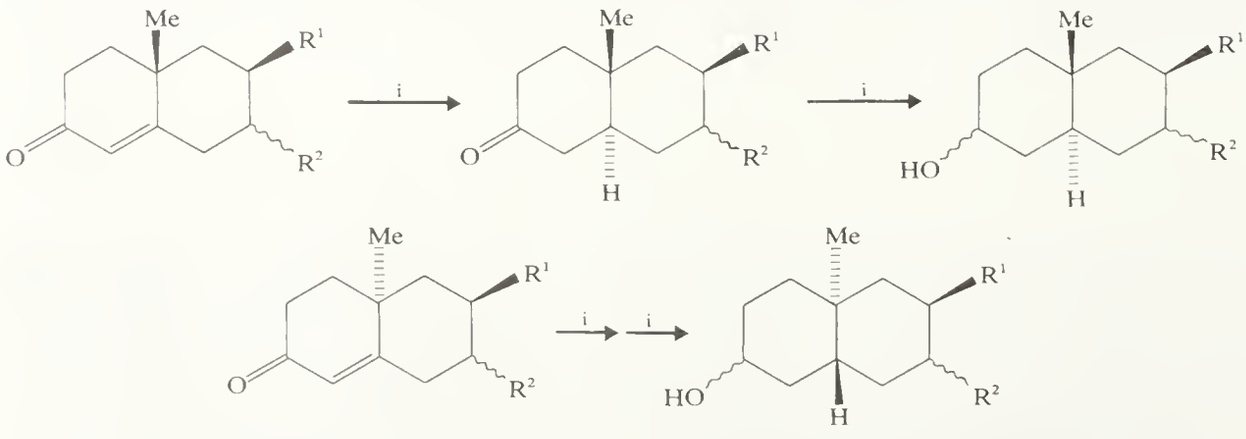


(33)

R^1, R^2 = Me; R^1, R^2 = Et; R^1 = Me, R^2 = Et; R^1 = Ph, R^2 = Me; R^1 = R^2 = Ph.

i, Li, NH_3, C_2H_5OH; ii, Jones' CrO_3 oxidation.

donors generally used to effect reduction to the alcohol are methanol or ethanol, whereas diethyl ether, ammonium chloride, or t-butanol can be used as proton sources if the ketone is not to be reduced further. The stereochemistry of reduction of fused cyclohexenones in which the β-carbon is at a ring-fusion position — for example, in steroidal 4-en-3-ones — is almost always subject to stereoelectronic control (see Scheme 55). The major product is the more stable of the two isomers (*cis* or *trans*) which has the newly



i, Li, NH_3, C_2H_5OH.

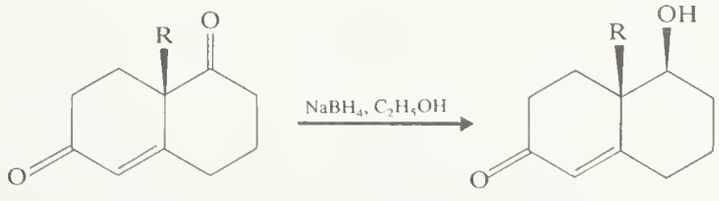
SCHEME 55

introduced β-hydrogen atom axial to the ketone ring.[36,401–403] Thus normal (10β) steroidal 4-en-3-ones give the 5α-H products, which have a *trans* A/B ring fusion; for the 10α-analogues, a *cis* A/B junction is more stable, and a mixture is formed although the *trans*-isomer predominates.[399,403] Normal work-up procedures allow equilibration and usually give the more stable configuration at the α-carbon atom, but kinetic protonation can be achieved to give the less-stable epimer.[399] The factors involved are discussed in Refs. 36, 399, 402, and 403. Many other functional groups, such as acetals, acetate groups, carboxylic acids, and Mannich bases are stable to the reduction conditions. Extended dienones are reduced initially to β,γ-enones which can be isolated, with care, if ammonium chloride is used as the proton source; usually, however, equilibration with the α,β-enone occurs.[401]

5.2.14.3 Complex metal hydride reductions

Many complex hydrides are available which are derived from lithium aluminium hydride, and sodium or other borohydrides, by replacement of one or more hydrogens by alkoxy or alkyl groups. Many reviews of reductions by these and other reagents are available.[36,404] Ref. 405 discusses their functional group selectivity, and Ref. 67 gives many examples of their use. The addition of Lewis acids such as aluminium chloride or boron trifluoride or other compounds to the complex metal hydrides gives 'mixed hydrides' which are also of value.[67,406] Kinetics of ketone reduction by lithium aluminium hydride and deuteride, and sodium aluminium hydride, have been measured, and references given to similar studies of sodium borohydride, and a number of aluminohydrides.[408] Lithium aluminium hydride, the standard reagent for reducing ketones to secondary alcohols, is very reactive and unselective, reducing virtually every other reductible group apart from isolated olefin groups. At the other end of the reactivity spectrum are sodium and zinc borohydrides, which reduce aldehydes, ketones, and acyl chlorides, and sodium cyanoborohydride, which reduces aldehydes and ketones under acidic but not neutral conditions.[405]

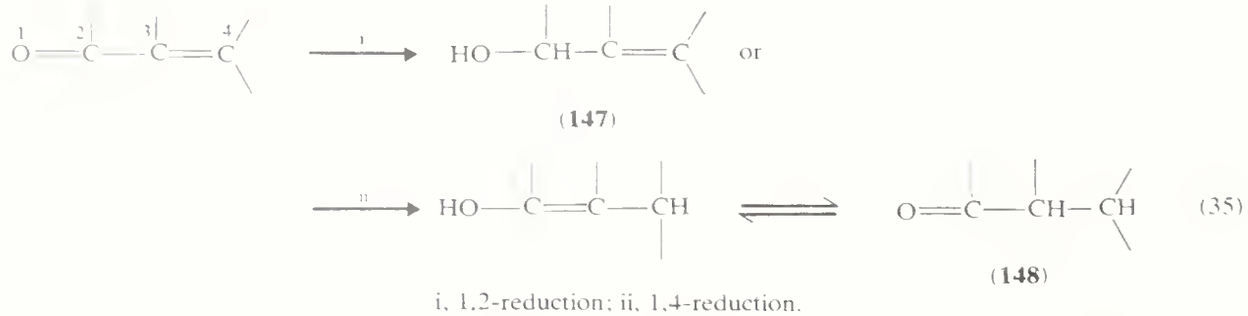
Saturated ketones are more reactive than α,β-unsaturated ketones towards hydride reduction, owing to the polarization $O{=}C{-}C{=} \leftrightarrow \bar{O}{-}C{=}C{-}\dot{C}$ which reduces the electrophilicity of the carbonyl group. Thus sodium borohydride can reduce saturated ketones whilst leaving α,β-enones (**146**) untouched[250] (equation 34). Lithium tri-t-butoxyaluminium hydride is even more selective for this purpose.[409] Sodium borohydride reduces methyl ketones faster than disubstituted ketones, and its selectivity for ketone groups at the various positions in steroids has been summarized.[404] The reduction of saturated ketones and the stereochemical consequences are discussed in Section 4.1.1.3. We shall now concentrate on the specific reduction of α,β-unsaturated ketones.



(146) (34)

5.2.14.4 Reduction of α,β-unsaturated ketones mainly at the olefinic bond

Despite the earlier discussion, sodium borohydride can be used to reduce α,β-enones. The solvents used and the degree of substitution at the β-carbon atom can drastically change the amount of 1,2- to 1,4-reduction, *i.e.* of reduction of the carbonyl group or of



(147)

(148)

i, 1,2-reduction; ii, 1,4-reduction.

(35)

the olefinic group; see (**147**) and (**148**) in equation (35). Sodium borohydride in pyridine effects 1,4-addition of hydrogen, to form the saturated ketone (**148**), which can be further reduced to the saturated alcohol by excess of reagent. In other solvents, mixtures of 1,4- and 1,2-addition occur, with larger substituents at the β-carbon encouraging more of the latter.[410] More specific complex hydride reagents are now available for reducing α,β-enones to saturated ketones, and supplement catalytic hydrogenation and lithium–ammonia reductions. A 1 : 4 molar mixture of lithium aluminium hydride and copper(I) iodide reacts with 1 mole of α,β-enone to give solely 1,4-addition. The active reagent is H_2AlI, and other reagents $H_nAl(Hal)_{3-n}$ were made but were less useful. Further reagent reduces the saturated ketone products.[411] Reaction of copper(I) bromide with 2 moles of lithium trimethoxyaluminium hydride or 1 mole of sodium bis-(2-methoxyethoxy)-aluminium hydride (RED-AL or Vitride) in THF gives a reagent considered to be copper(I) hydride which reduces α,β-enones to saturated ketones with high regiospecificity. The former reagent is preferred, although the latter works better with esters of α,β-unsaturated carboxylic acids.[412] The lithium and potassium tri-s-butylborohydrides (called L- and K-Selectride, respectively) in THF give 1,4-reduction of cyclohex-2-enones — with and without 2-substituents — to the saturated ketones, when used in equivalent quantities. In contrast, acyclic enones and β-substituted cyclohex-2-enones are reduced to allylic alcohols, and cyclopent-2-enones and cyclohept-2-enones give mixtures. Despite this lack of general specificity, the reagents are useful because the lithium enolate formed by 1,4-addition of L-Selectride can be alkylated at the α-carbon, using reactive alkyl or allylic halides.[413] The method is a convenient route from cyclohex-2-enones to 2-alkylcyclohexanones, as an alternative to the lithium–ammonia reduction–alkylation route (Section 5.2.14.2).

5.2.14.5 Reduction of the carbonyl group of α,β-unsaturated ketones

Lithium aluminium hydride in ether favours clean 1,2-reduction of α,β-enones, to give allylic alcohols, and can be one of the best reagents for this purpose.[409,410,414,415] Its low functional group selectivity can be a drawback. Corey and his co-workers studied a number of reagents which would reduce the carbonyl group of the 13-en-15-one function of prostaglandins, and aimed for high stereoselectivity as well. Sodium borohydride in ethanol and the less basic zinc borohydride in 1,2-dimethoxyethane gave excellent regiospecificity, as did a number of lithium trialkylborohydrides including thexyl di-s-butylborohydride and tri-s-butylborohydride (Selectride). Other complex trialkylborohydride ions gave up to 40% of 1,4-reduction, but the addition of HMPT as a Lewis base increased carbonyl reduction to *ca.* 97% of the total. Dialkylboranes were unsatisfactory, giving mainly 1,4-reduction.[416] Aluminium hydride, used in THF or diethyl ether, and usually prepared *in situ* from lithium aluminium hydride and aluminium chloride or sulphuric acid, is particularly useful for reducing cyclopent-2-enones to cyclopent-2-enols,[414] but its use, in general, for producing pure allylic alcohols is limited.[67,406] Di-isobutylaluminium hydride (DIBAL) in toluene, benzene, or dimethoxyethane reduces cyclopenten-2-ones to cyclopentenols, and 2-ene-1-4-diones to ene-1,4-diols in good yield; it is claimed to be superior to aluminium hydride for the former purpose, and

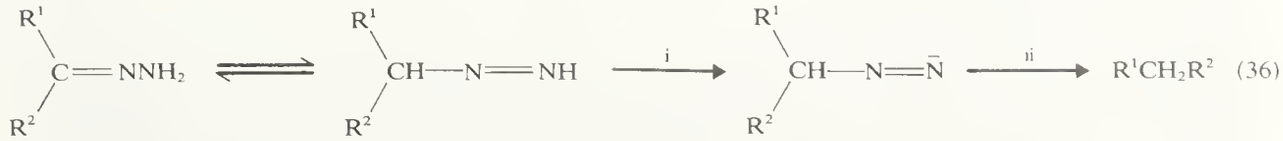
superior to the other reagents tried for the latter.[417] Many other functions, and especially olefinic groups, are affected by this reagent,[67,405] and the enone function of the prostaglandin side-chain was largely reduced to the saturated ketone.[416] Lithium tri-t-butoxyaluminium hydride is a very mild and selective reagent which reduces aldehydes, ketones, and acyl chlorides but not, for example, epoxides, lactones, or alkyl esters.[405] It is valuable in allowing specific reduction of saturated ketones in the presence of α,β-enones.[409] When it does reduce enones its behaviour varies: cholest-4-en-3-one is reduced to the allylic alcohol, cholest-4-en-3β-ol, with high regio- and stereo-specificity. A cyclopent-2-enone[414] and several α-alkylidenecyclopentanones were each reduced to the saturated ketones.[173] The reagent reduces α-bromo ketones to 2-bromo alcohols.[67] Diborane has an order of reactivity which is roughly the reverse of the hydride reducing agents, because it acts as a Lewis acid rather than a Lewis base.[36,405] It can reduce α,β-enones relatively selectively in the presence of saturated ketones, giving mainly the allylic alcohol.[418]

The reduction of acyclic and cyclic 1,2-diketones,[419] of α-ketols,[330] and of acyclic 1,3-diketones by sodium borohydride in methanol gives excellent yields of 1,2- and 1,3-diols, respectively. Cyclic 1,3-diketones are more acidic, and hydrolyse the borohydride faster than they are reduced.[419] The reduction of 1,3-diketones by lithium aluminium hydride is more complex — see Section 5.2.14.7. The complex aluminium hydride reagents reduce acyclic α-hydroxy ketones to *erythro*-1,2-diols;[280,330a] the degree of stereoselectivity varies greatly and in an irregular manner, but it can be very high.[330a]

5.2.14.6 Deoxygenation of carbonyl compounds

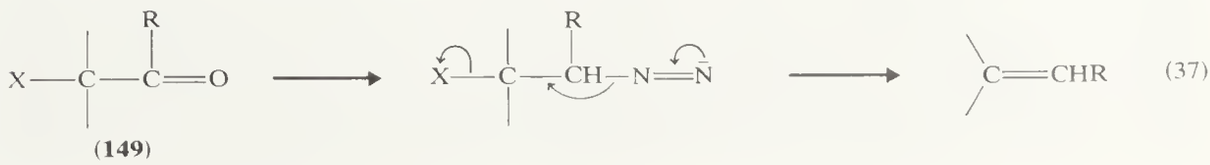
Most deoxygenations effect the reduction of a carbonyl to a methylene group, $>C{=}O \rightarrow >CH_2$; these are summarized first. Later we discuss reactions which convert a ketone, $-CO-CH<$, to an olefin, $-CH{=}C<$. The three standard routes used to reduce a carbonyl to a methylene group apply also to aldehydes. An extensive recent review gives typical procedures and advice on applications;[420] see also Ref. 36.

The most generally useful method for deoxygenation of saturated ketones is the Huang–Minlon modification of the Wolff–Kishner reduction (equation 36). The ketone



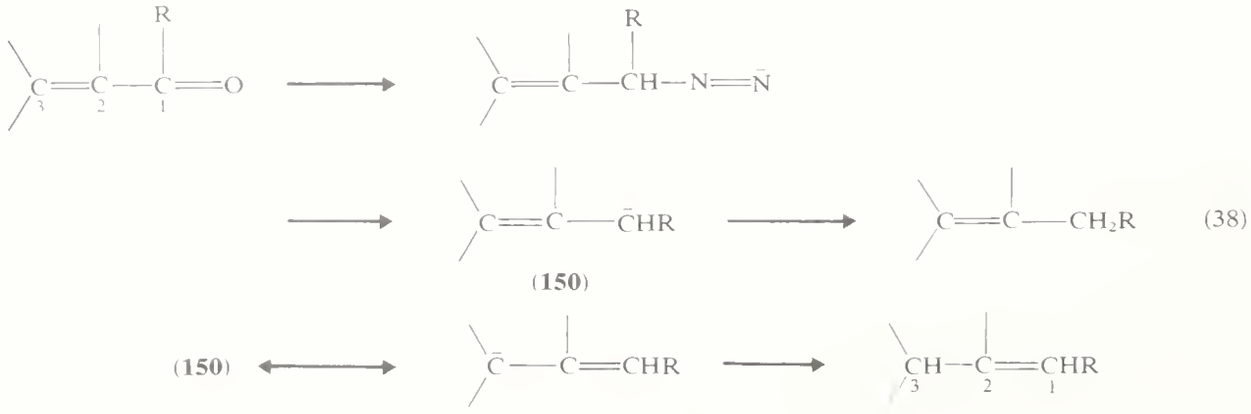
i, strong base; ii, 150–250 °C, loss N_2, $+H^+$. (36)

reacts with hydrazine hydrate or, less often and less safely, anhydrous hydrazine to form the hydrazone. This is decomposed, preferably *in situ*, by heating at 150–250 °C with sodium hydroxide, potassium hydroxide, or the metal alkoxide of the high-boiling glycol solvents which are generally employed. Various modifications allow reaction at lower temperatures, or application to sterically hindered ketones such as 11- or 15-keto steroids. Semicarbazones may be used instead of the parent ketones, especially if the latter are base-sensitive. Very easy reductive elimination occurs with α-ketols, their esters and ethers, and α-halo and α-amino ketones (**149**), to form alkenes (equation 37). These may be further reduced to alkanes by the di-imide which can form from hydrazine and air if this is not rigorously excluded.[420] α,β-Epoxy ketones form allylic alcohols by the same mechanism. Remote olefinic and hydroxy groups survive the reduction, and remote



(**149**) (37)

acetate groups merely hydrolyse to hydroxy groups. As expected, 3-hydroxy ketones (β-ketols) and their derivatives undergo elimination to form 2-enones which reduce normally to a 2,3-olefin; the double bond may isomerize to the 1,2-position by protonation of the allylic carbanion as shown in (**150**) in equation (38).

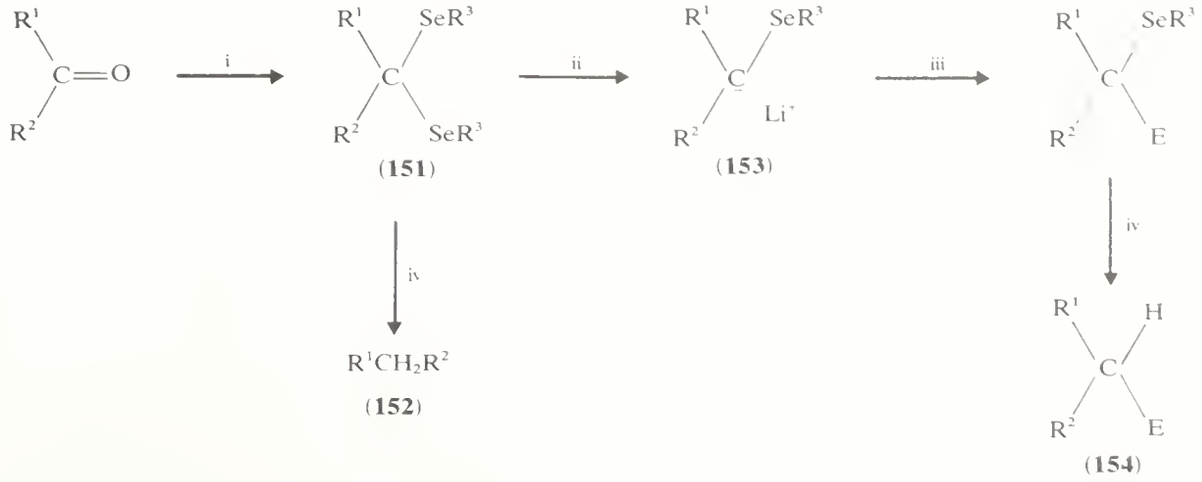


(38)

In the Clemmensen reduction[36,420] the ketone is treated with an excess of amalgamated zinc in 20–40% aqueous hydrochloric acid at reflux, often for prolonged periods. A water-miscible co-solvent (ethanol, acetic acid, or dioxan) can be added. More often an immiscible solvent (toluene, benzene, or xylene) is added to keep the bulk of the ketone and products out of the acidic mixture; this frequently improves the yields. Reductions under milder conditions, using only organic solvents and dry hydrogen chloride as the acid, are recommended for acid- and heat-sensitive compounds; for a review, see Ref. 421. Steric hindrance, for example in tertiary alkyl ketones and 11-keto steroids, limits yields and retards reduction. Reduction of α,β-unsaturated ketones, and of β,γ-unsaturated ketones which can isomerize to them, can give olefins but is usually incomplete. Remote olefinic groups are unaffected.[420] Tertiary alkyl ketones and other ketones which rearrange in acids do so under Clemmensen reduction conditions. Many α-substituted ketones undergo reductive cleavage of the α-substituent under these, as under milder, conditions (see Section 5.2.14.8). Some α,β-enones and β-diketones undergo skeletal rearrangements, *via* cyclopropanol intermediates, and reductions of γ- and δ-diketones are unreliable.[420–422]

The third major deoxygenation method, the Mozingo reaction, involves the formation of a thioacetal and then reductive desulphurization with an excess of Raney nickel. The ethylene or propylene dithioacetals (1,3-dithiolans and 1,3-dithians) are usually made from the dithiol, the ketone, and a Lewis acid (boron trifluoride etherate) or proton acid (perchloric or hydrogen chloride) as catalyst. For many examples, see Refs. 54 and 67. The Raney nickel is usually deactivated to avoid reduction of other groups (olefins, carbonyls, nitro, *etc.*). The catalyst-variables which can profoundly affect the course of the reactions have been studied.[420] Hindered ketones form thioacetals with difficulty, and 11-keto steroids do not react.[54] This deoxygenation method is usually the best for small-scale reduction of relatively unhindered ketones, and for α,β-unsaturated ketones. The latter form the dithioacetals without double-bond migration,[54] but some isomerized or reduced olefin may be formed in the reduction step.[420]

Other deoxygenation methods include the conversion of the ketone to its toluene-*p*-sulphonylhydrazone, by reaction with toluene-*p*-sulphonylhydrazine, and then reduction with sodium borohydride or, preferably, sodium cyanoborohydride.[423] This allows base-sensitive carbonyl compounds, such as β-diketones and β-keto esters, to be reduced specifically and cleanly. In a versatile variant of the Mozingo reaction, outlined in Scheme 56, the selenoacetal (**151**) is reduced with Raney nickel or lithium in diethylamine to the hydrocarbon (**152**). The selenoacetal can also be converted into the stabilized α-seleno carbanion (**153**), which is alkylated by reactive halides and reduced to the hydrocarbon (**154**; E = alkyl). The carbanion (**153**) can also be deuteriated or brominated, then reduced



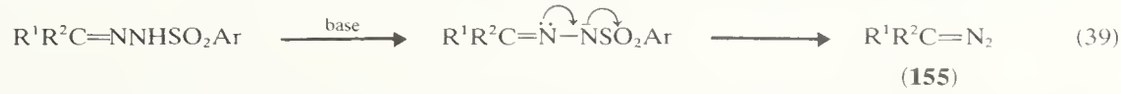
i, R^3SeH; ii, Bu^nLi; iii, H_2O, D_2O, alkyl or allyl halide, Br_2 or *N*-bromosuccinimide; iv, Raney Ni or Li, $C_2H_5NH_2$.

SCHEME 56

to the deuterio or bromo products (**154**; E = D or Br).[424] Ketones can also be reduced to the secondary alcohol, whose derived toluene-*p*-sulphonate or halide can be reduced by metal hydrides (see Section 11.19.3).

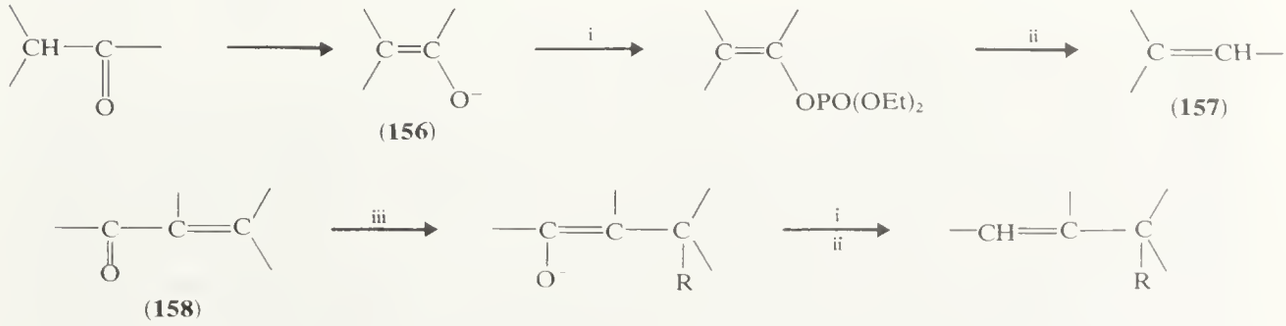
5.2.14.7 Deoxygenation of ketones to form olefins

For a review, see Ref. 425. In the Bamford–Stevens reaction (equation 39) the tosylhydrazone of an aliphatic or cyclic ketone is treated with a strong base to form a diazo compound (**155**). Its subsequent fate depends on the conditions (protic or aprotic)



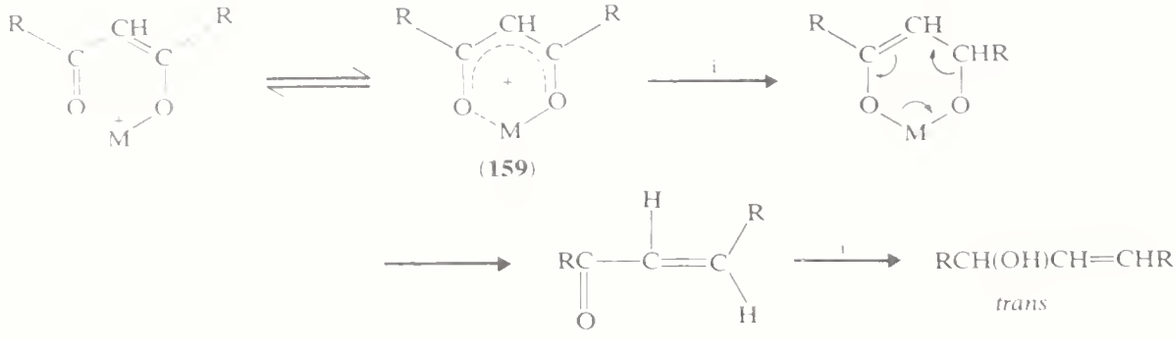
(39)

and the base used. It may lose nitrogen to form a carbene, gain a proton to form a carbenium ion, or deprotonate to form a vinylic anion. The products are frequently alkenes, but skeletal rearrangements may be important.[36,425] In another reaction outlined in Scheme 57, the ketone is converted into its enolate ion (**156**) which reacts with diethyl phosphorochloridate to give the enol phosphate. Lithium in ammonia or ethylamine reduces this to the olefin (**157**).[426] The published work used sodium hydride as base to form the enolate, but other methods (Section 5.2.4) should also work and allow regio-specific reactions. The enolates were also made from α,β-unsaturated ketones (**158**), as shown in Scheme 57, and allow olefin formation with or without an alkylation step.[426,427]



i, $ClPO(OEt)_2$; ii, Li, NH_3 or Li, $EtNH_2$; iii, Li, NH_3 for R=H, $LiMe_2Cu$ or $LiEt_2Cu$ for R = Me or Et.

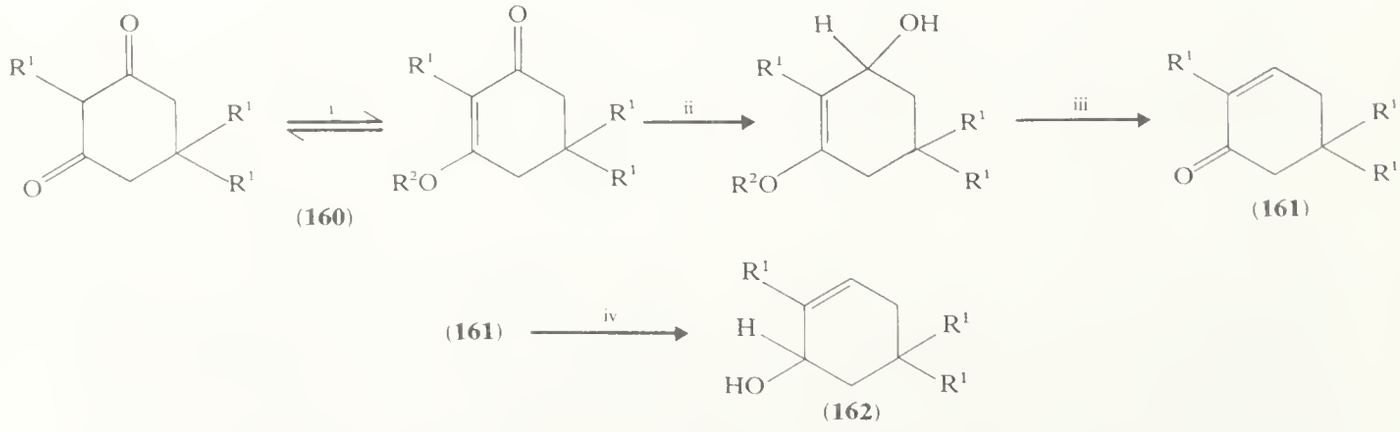
SCHEME 57



(40)

i, $LiAlH_4$; M = Al cation.

Reduction of enolizable β-diketones with lithium aluminium hydride in diethyl ether gives mixtures of products, and sometimes needs forcing conditions. The keto and enol forms seem to react separately, the former giving 1,3-diols and the latter giving allylic alcohols and, if excess of the reagent is avoided, α,β-unsaturated ketones. These deoxygenated products are believed to arise *via* the enolate salt (**159**) (equation 40). Complete conversion of the diketone to the enolate before reduction allows this path to dominate, and gives a good route to stereospecifically *trans* allylic alcohols.[428] A similar reaction (see Scheme 58) converts the cyclic diketone (**160**) to the cyclohexenol (**162**),[255] and enol ethers[79,429] and enol acetates of β-diketones to α,β-unsaturated ketones. The ketone group is moved in the latter cases. For deoxygenation of α,β-unsaturated ketones by reduction to the allylic alcohols and reductive dehydroxylation using 'dichloroaluminium hydride', see Refs. 406 and 415.



i, enolization (R^2 = H) or enol ether formation (R^2 = alkyl); ii, 1 equiv. $LiAlH_4$; iii, H_3O^+; iv, excess $LiAlH_4$.

SCHEME 58

5.2.14.8 Reductive cleavage of α-substituted ketones

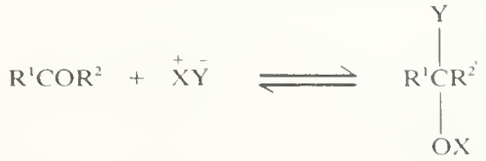
Upon reduction many ketones lose an α-substituent if this can depart as a stable anion. Most reducing agents, for example, readily reduce α-halo, α-hydroxy, α-alkoxy and α-acyloxy ketones and their vinylogues to the parent ketones. Zinc in acetic or dilute aqueous acids, and chromium(II) salts in acetic acid or acetone, allow mild and highly specific reaction.[36,401,430] The ease of dehalogenation decreases in the order iodides > bromides > chlorides ≫ fluorides, and axial leaving groups are removed more readily than equatorial from cyclohexanones.[430] If the carbonyl group is strongly hindered (*e.g.* in 12-hydroxy-11-keto steroids), elimination of a hydroxy group is difficult. Reduction of the α-ketol acetate with lithium or calcium in ammonia still succeeds, and is the preferred method.[399,430] The α-halo ketone function can be reduced to the parent ketone, without

reducing α-acetoxy ketones, using sodium borohydride deactivated by lead(II) acetate or other salts,[406] and to an α-halo alcohol by calcium trimethoxyborohydride or, less well, by sodium borohydride.[406]

5.2.15 ADDITIONS TO THE CARBONYL GROUP OF KETONES, PROTECTION METHODS, AND BASICITY

5.2.15.1 Additions

The many ionic reagents which add to the carbonyl group of aldehydes also add to ketones. These additions (equation 41) to form (**163**) are discussed in Section 5.1.5, which also gives cross-references to other sections in which the chemistry of the adducts is developed. General reviews are available on additions,[431] and on the dependence of addition rates on the reagents, catalysts, and pH.[432] Ref. 431 lists the dissociation constants for many adducts, and explains their variation with structure, and with the ring-size of cyclic ketones. In general, much smaller amounts of adducts are present in equilibrium with ketones than with related aldehydes. For simple aliphatic ketones which lack electron-attracting groups (such as α-halogens), the equilibria can lie strongly on the side of the ketone; this is the case for hydration, bisulphite and thiol additions, and — for many ketones — for the addition of alcohols and of hydrogen cyanide.[431] The following discussion is limited to the use of ketone-protecting groups.



(41)

(**163**)

5.2.15.2 Protecting groups

The same groups are frequently used to protect aldehyde and ketone groups during other reactions. Recent reviews are available.[433] Acetals, $R^1R^2C(OR)_2$, are formed by acid-catalysed reaction of ketones with alcohols, ROH, or alkane-1,2- or 1,3-diols, or with other acetals or orthoesters, $(RO)_3CH$. The reaction is the same as that which forms the acetals $R^1CH(OR)_2$ from aldehydes, and both types of derivative will be called 'acetals', except when the distinction is essential. Acetals derived from alkanols are cleaved by acidic hydrolysis. Some new acetals have the potential advantage of being cleaved under non-acidic conditions. The mono- and di-2,2,2-trichloroethyl acetals,[434] and 5,5-dibromo-1,3-dioxans,[435] can be made from the corresponding alcohol or 1,3-diol. The former groups are more stable towards acid than are methyl or ethyl acetals, and all are stable towards many other reagents. They are cleaved by specific, mild, metal reductions. The 5-methylene-1,3-dioxans,[436] and 4-bromomethyl-1,3-dioxolans,[437] can also be of value, but the latter have the disadvantage of introducing a new chiral centre into the molecule. A standard acetal formation method is suitable for use with α-bromo ketones and neither it nor the acid-induced hydrolysis affects the ratio of α- to α′-bromo ketone isomers.[150] Acetal formation from α,β-unsaturated ketones, including steroidal 4-ene-3-ones, gives a double-bond migration to the β,γ-position when the 'usual' acid-catalysed reactions are used.[67,118] The double bond does, however, revert to the α,β-position upon regeneration of the ketone by dilute acid hydrolysis. The initial isomerization can be avoided by using a very small amount of toluene-*p*-sulphonic acid monohydrate or adipic acid[67] as the catalyst. It is also avoided in thioacetal formation. Acetals are cleaved under very weakly acidic conditions, which can include the use of dried magnesium sulphate.[67]

The preparation of thioacetals from α,β-enones by the usual method (thiol or alkanedithiol with a trace of acid) proceeds without isomerization. The derivatives are stable towards dilute alkali, hydride reducing agents, and chromic oxide in pyridine, but are sensitive to many oxidation conditions and are cleaved by hydrogenation with Raney nickel. Cyclic dithioacetals (1,3-dithiolans and 1,3-dithians) are usually cleaved by hydrolysis in the presence of mercury(II) chloride and mercury(II) oxide or cadmium carbonate,[18,118] by oxidative hydrolysis using *N*-halogenosuccinimides,[118] 1-chlorobenztriazole,[438] or aqueous chloramine-T (sodium *N*-chlorotoluene-*p*-sulphonamide),[439] or by methyl iodide in methanol or aqueous acetone.[440] The chloramine-T cleavage applies also to 1,3-oxathiolans (ethylene hemithioacetals).[439] Acetals can be converted into 1,3-dithians by boron trifluoride-catalysed reaction with substituted propane-1,3-dithiols.[441]

The regeneration of saturated and unsaturated ketones from their oximes, arylhydrazones — including dinitrophenylhydrazones and tosylhydrazones — has been greatly improved. The derivative is exchanged with excess of acetone at 20–80 °C under neutral conditions, in a very simple procedure. The use of hexadeuterioacetone allows perdeuteriation of enolizable α-hydrogen atoms.[442] Methanolic or aqueous thallium(III) nitrate regenerates ketones from their oximes, semicarbazones, and phenylhydrazones, but not from 2,4-dinitrophenylhydrazones; the method is satisfactory for α,β-olefinic ketones but not for compounds having isolated olefinic bonds.[443] Dinitrophenylhydrazones of saturated and α,β-olefinic ketones are also cleaved by titanium(III) chloride in aqueous 1,2-dimethoxyethane.[444] Ketones are obtained from the acetates of their oximes by reduction with neutral chromium(II) acetate solutions. This reaction is particularly fast for conjugated enones and alkyl aryl ketones, but does not affect acetals, hemithioacetals, esters, or oxirans.[16]

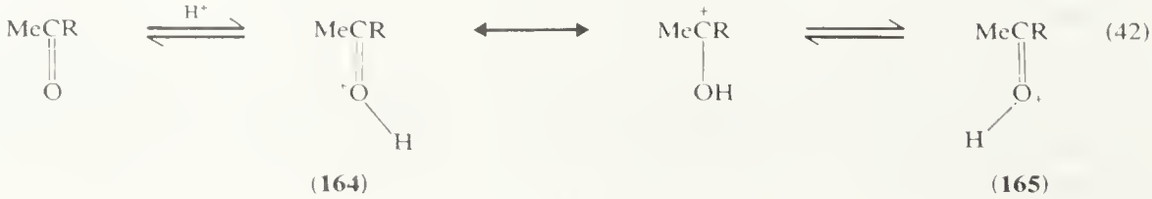
For conformational studies and n.m.r. spectroscopic data on the 2-substituted and 2,2-disubstituted 1,3-dioxans and 1,3-dithians derived from aldehydes and ketones, see Ref. 441 and references cited there.

Resolving agents for ketones (*inter alia*) have been reviewed.[445]

5.2.15.3 Basicity of ketones

For quantitative and mechanistic studies of reactions which involve the cations of ketones it is necessary to have basicity data. Aliphatic ketones are relatively weak bases, butan-2-one and pentan-3-one being half-protonated in *ca.* 80% by weight sulphuric acid–water at 25 °C (H_0, *ca.* −7.6). Accurate measurements of basicities of this order are difficult, owing to condensation reactions of the ketones. Acidity function methods are usually needed to give estimates of thermodynamic pK values, which have potentially large errors inherent in them.[446] Methods which use the heats of protonation rather than indicator ratio measurements can be valuable.[447] For selected data on many ketones, see Refs. 446 and 447, and for recent measurements, see Refs. 448 and 449. α,β-Olefinic ketones are much more basic than their saturated analogues. For example, cyclohex-2-enone is half-protonated in *ca.* 65% sulphuric acid (H_0, -5.0 ± 0.2) compared with cyclohexanone in 75% sulphuric acid (H_0, −6.6); the difference in estimated thermodynamic pK values is, however,[449] only *ca.* 0.4 units. Many data on cyclic and steroidal α,β-enones, and an empirical structure–basicity correlation, have been published.[450] Heats of mono- or di-protonation of 1,3- and 1,4-diketones in fluorosulphuric acid have been measured.[451]

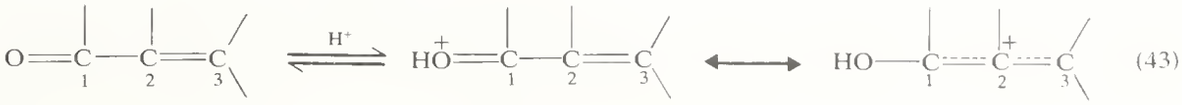
The cations of constitutionally unsymmetrical alkanones have substantial double bond character in the C—O bond and can have two stercoisomers (**164**) and (**165**) whose



(42)

(**164**) (**165**)

relative stabilities vary with the size of the group R (equation 42). As R becomes larger, isomer (**164**) becomes less important. *Ab initio* MO calculations suggest that the ions interconvert by movement of the hydroxyl proton in the plane of the molecule, and not by rotation about the C—O bond. For a review of n.m.r. spectroscopic studies of the cations of ketones and other compounds, see Ref. 452. The protonation of α,β-olefinic ketones and aldehydes occurs on the carbonyl oxygen. The positive charge density, deduced from ^{13}C n.m.r. spectroscopic measurements, is *ca.* 0.1–0.3 units at C-3, rather less at C-1, none at C-2, and the remainder at the carbonyl oxygen atom (equation 43). Protonation of β,γ-enones occurred at the γ-carbon (C-4) to give rapid isomerization to the cations of the α,β-enones.[453] Reaction of α,β-unsaturated ketones with hydrogen halides can lead to carbonyl protonation, or to addition to the olefinic or acetylenic group if the β-halo ketone which is formed is sufficiently stable.[454]



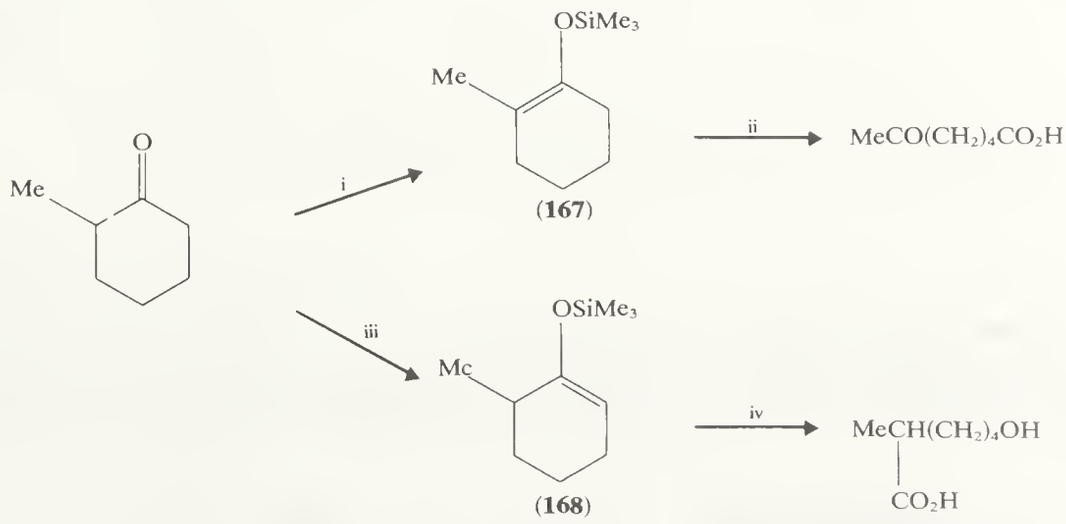
(43)

5.2.16 CLEAVAGE OF KETONES

The most general cleavage method for ketones uses the Baeyer–Villiger oxidation (see Section 5.2.17.1). This allows cleavage on the side of the carbonyl group which bears the better migrating group — R^2 in the case shown in equation (44) — to form an ester or a lactone (**166**). Cleavage can potentially be effected at either side of a ketone group by

(44)

ozonolysis of the corresponding trimethylsilyl enol ethers; see (**167**) and (**168**) in Scheme 59 and Section 5.2.4. The silyl ethers are ozonized selectively in the presence of remote olefinic groups. In many cases this method should allow cleavage of the bond which is not cleaved in the Baeyer–Villiger reaction. Because the silyl ethers can be made in other ways (see Section 5.2.4) the method allows elaboration and cleavage of, for example, α,β-olefinic ketones.[455] Methyl ketones RCOMe give the carboxylic acids RCO_2H or their esters, together with a haloform, upon halogenation under alkaline conditions. Excess of halogen or of hypohalites gives an intermediate trihalomethyl ketone, which is cleaved by hydroxide or alkoxide ion from the solvent. For a review of the haloform

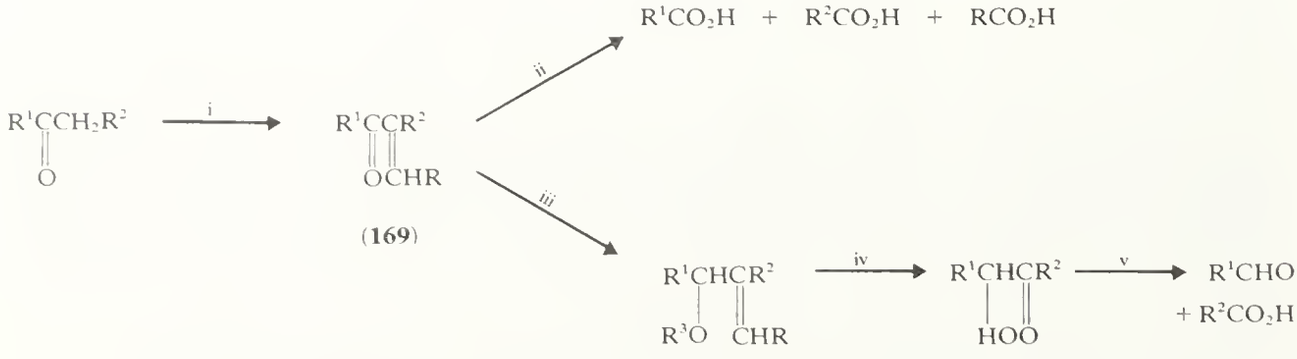


i, thermodynamically controlled enol silyl ether formation; ii, O_3; work-up with Me_2S, giving a keto acid; iii, enolate formation under kinetic control; Me_3SiCl; iv, O_3; work-up with $NaBH_4$, giving a hydroxy acid.

SCHEME 59

cleavage, see Ref. 456. The reaction is not specific for methyl ketones; constitutionally symmetrical ketones or those which can be halogenated on only one α-methylene group can give α,α-dihalo ketones which are cleaved and hydrolysed to give two carboxylic acid functions.[67,456] Alternatively, cleavage can give an acid and a chain which terminates in a synthetically useful dihalomethyl group.[458] Non-enolizable ketones R^1COR^2 are cleaved by potassium t-butoxide with water in ether or other aprotic solvents to give an acid R^1CO_2H and hydrocarbon function R^2H.[459]

Many oxidative cleavages are available.[281,456] Chromic acid effects fission on either side of the carbonyl group, to form two carboxylic acids or an acid and a ketone; cyclic ketones give α,ω-dicarboxylic acids. Nitric acid can be used, but is relatively unspecific.[456] The conditions required for these oxidations are severe and unselective. Cleavage is greatly facilitated by converting methylene ketones into α-benzylidene or α-furfurylidene ketones by condensation with benzaldehyde or furfural (Section 5.2.7.1), and then by oxidizing with permanganate, ozone, or alkaline hydrogen peroxide.[117,456] This gives a diacid, or two acids with the same total number of carbon atoms as the ketone. The method has been used in contracting cyclohexanones to cyclopentanones in steroid syntheses. The α-alkylidene ketones (**169**) can be cleaved in less direct ways, *via* an α-hydroxy ketone.[117] The α-hydroxy ketone function is readily cleaved to a ketone plus a carboxylic acid, or to two acids using periodate[460] or lead tetra-acetate.[339] The α-diketone group is cleaved to two acids by the same reagents or by alkaline hydrogen peroxide.[67,456] Thus any of the routes given in Sections 5.2.10.1 and 5.2.11.1 for converting ketones into these α-oxygenated ketones can constitute cleavage methods. A methylene ketone can also be converted (see Scheme 60) into an α-formyl ketone (α-hydroxymethylene ketone) (**169**; R = OH) which, in common with cyclic β-diketones,[460] is cleaved to two acids or a diacid, with loss of the formyl carbon, using periodate.[312] Hydrogen peroxide cleavage can also be used on β-diketones or β-keto aldehydes, but in some cases a skeletal rearrangement occurs instead.[303]



i, HCO_2Et, NaOEt, for R = OH; PhCHO, OH^- for R = Ph; furfural, OH^- for R = furanyl; ii, O_3 or $NaIO_4$ or H_2O_2/OH^-; iii, $NaBH_4$; protect alcohol; iv, O_3; v, $NaIO_4$.

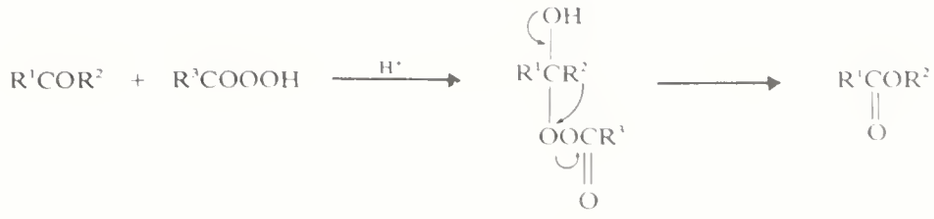
SCHEME 60

5.2.17 REARRANGEMENTS OF KETONES

In the reactions to be discussed a bond to the carbonyl group is broken or made in a skeletal rearrangement. For a general review, see Ref. 461.

5.2.17.1 Baeyer–Villiger oxidation

Upon treatment with peroxy acids, acyclic ketones undergo an oxidative rearrangement, with the formation of esters; cyclic ketones form lactones in the same way.[456] The process involves (equation 45) the intramolecular migration of a group from the carbonyl centre

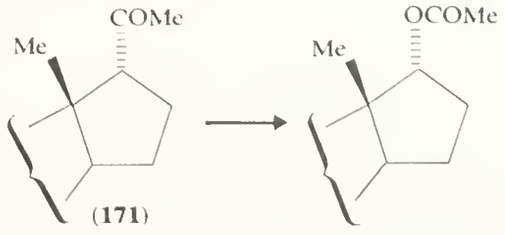


(45)

(170)

to the peroxide-oxygen in an electron-deficient species such as (**170**). Usually the more electron-releasing group of R^1 and R^2 in (**170**) migrates; the order of ease of migration of alkyl groups is thus tertiary > secondary > primary. As in other cationic 1,2-rearrangements, the migrating group retains its stereochemical configuration.[22,456] Rearrangement of α,β-olefinic ketones can give enol esters or enol lactones by preferential migration of the vinylic group. Although isolated olefinic groups are subject to epoxide formation, the α,β-enones are not epoxidized by (electrophilic) peroxy acids.

Reagents used for the rearrangement include peracetic acid (especially for converting cyclic ketones into lactones), *m*-chloroperbenzoic acid (used extensively to convert acetylcyclopentanes to cyclopentyl acetates in the steroid and prostaglandin series), peroxymaleic cid (which is inexpensive), and peroxytrifluoroacetic acid (which gives the most reliable results). All of the aliphatic peroxy acids mentioned can be made *in situ*, as can Caro's acid (peroxymonosulphuric acid), which has been frequently used. Many applications of the rearrangement are given in Ref. 67. See, for example, (**171**)–(**173**) in equations (46)–(48).

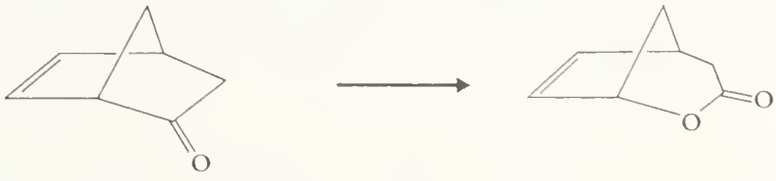


(46)

(171)

(47)

(172)

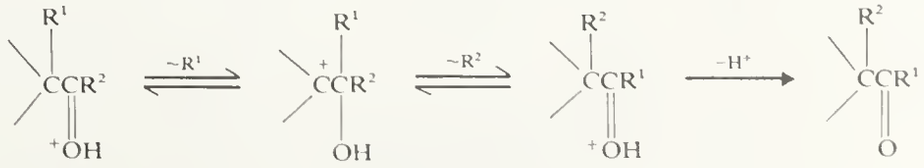


(48)

(173)

5.2.17.2 Ketone isomerizations

Many ketones undergo isomerization to other ketones upon treatment with strong mineral acids. Aldehydes can isomerize to ketones by a similar, but easier, process. For reviews, see Refs. 461 and 462, and for recent studies, see Refs. 27 and 28. The carbonyl compound is protonated (equation 49) to give the ion (**174**), which slowly undergoes



(49)

(174) (175)

1. $Me_3CCOCMe_3 \xrightarrow{i} Me_3CC(Me)_2COMe$

2. $MeCH_2COCH_2Me \xrightarrow{ii} MeCH_2CH_2COMe$

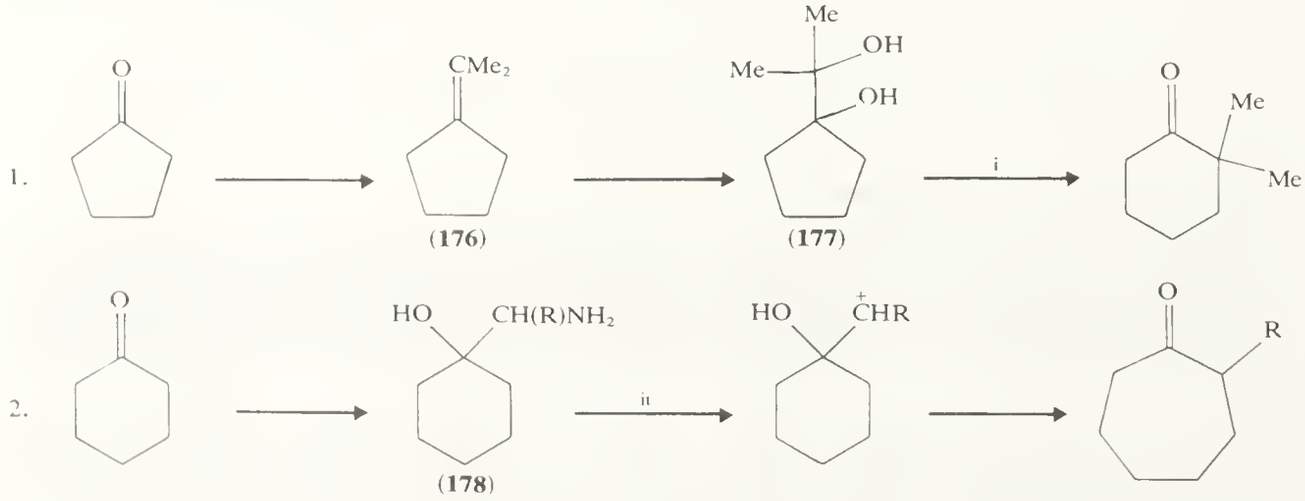
i, conc. H_2SO_4, 25 °C, 24 h, ii, 70% $HClO_4$, 90 °C, 3 h.

SCHEME 61

rearrangement by migration of a group from the α-carbon to the carbonyl-carbon atom and then back-migration of the same group or of the α′-carbon atom. The intramolecular reaction is facilitated by factors which stabilize the cation (**175**); relatively easy rearrangement is found (see Scheme 61) in α-branched alkyl ketones, and aryl ketones in which an aryl group can migrate. In general, however, the isomerizations are slow and require strongly acidic media, often with elevated reaction temperatures. Alkyl ketones isomerize to methyl ketones when possible, because the latter are most stable; many data on the equilibria between isomeric ketones are given by Fry.[462] Acylcyclopentanes interconvert with 2-alkylcyclohexanones, and 2,2-dialkylcycloheptanones undergo ring-contraction to 1-acylalkylcyclohexanes.[462] The rearranging cation (**175**) is also accessible in the pinacol rearrangements of diols, and many studies of the latter reaction are relevant.[27,28,462] Migrations of the oxygen function are often found under the strongly acidic conditions indicated above. They are slower than alkyl migrations and appear to arise (formally) by a 1,2-shift of the hydroxyl function in cations (**175**); they are often demonstrated by carbon-labelling experiments. Pentan-2-one can thus be equilibrated (see Scheme 61) with the less stable pentan-3-one and long-chain ketones can have the carbonyl group passed very slowly along the chain.[462]

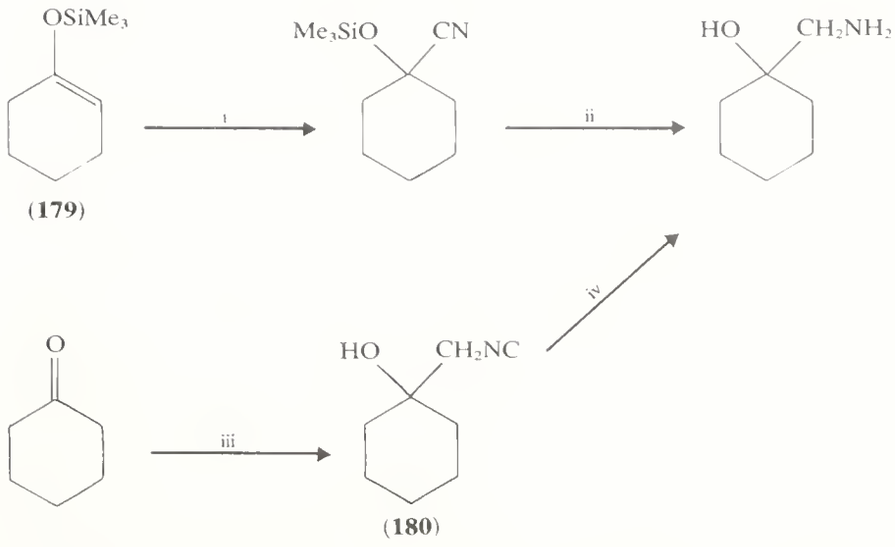
5.2.17.3 Ring-expansions and homologations of ketones

For a review, see Ref. 463. Cyclic ketones can be converted into their homologues in a number of ways; most are indirect. They can give exocyclic olefins (alkylidenecycloalkanes) (**176**) *via* the Wittig reaction or related processes, and then formation of the diol (**177**) is followed by pinacol rearrangement as shown in Scheme 62. Pinacolic deaminations are frequently used (the Tiffeneau–Demjanov rearrangement).[463,464] The ketone is converted (see Scheme 62) into a 1-aminomethylcycloalkanol (**178**) which is treated with nitrous acid to form the homologated ketone. The method is used widely for preparing five- to nine-membered rings, and particularly for preparing the cyclohexanone D-ring of D-homo steroids.[56,463,464] The aminomethylcycloalkanol is usually made by reduction of the cyanohydrin — from the ketone and hydrogen cyanide, or aqueous



i, H_3O^+; ii, HNO_2.

SCHEME 62



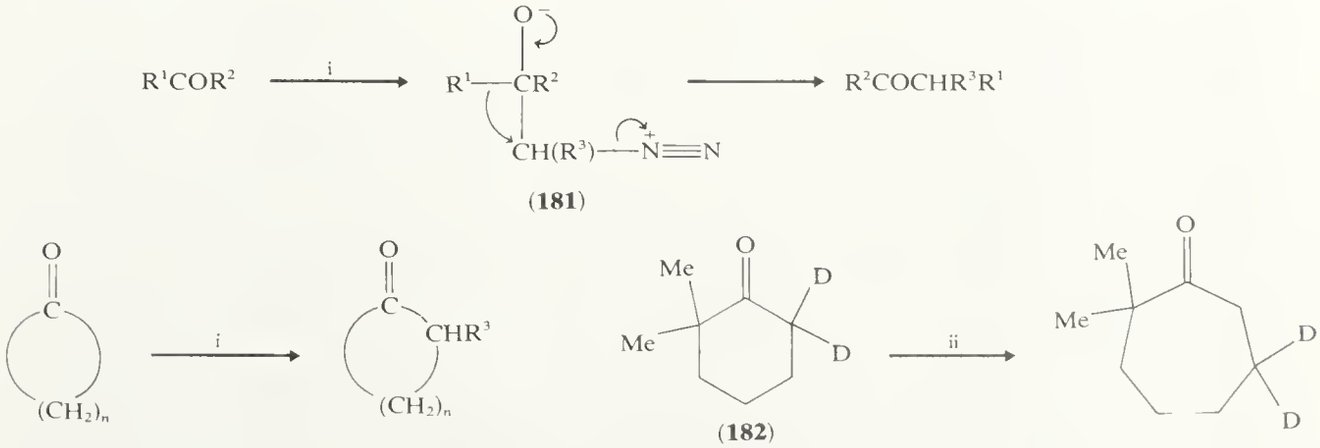
i, 49% HCN + trace H_2SO_4; ii, $LiAlH_4$, then H_2O; iii, $LiCH_2NC$, from MeNC + Bu^nLi in THF; iv, HCl, MeOH.

SCHEME 63

sodium cyanide and sodium bisulphite — or of the nitroalkylcycloalkanol. The latter is made by base-catalysed addition of enolizable nitroalkanes to the ketone, or by the ring-opening of the epoxide of an alkylidenecycloalkane (**176**) with a nitroalkane anion.[463] Other methods are available.[464] A new preparation of aminomethylcycloalkanols is valuable when others fail; in this the trimethylsilyl enol ether derived from the ketone reacts as shown for (**179**)[63] and (**180**)[465] in Scheme 63.

Ketones, and aldehydes, react with diazomethane to form homologated products as shown in Scheme 64. The intermediate (**181**) rearranges intramolecularly, and the better electron-donating group, R^1, might be expected to migrate to the potential cationic centre. In fact, the order of migrating ability is phenyl > $Me_2C{=}CH$ > Me ≈ Pr^n > Pr^i > benzyl > Bu^t, which is different from that found in typical cationic rearrangements;[463] see, for example, (**182**)[466] in Scheme 64. Other diazoalkanes, and esters of diazoacetic acid, effect similar rearrangements. The major application is to the conversion of constitutionally symmetrical cycloalkanones to their homologues, and especially for expanding six- or larger-membered rings. The reaction with α,β-olefinic ketones must be catalysed by Lewis acids, and involves migration of the vinylic α-carbon atom to form a β,γ-olefinic ketone.[90,463]

See also Refs. 203 and 467 for homologations which lead to ketones and α-chloro ketones.

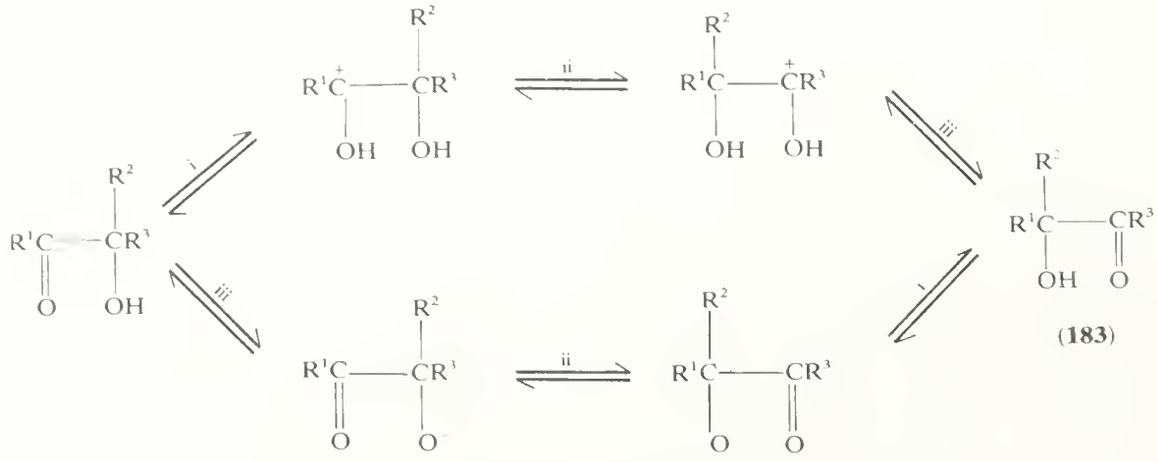


i, R^3CHN_2; R^3 = H, alkyl, or aryl, or CO_2alkyl; ii, CH_2N_2.

SCHEME 64

5.2.17.4 Rearrangements of α-ketols; the acyloin rearrangement

α-Hydroxy ketones rearrange under acidic or basic conditions to give isomeric hydroxy ketones (**183**), as shown in Scheme 65. For reviews, see Refs. 56, 461, and 463. In many cases, but by no means all, the different reagents give the same products. The main application of the rearrangement has been in the ring-expansion of 17-hydroxy-20-keto steroids to D-homo steroids; the products depend on the configurations of the acetyl and hydroxy groups and on the reaction conditions.[56,463] If the group R^1 in (**183**) is hydrogen the isomerization can occur merely by enolization to an enediol and reprotonation. The ketol rearrangements are very common in carbohydrates, *e.g.* in the interconversion of α-hydroxy aldehydes, such as mannose, and α-hydroxymethyl ketones, such as fructose. Similar rearrangements occur in α-amino ketones and α-hydroxyimines.[463]



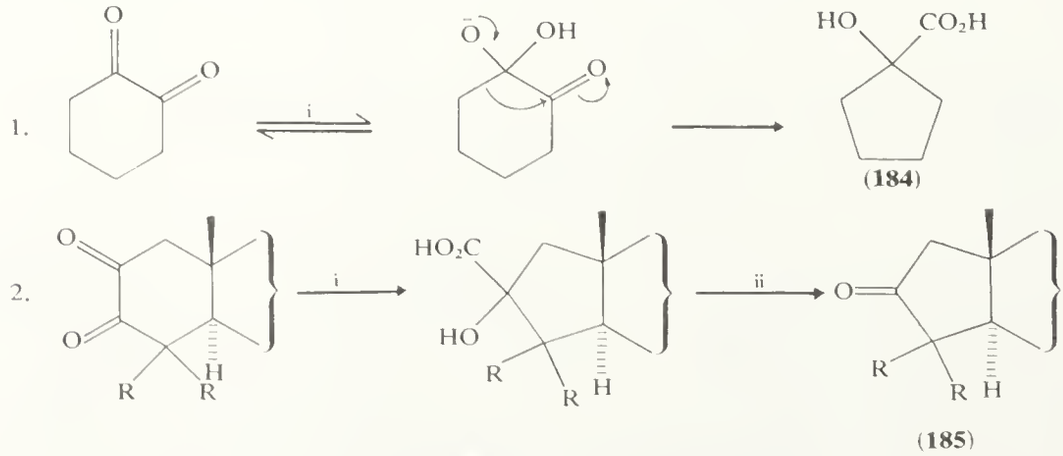
(**183**)

i, H^+; ii, $-R^2$; iii, $-H^+$.

SCHEME 65

5.2.17.5 Rearrangements of α-diketones

The benzilic acid rearrangement, which converts aromatic 1,2-diketones into benzilic acid or its esters by reaction with hydroxide or alkoxide ions, applies also to aliphatic and alicyclic 1,2-diketones. For reviews, see Refs. 461, 468, and 469. The reaction is valuable (see Scheme 66) for contracting cyclic diketones, and particularly cyclohexane-1,2-diones to 1-hydroxycyclopentanecarboxylic acids (**184**).[468] The application to steroids allows A-nor- and C-nor-steroids to be prepared, *e.g.* (**185**) in Scheme 66. The attack by base appears to be at C-3, for both 3,4-diketo- and 2,3-diketo-cholestane, but the site of attack



(**184**)

(**185**)

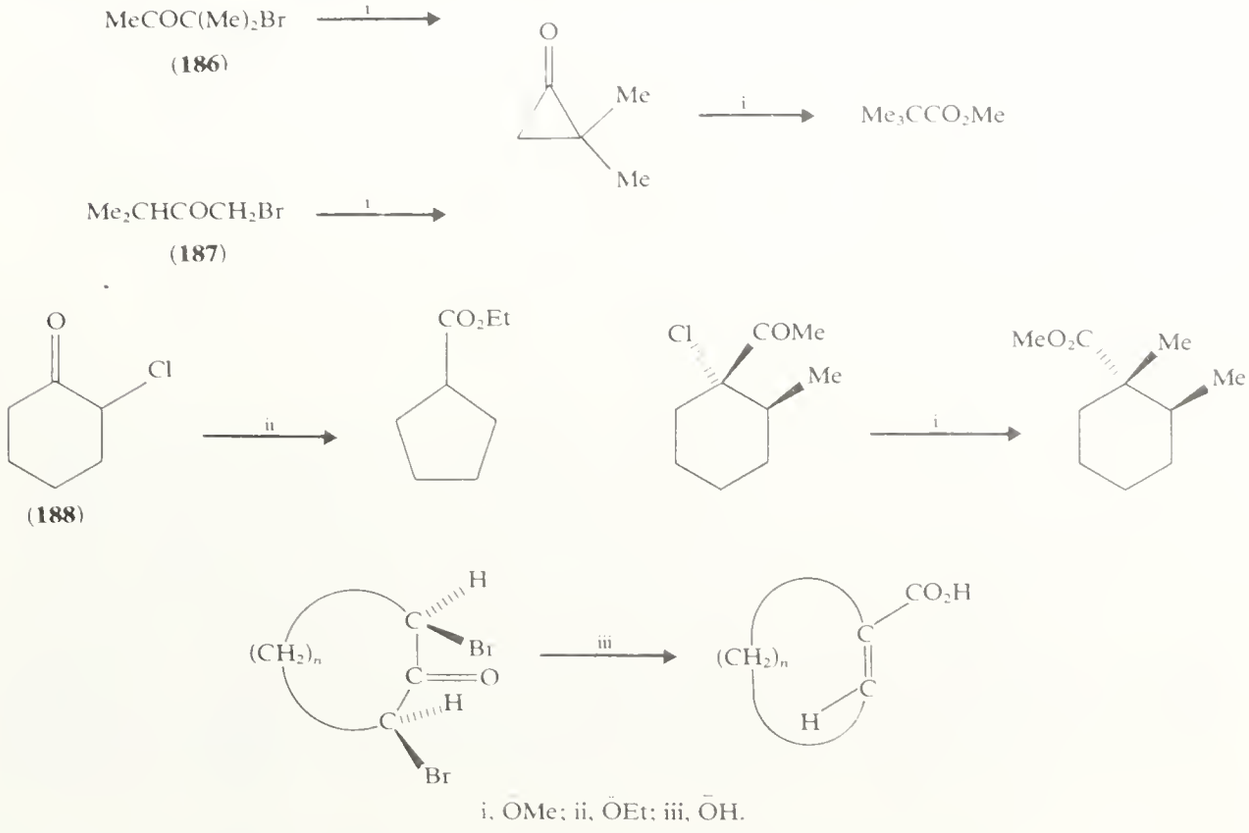
i, OH^-; R = H or Me; ii, $Pb(OAc)_4$.

SCHEME 66

does not alter the nature of the product. Compounds which can be converted by base into α-diketones, *e.g.* α,α-dihalogeno ketones, often give the same rearrangement.

5.2.17.6 The Favorskii rearrangement of α-halo ketones

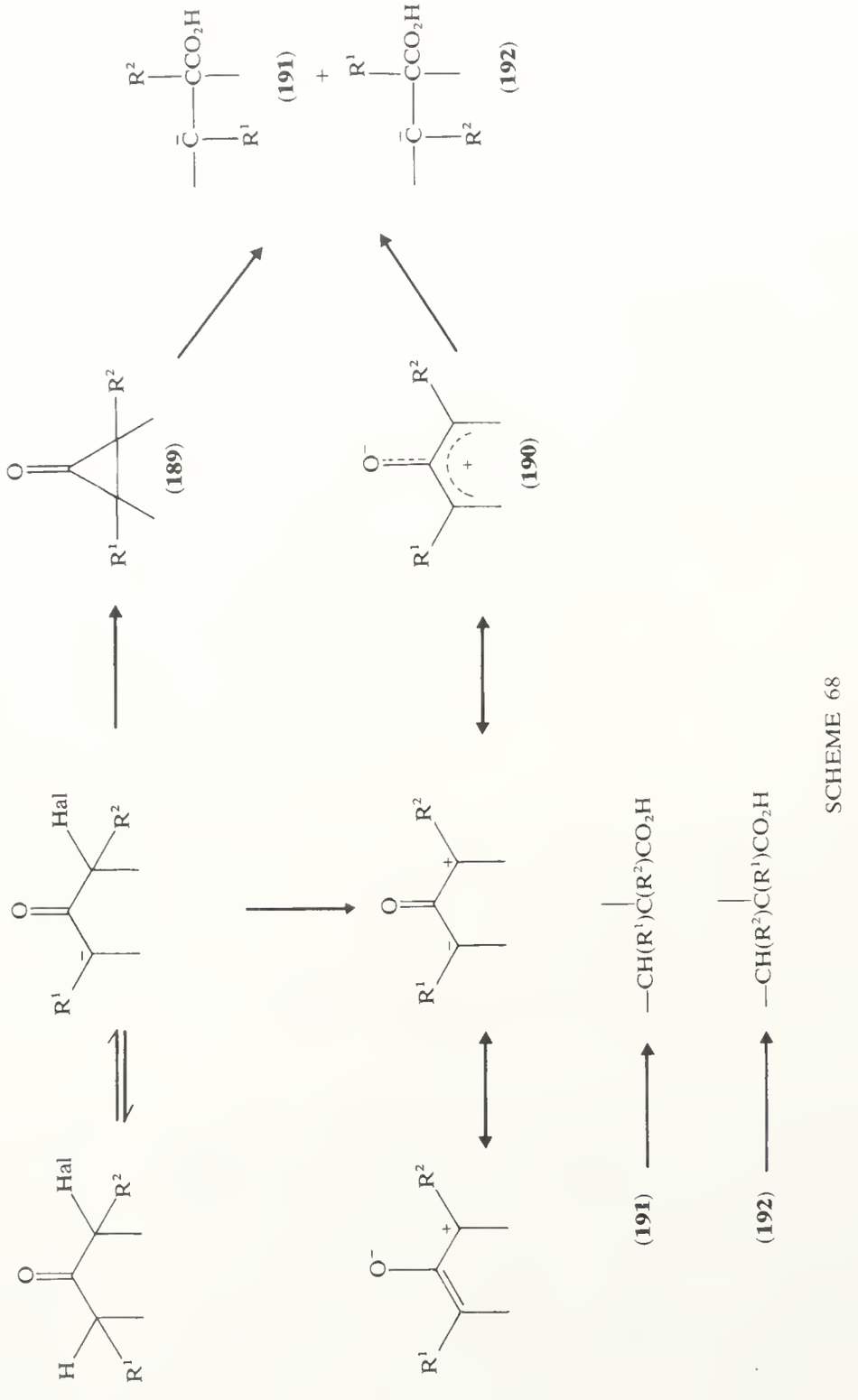
The Favorskii rearrangement occurs when α-halo ketones are treated with nucleophilic bases (*e.g.* hydroxide or alkoxide ions, or amines) to give the salts, esters, or amides of carboxylic acids, with a skeletal rearrangement. For reviews, see Refs. 468 and 470. Although the reaction is most often applied to monohalo ketones, it also occurs with α,α- and α,α′-dihalo ketones (to give α,β-olefinic acids), with α,β-dihalo ketones (to give β,γ-olefinic acids initially), and with α,α,α′-trihalo ketones (to give mainly α-halo-α,β-olefinic acid derivatives). Some examples are shown in Scheme 67.



i, $\bar{O}Me$; ii, $\bar{O}Et$; iii, $\bar{O}H$.

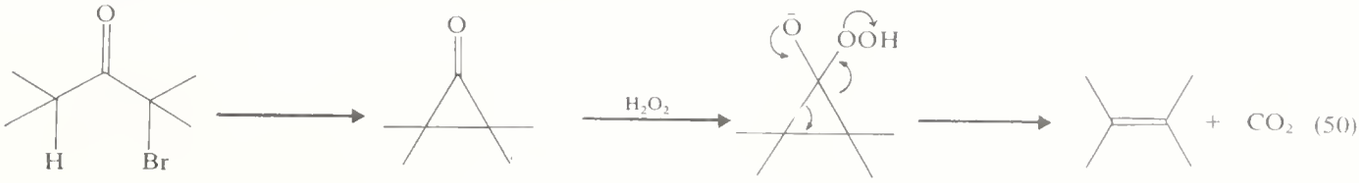
SCHEME 67

Two mechanisms commonly operate. In the first (the Loftfield mechanism) an α′-proton is removed by the base, and the α-halogen expelled to form a symmetrical intermediate. This is formulated (see Scheme 68) as a cyclopropanone (**189**) or as a zwitterion (**190**). These intermediates represent the ends of a spectrum of structures which differ in the degree of bonding between the α- and α′-carbon atoms, and whose importance depends on the polarity of the reaction medium and on the structure of the reactants. Attack by the base on the carbonyl group of (**189**), accompanied by cleavage of the cyclopropanone ring, or migration in (**190**) of the α-carbon to the α′-centre (or *vice versa*), gives the rearrangement products (**191**) and (**192**). The symmetry of the intermediates implies (see Scheme 67) that the isomeric α- and α′-halo derivatives of a ketone, *e.g.* (**186**) and (**187**), can lead to the same product or mixture of products. The more stable of carbanions (**191**) and (**192**) is formed preferentially; when only alkyl substituents are present, this has the less alkylated β-carbon and the more alkylated α-carbon. The Favorskii rearrangement is thus very useful for preparing heavily α-substituted acids. The ring-contraction of α-halocycloalkanones, *e.g.* (**188**), is synthetically valuable; for many examples, see Refs.



SCHEME 68

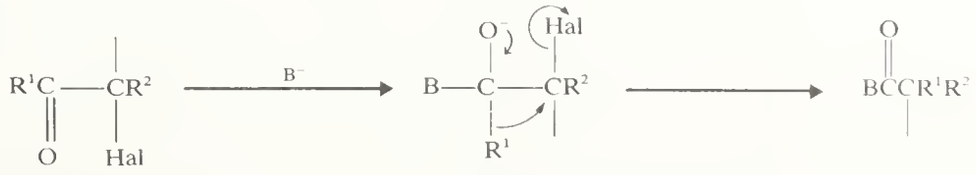
56 and 468. A number of cyclopropanones have been prepared, and undergo ring-opening in the manner required for the rearrangement.[471] Their formation and trapping by alkaline hydrogen peroxide allows α-halo ketones to be degraded to olefins (equation 50) *via* an intermediate of type (**193**).[472]



(50)

(**193**)

The second mechanism for the Favorskii rearrangement, the semibenzilic route, resembles that of the benzilic acid rearrangement. It is postulated when formation of (**189**) or (**190**) is prevented by the absence of an α′ proton or by severe ring-strain, steric hindrance, or Bredt's rule interdiction of enolate formation. The ketone function is attacked by base to form an intermediate (**194**) which rearranges with loss of halide ion (equation 51). In contrast to the previous mechanisms, isomeric halo ketones give isomeric products.



(51)

(**194**)

The rearrangement shows strong stereochemical control. The cyclopropanone and semibenzilic mechanisms both imply an inversion of configuration at the α-carbon atom when the migrating group replaces the halide, and a preferred orientation for the halogen if it is to be lost in a concerted process. Axial α-halocyclohexanones frequently do not rearrange. Incursion of the zwitterion mechanism removes the stereospecificity.[468,470] Related rearrangements occur with α-epoxy ketones.

Common side reactions include the formation of α-epoxy ethers, which arise particularly when the halo ketones react with alkoxides in ether solution. They lead to α-hydroxy ketones or α-hydroxy acetals upon aqueous work-up, but do not give Favorskii products. The halogen can also be directly displaced to form an unrearranged α-hydroxy- or an α- or α′-alkoxy ketone (see Sections 5.2.6.1 and 5.2.11.1).

5.2.18 PHOTOCHEMICAL REACTIONS OF KETONES

Many cleavages, rearrangements, and addition reactions of ketones have been effected photochemically. For a review of cyclic ketone photochemistry, with much spectroscopic data, see Ref. 473; for photochemical rearrangements of conjugated cyclic ketones, see Ref. 474; for the photoaddition of carbonyl compounds to olefins to form oxetans see Ref. 475; for the cleavage of cyclic alkanones, see Ref. 476; for the photochemistry of α-dicarbonyl compounds, see Ref. 477.

5.2.19 SPECTRA OF KETONES

5.2.19.1 Infrared spectroscopy

The carbonyl group of ketones gives a strong characteristic peak in the i.r. spectrum at about 1720 cm^{-1} (C=O stretching frequency). The position is changed by inclusion in small rings (increase in frequency with decrease in ring size), by conjugation with olefinic

or other unsaturated groups (decrease in frequency), and by electronegative groups on the α-carbon atom or directly attached (increase in frequency). These effects, and correlations of frequency with structure, are well documented.[478]

5.2.19.2 Ultraviolet spectroscopy

Conjugated unsaturated ketones give very strong u.v. absorption ($\varepsilon \approx 10^4$), due to $\pi \rightarrow \pi^*$ electronic transitions, in the wavelength region 215–275 nm as well as the weak $n \rightarrow \pi^*$ absorption ($\varepsilon \approx 10$–10^2) in the region 270–320 nm, characteristic of the carbonyl group itself. The position and intensity of these peaks have been related to the structure of the ketones. Woodward and the Fiesers have formulated empirical rules which relate the wavelength of maximum $\pi \rightarrow \pi^*$ absorption to the number, type, and position of substituents on α,β-unsaturated ketones, to the ring size of cyclic compounds, and to the solvent used in measuring the spectra.[479]

5.2.19.3 ^{1}H Nuclear magnetic resonance spectroscopy

In proton nuclear magnetic resonance (^{1}H n.m.r.) spectra the carbonyl group itself is of course inactive, but protons on the adjacent carbon atom appear in a characteristic position (δ 2.1) which is modified in a predictable manner by the attachment of other substituents. The configuration of α-substituents can often be studied using the chemical shift of the remaining α-proton and its coupling constants with β- or sometimes α′-protons. This is particularly useful with α-halocyclohexanones. In α,β-unsaturated ketones the typical electron shifts leave the β-carbon somewhat electron deficient, so that protons attached to it are strongly deshielded (moved to higher δ values) than those on the α-carbon. Methyl groups attached to the β-carbon are similarly, but less strongly, deshielded. The *cis* or *trans* disposition of protons, and sometimes of alkyl groups, is reflected in the coupling constant between them. For a recent review, see Ref. 480; for the ^{1}H n.m.r. spectra of steroids, see Ref. 481.

Two valuable techniques allow extra information to be gained from standard ^{1}H and ^{13}C n.m.r. spectroscopy. They are especially valuable in analysing complex spectra where peaks due to different groups fall close together, and in studies of the conformations of mobile molecules. Solvent shift studies use spectra of the ketones in the usual solvents, carbon tetrachloride or deuteriochloroform, and spectra of solutions in associating solvents, usually benzene or hexadeuteriobenzene. Protons which lie in a geometrical plane through the carbonyl carbon, perpendicular to the C=O bond, resonate at the same chemical shift in both types of solvent. Those lying to the side of the plane remote from the carbonyl oxygen resonate at higher field in benzene, the solvent shift, $\delta_{CCl_4} - \delta_{C_6H_6}$, being larger as the protons become more remote. Protons lying on the oxygen side of the plane show a negative solvent shift.[168,480] Lanthanide shift reagents are used frequently in a related, and more powerful, way. Their addition to solutions of ketones — and many other classes of compound — effects a shift in the resonances of protons and carbon atoms which becomes greater as the observed atom becomes closer to the lanthanide atom (and the carbonyl oxygen). Some reagents cause an upfield, and some a downfield, shift.[482]

5.2.19.4 ^{13}C Nuclear magnetic resonance spectroscopy

In recent years, ^{13}C n.m.r. spectra of many ketones have been measured. The information provided about the type of carbonyl groups in a compound (*e.g.* ketone, aldehyde, ester) greatly increases that available from i.r. spectra. The carbonyl carbon of acyclic and cyclic ketones gives a strong signal at 200–220 p.p.m. downfield from tetramethylsilane. Methyl groups attached to the α- and β-carbon atoms cause moderate downfield shifts, whereas α,β-unsaturation and α-substitution with electronegative groups, such as halogen, hydroxyl, and other ketone groups leads to stronger upfield shifts.[483]

5.2.19.5 Circular dichroism and optical rotatory dispersion

Optical rotatory dispersion spectra, and circular dichroism spectra which have largely supplanted them as the major chiroptical technique, are applied to optically active (chiral) ketones. They are of particular importance in determinations of relative and absolute configurations, and in conformational analysis. Polarizable α-substituents, such as halogen, hydroxy, or acetoxy groups, or α,β- and $\beta\gamma$-unsaturation, lead to strong Cotton effects in the u.v. spectral region, but suitably placed remote substituents can also give strong spectra. The subject is reviewed in monographs.[484] References to more recent work, and important contributions to the empirical theory of the techniques, are in Ref. 485.

5.2.19.6 Some spectroscopic data

In the following section are selected references to useful sources of spectroscopic data which modify or extend those available in the books already cited.

Simple aliphatic and alicyclic ketones (^{13}C n.m.r. and solvent shifts, i.r.)[449,486] and their cations;[449] methylcyclohexanones (i.r., ^{1}H n.m.r.) and benzene solvent shifts.[487] α,β-Unsaturated ketones, including cyclic enones and cyclohexenones, often with discussions of preferred conformations (i.r. and ^{1}H n.m.r.),[488] (^{1}H n.m.r. and benzene solvent shifts),[489] (^{13}C n.m.r.),[490] (u.v. and theoretical calculations).[10] β-Oxy-α,β-unsaturated ketones (u.v. and i.r.);[491] linear conjugated dienones (i.r., u.v., ^{1}H n.m.r.).[492] Alkylcyclopent-2-enones (i.r., u.v., ^{1}H n.m.r.),[493] α-methylenecycloalkanones,[493b] and α,α'-cycloalkadienones (i.r., u.v., ^{1}H n.m.r.).[140]

For ^{1}H n.m.r. data on 2-bromo- and 2,6-dibromo-cyclohexanones, see Ref. 168; α,α'-dibromo ketones (aliphatic and cyclic),[160,338] α-chloro ketones,[138] α-bromo ketones and their acetals (i.r. and ^{1}H n.m.r.),[70] and α-, β-,[376,494] and γ-chloro ketones.[494] For data on α-hydroxy ketones (^{1}H n.m.r.), see Refs. 330a and 495; for α-acetoxy ketones, see Ref. 338 and 495; β-hydroxy ketones (i.r. and ^{1}H n.m.r.);[175] Mannich bases (2-dialkylaminomethyl ketones) and their salts (^{1}H n.m.r.).[185] Further data on steroidal ketones (^{1}H n.m.r.),[496] (^{13}C n.m.r.);[497] on the ketones and their cations (^{13}C n.m.r. and u.v.).[449] For data on the ^{1}H n.m.r. and lanthanide-induced shifts of saturated, unsaturated, and cyclic ketones see Ref. 498. For protonated aliphatic, alicyclic, and α,β-unsaturated ketones (^{1}H n.m.r. and ^{13}C n.m.r.), see Refs. 452 and 453; for the u.v., ^{1}H, and ^{13}C n.m.r. of the cations of both *cis*- and *trans*-isomers, see Ref. 499.

References

1. I.U.P.A.C. Definitive rules for nomenclature of organic chemistry, Section C, 1965; *Pure Appl. Chem.*, 1965, **11,** 3.
2. J. D. Cox and G. Pilcher, 'Thermochemistry of Organic and Organometallic Compounds,' Academic, London, 1970.
3. J. Berthier and J. Serre, in Ref. 4, chapter 1.
4. 'The Chemistry of the Carbonyl Group,' ed. S. Patai, Interscience, London, 1966.
5. J. E. Dubois and H. Herzog, *J.C.S. Chem. Comm.*, 1972, 932; H. K. Eigenmann, D. M. Golden, and S. W. Benson, *J. Phys. Chem.*, 1973, **77,** 1687.
6. W. J. Hehre and J. A. Pople, *J. Amer. Chem. Soc.*, 1970, **92,** 2191.
7. R. Ditchfield, J. E. Del Bene, and J. A. Pople, *J. Amer. Chem. Soc.*, 1972, **94,** 703.
8. N. L. Allinger, G. A. Lane, and G. L. Wang, *J. Org. Chem.*, 1974, **39,** 704; N. L. Allinger, *Adv. Phys. Org. Chem.*, 1976, **13,** 1.
9. P. Müller and J. C. Perlberger, *J. Amer. Chem. Soc.*, 1975, **97,** 6862.
10. T. Liljefors and N. L. Allinger, *J. Amer. Chem. Soc.*, 1976, **98,** 2745.
11. D. D. Faulk and A. Fry, *J. Org. Chem.*, 1970, **35,** 364.
12. E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, 'Conformational Analysis,' Interscience, New York, 1965; M. J. T. Robinson, *Pure Appl. Chem.*, 1971, **25,** 635.
13. M. Langlais, A. Buzas, G. Soussan, and P. Freon, *Compt. rend.*, 1965, **261C,** 2920.
14. D. A. Shirley, *Org. Reactions*, 1954, **8,** 28.
15. E. J. Corey and K. Achiwa, *J. Amer. Chem. Soc.*, 1969, **91,** 1429.

16. E. J. Corey and J. E. Richman, *J. Amer. Chem. Soc.*, 1970, **92**, 5276.
17. D. Seebach, *Synthesis*, 1969, 17.
18. E. J. Corey and B. W. Erickson, *J. Org. Chem.*, 1971, **36**, 3553.
19. D. Seebach and E. J. Corey, *J. Org. Chem.*, 1975, **40**, 231.
20. G. T. Rodeheaver and D. F. Hunt, *Chem. Comm.*, 1971, 818.
21. M. J. Jorgenson, *Org. Reactions*, 1970, **18**, 1.
22. H. O. House and T. M. Bare, *J. Org. Chem.*, 1968, **33**, 943.
23. J. A. Gautier, M. Miocque, and L. Mascrier-Demagny, *Bull. Soc. chim. France*, 1967, 1551.
24. J. A. Marshall, M. T. Pike, and R. D. Carroll, *J. Org. Chem.*, 1966, **31**, 2933.
25. G. H. Posner, *Org. Reactions*, 1975, **22**, 253.
26. J. E. MacPhee and J. E. Dubois, *Tetrahedron Letters*, 1972, 467.
27. J. E. Dubois and P. Bauer, *J. Amer. Chem. Soc.*, 1976, **98**, 6993.
28. P. Bauer and J. E. Dubois, *J. Amer. Chem. Soc.*, 1976, **98**, 6999.
29. J. P. Collman, S. R. Winter, and D. R. Clark, *J. Amer. Chem. Soc.*, 1972, **94**, 1788; J. P. Collman, *Accounts Chem. Res.*, 1975, **8**, 342.
30. M. P. Cooke, Jr. and R. M. Parlman, *J. Amer. Chem. Soc.*, 1975, **97**, 6863.
31. J. M. Conia, *Angew. Chem. Internat. Edn.*, 1968, **7**, 570.
32. A. I. Meyers and E. M. Smith, *J. Org. Chem.*, 1972, **37**, 4289.
33. A. I. Meyers, E. M. Smith, and M. S. Ao, *J. Org. Chem.*, 1973, **38**, 2129.
34. A. I. Meyers, A. C. Kovelesky, and A. F. Jurjevich, *J. Org. Chem.*, 1973, **38**, 2136.
35. G. R. Malone and A. I. Meyers, *J. Org. Chem.*, 1974, **39**, 623.
36. H. O. House, 'Modern Synthetic Reactions,' Benjamin, Menlo Park, 1972, 2nd edn.
37. S. Forsen and M. Nilsson, in Ref. 38, chapter 3.
38. 'The Chemistry of the Carbonyl Group,' ed. J. Zabicky, Interscience, London, 1970, vol. 2.
39. P. Alcais and R. Brouillard, *J.C.S. Perkin II*, 1972, 1214.
40. H. M. R. Hoffmann and E. A. Schmidt, *J. Amer. Chem. Soc.*, 1972, **94**, 1373; E. A. Schmidt and H. M. R. Hoffmann, *ibid.*, p. 7832.
41. V. Dave and E. W. Warnhoff, *Tetrahedron Letters*, 1976, 4695.
42. J. d'Angelo, *Tetrahedron*, 1976, **32**, 2979.
43. H. O. House and V. Kramar, *J. Org. Chem.*, 1963, **28**, 3362.
44. H. O. House and B. M. Trost, *J. Org. Chem.*, 1965, **30**, 1341.
45. H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, 1969, **34**, 2324.
46. G. Stork and P. F. Hudrlik, *J. Amer. Chem. Soc.*, 1968, **90**, 4462.
47. R. Gompper, *Angew. Chem. Internat. Edn.*, 1964, **3**, 560.
48. H. O. House, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, 1971, **36**, 2361.
49. R. P. Bell, G. R. Hillier, J. W. Mansfield, and D. G. Street, *J. Chem. Soc.* (*B*), 1967, 827.
50. A. A. Bothner-By and C. Sun, *J. Org. Chem.*, 1967, **32**, 492.
51. C. Rappe and W. H. Sachs, *J. Org. Chem.*, 1967, **32**, 3700.
52. J. E. Dubois, P. Alcais, R. Brouillard, and J. Toullec, *J. Org. Chem.*, 1971, **36**, 4129.
53. H. O. House, R. A. Auerbach, M. Gall, and N. P. Peet, *J. Org. Chem.*, 1973, **38**, 514.
54. J. F. W. Keana, in Ref. 55, chapter 1.
55. 'Steroid Reactions, an Outline for Organic Chemists,' ed. C. Djerassi, Holden-Day, San Francisco, 1963.
56. D. N. Kirk and M. P. Hartshorn,'Steroid Reaction Mechanisms,' Elsevier, Amsterdam, 1968.
57. A. J. Liston and P. Toft, *J. Org. Chem.*, 1969, **34**, 2288.
58. O. R. Rodig and G. Zanati, *J. Org. Chem.*, 1967, **32**, 1423; P. Toft and A. J. Liston, *J. Chem. Soc.* (*C*), 1971, 439.
59. P. F. Hudrlik, in Ref. 60, pp. 127 *et seq.*
60. 'New Applications of Organometallic Reagents in Organic Synthesis,' ed. D. Seyferth, Elsevier, Amsterdam, 1976.
61. D. Seebach and V. Ehrig, *Angew. Chem. Internat. Edn.*, 1972, **11**, 127.
62. D. H. R. Barton, R. H. Hesse, M. M. Pechet, and T. J. Tewson, *J.C.S. Perkin I*, 1973, 2365.
63. W. E. Parham and C. S. Roosevelt, *Tetrahedron Letters*, 1971, 923.
64. C. A. Brown, *J. Org. Chem.*, 1974, **39**, 1324.
65. T. Cuvigny, M. Larchevêque, and H. Normant, *Annalen*, 1975, 719.
66. R. M. Coates, L. O. Sandefur, and R. D. Smillie, *J. Amer. Chem. Soc.*, 1975, **97**, 1619.
67. L. F. Fieser and M. Fieser, 'Reagents for Organic Synthesis,' Wiley, New York, 1967, vol. 1, to 1975, vol. 5,
68. G. Stork and G. A. Kraus, *J. Amer. Chem. Soc.*, 1976, **98**, 2351.
69. J. J. Panouse and C. Sannié, *Bull. Soc. chim. France*, 1956, 1272.
70. M. Gaudry and A. Marquet, *Bull. Soc. chim. France*, 1969, 4178.
71. H. D. Zook and J. A. Miller, *J. Org. Chem.*, 1971, **36**, 1112.
72. G. J. Heiszwolf and H. Kloosterziel, *Chem. Comm.*, 1966, 51.
73. S. J. Rhoads, J. K. Chattopadhyay, and E. E. Waali, *J. Org. Chem.*, 1970, **35**, 3352.
74. R. A. Lee, C. McAndrews, K. M. Patel, and W. Reusch, *Tetrahedron Letters*, 1973, 965.
75. P. G. Sammes and T. W. Wallace, *J.C.S. Perkin I*, 1975, 1377.
76. J. M. Conia and C. Girard, *Tetrahedron Letters*, 1973, 2767.
77. C. Girard and J. M. Conia, *Tetrahedron Letters*, 1974, 3327; C. Girard, P. Amice, J. P. Barnier, and J. M. Conia, *ibid.*, p. 3329.

78. M. E. Jung and C. A. McCombs, *Tetrahedron Letters*, 1976, 2935.
79. G. Stork and R. L. Danheiser, *J. Org. Chem.*, 1973, **38,** 1775.
80. C. Girard and J. M. Conia, *Tetrahedron Letters*, 1974, 3333.
81. G. M. Rubottom and D. S. Krueger, *Tetrahedron Letters*, 1977, 611.
82. A. J. Waring, M. R. Morris, and M. M. Islam, *J. Chem. Soc.* (*C*), 1971, 3274.
83. A. Suzuki, K. Ohmori, and M. Itoh, *Tetrahedron*, 1969, **25,** 3707.
84. A. C. Rojas and J. K. Crandall, *J. Org. Chem.*, 1975, **40,** 2225.
85. H. O. House, A. V. Prabhu, and W. V. Phillips, *J. Org. Chem.*, 1976, **41,** 1209.
86. J. E. Dubois and P. Fellmann, *Compt. rend.*, 1972, **274C,** 1307.
87. H. O. House and J. M. Wilkins, *J. Org. Chem.*, 1976, **41,** 4031.
88. D. J. Cram, 'Fundamentals of Carbanion Chemistry,' Academic, New York, 1965.
89. K. G. Lewis and G. J. Williams, *Tetrahedron Letters*, 1965, 4573.
90. N. Heap and G. H. Whitham, *J. Chem. Soc.* (*B*), 1966, 164.
91. D. L. Whalen, J. F. Weimaster, A. M. Ross, and R. Radhe, *J. Amer. Chem. Soc.*, 1976, **98,** 7319.
92. R. M. Pollack and R. H. Kayser, *J. Amer. Chem. Soc.*, 1976, **98,** 4174.
93. P. J. Hattersley, I. M. Lockhart, and M. Wright, *J. Chem. Soc.* (*C*), 1969, 217.
94. D. Caine and B. J. L. Huff, *Tetrahedron Letters*, 1966, 4695.
95. H. O. House, B. A. Tefertiller, and H. D. Olmstead, *J. Org. Chem.*, 1968, **33,** 935.
96. G. Stork and P. F. Hudrlik, *J. Amer. Chem. Soc.*, 1968, **90,** 4464.
97. I. Kuwajima and E. Nakamura, *J. Amer. Chem. Soc.*, 1975, **97,** 3257.
98. T. A. Spencer, R. W. Britton, and D. S. Watt, *J. Amer. Chem. Soc.*, 1967, **89,** 5727.
99. H. C. Brown, M. M. Rogic, and M. W. Rathke, *J. Amer. Chem. Soc.*, 1968, **90,** 6218.
100. H. C. Brown, M. M. Rogic, H. Nambu, and M. W. Rathke, *J. Amer. Chem. Soc.*, 1969, **91,** 2147; H. C. Brown, H. Nambu and M. M. Rogic, *ibid.*, p. 6852.
101. I. J. Borowitz, E. W. R. Casper, R. K. Crouch, and K. C. Yee, *J. Org. Chem.*, 1972, **37,** 3873.
102. G. H. Posner and J. J. Sterling, *J. Amer. Chem. Soc.*, 1973, **95,** 3076.
103. C. Lion and J. E. Dubois, *Tetrahedron*, 1975, **31,** 1223; J. E. Dubois and C. Lion, *ibid.*, p. 1227.
104. J. R. Bull and A. Tuinman, *Tetrahedron Letters*, 1973, 4349.
105. J. E. McMurry and S. J. Isser, *J. Amer. Chem. Soc.*, 1972, **94,** 7132.
106. H. Laurent and R. Wiechert, in Ref. 107, vol. II, chapter 10.
107. 'Organic Reactions in Steroid Chemistry,' ed. J. Fried and J. A. Edwards, Van Nostrand Reinhold, New York, 1972.
108. H. A. Smith, B. J. L. Huff, W. J. Powers, and D. Caine, *J. Org. Chem.*, 1967, **32,** 2851.
109. R. E. Ireland and J. A. Marshall, *J. Org. Chem.*, 1962, **27,** 1615.
110. R. M. Coates and R. L. Sowerby, *J. Amer. Chem. Soc.*, 1971, **93,** 1027.
111. A. R. Greenaway and W. B. Whalley, *J.C.S. Perkin I*, 1976, 1385.
112. R. M. Coates and L. O. Sandefur, *J. Org. Chem.*, 1974, **39,** 275.
113. E. J. Corey and R. H. K. Chen, *Tetrahedron Letters*, 1973, 3817; I. Shahak and Y. Sasson, *ibid.*, p. 4207.
114. E. J. Corey and D. Enders, *Tetrahedron Letters*, 1976, 3.
115. T. M. Harris and C. M. Harris, *Org. Reactions*, 1969, **17,** 155.
116. R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelly, *J. Chem. Soc.*, 1957, 1131; J. L. Beton, T. G. Halsall, E. R. H. Jones, and P. C. Phillips, *ibid.*, p. 753; B. Gaspert, T. G. Halsall, and D. Willis, *ibid.*, 1958, 624.
117. D. Lednicer in 'Advances in Organic Chemistry, Methods and Results,' ed. E. C. Taylor, Wiley-Interscience, New York, 1972, vol. 8, and references cited in Refs. 36, 109 and 118.
118. M. T. Thomas and A. G. Fallis, *J. Amer. Chem. Soc.*, 1976, **98,** 1227.
119. J. D. McChesney and A. F. Wycpalek, *Chem. Comm.*, 1971, 542.
120. Y. Nakadaira, J. Hayashi, H. Sato, and K. Nakanishi, *J.C.S. Chem. Comm.*, 1972, 282; F. H. Bottom and F. J. McQuillin, *Tetrahedron Letters*, 1967, 1975.
121. J. M. Conia and F. Rouessac, *Bull. Soc. chim. France*, 1963, 1925.
122. M. S. Newman, V. De Vries, and R. Darlak, *J. Org. Chem.*, 1966, **31,** 2171.
123. J. A. Marshall and A. R. Hochstetler, *J. Amer. Chem. Soc.*, 1969, **91,** 648.
124. G. Stork and J. Benaim, *J. Amer. Chem. Soc.*, 1971, **93,** 5938.
125. R. A. Lee and W. Reusch, *Tetrahedron Letters*, 1973, 969.
126. P. A. Hart, in Ref. 55, chapter 4.
127. W. G. Nigh, in Ref. 128, part B, chapter 1.
128. 'Oxidation in Organic Chemistry,' ed. W. S. Trahanovsky, Academic, New York, 1973.
129. A. E. Pohland and W. R. Benson, *Chem. Rev.*, 1966, **66,** 161.
129a. J. W. Thorpe and J. Warkentin, *Canad. J. Chem.*, 1973, **51,** 927.
130. C. G. Swain and R. P. Dunlap, *J. Amer. Chem. Soc.*, 1972, **94,** 7204.
131. A. C. Knipe and B. G. Cox, *J. Org. Chem.*, 1973, **38,** 3429.
132. J. W. Thorpe and J. Warkentin, *Canad. J. Chem.*, 1972, **50,** 3229 and following papers.
133. G. C. Levy, *Chem. Comm.*, 1969, 1257; G. C. Levy, J. D. Cargioli, and W. Racela, *J. Amer. Chem. Soc.*, 1970, **92,** 6238.
134. P. Metzger, A. Casadevall, and E. Casadevall, *Tetrahedron*, 1975, **31,** (a) 733, (b) 743.
135. K. E. Teo and E. W. Warnhoff, *J. Amer. Chem. Soc.*, 1973, **95,** 2728.
136. G. Pattenden, *J. Chem. Soc.* (*C*), 1970, 1404.

137. J. Colonge and J. Grenet, *Bull. Soc. chim. France*, 1954, 1304; J. E. Dubois, G. Schutz, and J. M. Normant, *ibid.*, 1966, 3578.
138. Y. Jasor, M. Gaudry, A. Marquet, and M. Bettahar, *Bull. Soc. chim. France*, 1973, 2732.
139. E. R. H. Jones and D. J. Wluka, *J. Chem. Soc.*, 1959, 907; A. R. Davies and G. H. R. Summers, *J. Chem. Soc. (C)*, 1967, 1227.
140. E. W. Garbisch, Jr., *J. Org. Chem.*, 1965, **30,** 2109.
141. N. C. Deno and R. Fishbein, *J. Amer. Chem. Soc.*, 1973, **95,** 7445.
142. A. Marquet, M. Dvolaitzky, H. B. Kagan, L. Mamlok, C. Ouannes, and J. Jacques, *Bull. Soc. chim. France*, 1961, 1822.
143. A. Marquet and J. Jacques, *Bull. Soc. chim. France*, 1962, 90.
144. C. Djerassi and C. R. Scholz, *J. Amer. Chem. Soc.*, 1948, **70,** 417.
145. D. V. C. Awang and S. Wolfe, *Canad. J. Chem.*, 1969, **47,** 706.
146. V. W. Armstrong, N. H. Chishti, and R. Ramage, *Tetrahedron Letters*, 1975, 373.
147. D. P. Wyman and P. R. Kaufman, *J. Org. Chem.*, 1964, **29,** 1956; D. P. Wyman, P. R. Kaufman, and W. R. Freeman, *ibid.*, p. 2706.
148. V. Caló, L. Lopez, G. Pesce, and P. E. Todesco, *Tetrahedron*, 1973, **29,** 1625.
149. M. Gaudry and A. Marquet, *Bull. Soc. chim. France*, 1969, 4169.
150. M. Gaudry and A. Marquet, *Tetrahedron*, 1970, **26,** 5611, 5617.
151. Y. Jasor, M. Gaudry, and A. Marquet, *Bull. Soc. chim. France*, 1973, 2735.
152. J. F. W. Keana and R. R. Schumaker, *Tetrahedron*, 1970, **26,** 5191.
153. J. A. Hogg, F. H. Lincoln, A. H. Nathan, A. R. Hanze, W. P. Schneider, P. F. Beal, and J. Korman, *J. Amer. Chem. Soc.*, 1955, **77,** 4438; J. R. Hanson and T. D. Organ, *J. Chem. Soc. (C)*, 1970, 1065.
154. T. S. Burton, M. P. L. Caton, E. C. J. Coffee, T. Parker, A. J. Stuttle, and G. L. Watkins, *J.C.S. Perkin I*, 1976, 2550.
155. H. Piotrowska, W. Wojnarowski, B. Waegell, and G. Ourisson, *Bull. Soc. chim. France*, 1965, 3511.
156. R. H. Reuss and A. Hassner, *J. Org. Chem.*, 1974, **39,** 1785; I. Sasson and J. Labovitz, *ibid.*, 1975, **40,** 3670.
157. K. A. Hill and P. L. Stotter, *J. Org. Chem.*, 1973, **38,** 2576.
158. J. Martel, E. Toromanoff, J. Mathieu, and G. Nomine, *Tetrahedron Letters*, 1972, 1491.
159. J. Hooz and J. N. Bridson, *Canad. J. Chem.*, 1972, **50,** 2387.
160. H. M. R. Hoffmann, K. E. Clemens, E. A. Schmidt, and R. H. Smithers, *J. Amer. Chem. Soc.*, 1972, **94,** 3201.
161. F. G. Bordwell and K. M. Wellman, *J. Org. Chem.*, 1963, **28,** 1347.
162. W. Coppens and N. Schamp, *Bull. Soc. chim. belges*, 1972, **81,** 643.
163. S. F. Reed, Jr., *J. Org. Chem.*, 1965, **30,** 2195.
164. D. C. Bishop, S. C. R. Meacock, and W. R. N. Williamson, *J. Chem. Soc. (C)*, 1966, 670; R. E. Bowman, A. C. White, and W. R. N. Williamson, *J. Chem. Soc.*, 1964, 1086.
165. A. T. Nielsen and W. J. Houlihan, *Org. Reactions*, 1968, **16,** 1.
166. E. F. Landau and E. P. Irany, *J. Org. Chem.*, 1947, **12,** 422.
167. J. Colonge and L. Cumet, *Bull. Soc. chim. France*, 1947, 838.
168. K. L. Cook and A. J. Waring, *J.C.S. Perkin I*, 1973, 529.
169. J. E. Dubois and P. Fellmann, *Tetrahedron Letters*, 1972, 5085.
170. D. H. R. Barton, F. McCapra, P. J. May, and F. Thudium, *J. Chem. Soc.*, 1960, 1297.
171. G. Stork and M. Isobe, *J. Amer. Chem. Soc.*, 1975, **97,** 6260.
172. G. Stork and J. d'Angelo, *J. Amer. Chem. Soc.*, 1974, **96,** 7114.
173. J. B. Wiel and F. Rouessac, *J.C.S. Chem. Comm.*, 1976, 446.
174. H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, *J. Amer. Chem. Soc.*, 1973, **95,** 3310.
175. G. Stork, G. A. Kraus, and G. A. Garcia, *J. Org. Chem.*, 1974, **39,** 3459.
176. W. A. Kleschick, C. T. Buse, and C. H. Heathcock, *J. Amer. Chem. Soc.*, 1977, **99,** 247.
177. T. Mukaiyama, K. Banno, and K. Narasaka, *J. Amer. Chem. Soc.*, 1974, **96,** 7503.
178. L. Birkofer, S. M. Kim, and H. D. Engels, *Chem. Ber.*, 1962, **95,** 1495.
179. E. J. Corey and D. Enders, *Tetrahedron Letters*, 1976, 11.
180. H. Reiff, in Ref. 181, 1971, vol. 6, p. 48.
181. 'Newer Methods of Preparative Organic Chemistry,' ed. W. Foerst, Academic, New York, 1964.
182. H. Hellmann and G. Opitz, *Angew. Chem.*, 1956, **68,** 265.
183. H. O. House and B. M. Trost, *J. Org. Chem.*, 1964, **29,** 1339.
184. M. Brown and W. S. Johnson, *J. Org. Chem.*, 1962, **27,** 4706.
185. G. L. Buchanan, A. C. W. Curran, and R. T. Wall, *Tetrahedron*, 1969, **25,** 5503.
186. T. A. Spencer, D. S. Watt, and R. J. Friary, *J. Org. Chem.*, 1967, **32,** 1234.
187. Y. Jasor, M. Gaudry, M. J. Luche, and A. Marquet, *Tetrahedron*, 1977, **33,** 295; *J.C.S. Chem. Comm.*, 1974, 253.
188. J. Hooz and J. N. Bridson, *J. Amer. Chem. Soc.*, 1973, **95,** 602.
189. S. Danishefsky, T. Kitahara, R. McKee, and P. F. Schuda, *J. Amer. Chem. Soc.*, 1976, **98,** 6715.
190. R. A. Micheli, Z. G. Hajos, N. Cohen, D. R. Parrish, L. A. Portland, W. Sciamanna, M. A. Scott, and P. A. Wehrli, *J. Org. Chem.*, 1975, **40,** 675.
191. O. Touster, *Org. Reactions*, 1953, **7,** 327.
192. A. F. Ferris, *J. Org. Chem.*, 1959, **24,** 1726.
193. S. M. Parmerter, *Org. Reactions*, 1959, **10,** 1.

194. R. R. Phillips, *Org. Reactions*, 1959, **10,** 143.
195. E. D. Bergmann, D. Ginsburg, and R. Pappo, *Org. Reactions*, 1959, **10,** 179.
196. G. Stork and L. Maldonado, *J. Amer. Chem. Soc.*, 1974, **96,** 5272.
197. O. Eisenstein, J. M. Lefour, C. Minot, N. T. Anh, and G. Soussan, *Compt. rend.*, 1972, **274C,** 1310.
198. A. G. Schultz and Y. K. Yee, *J. Org. Chem.*, 1976, **41,** 4044.
199. D. Seebach and K. H. Geisse, in Ref. 60, chapter 1.
200. M. W. Rathke, *Org. Reactions*, 1975, **22,** 423; J. C. Dubois, J. P. Gnette, and H. B. Kagan, *Bull. Soc chim. France*, 1966, 3008.
201. R. A. Raphael, 'Acetylenic Compounds in Organic Synthesis,' Butterworths, London, and Academic, New York, 1955, chapter 1.
202. E. J. Corey, B. W. Erickson, and R. Noyori, *J. Amer. Chem. Soc.*, 1971, **93,** 1724.
203. H. Taguchi, H. Yamamoto, and H. Nozaki, *Tetrahedron Letters*, 1976, 2617.
204. J. E. Baldwin, G. A. Höfle, and O. W. Lever, Jr., *J. Amer. Chem. Soc.*, 1974, **96,** 7125.
205. D. Seebach, *Angew. Chem. Internat. Edn.*, 1969, **8,** 639.
206. E. J. Corey and D. Seebach, *Angew. Chem. Internat. Edn.*, 1965, **4,** 1075, 1077.
207. E. J. Corey and D. Crouse, *J. Org. Chem.*, 1968, **33,** 298.
208. A. W. Johnson, 'Ylid Chemistry,' Academic, New York, 1966.
209. R. L. Sowerby and R. M. Coates, *J. Amer. Chem. Soc.*, 1972, **94,** 4758.
210. G. H. Posner, *Org. Reactions*, 1972, **19,** 1, and J. F. Normant, in Ref. 60, pp. 219 *et seq.*
211. H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, 1966, **31,** 3128.
212. G. M. Whitesides, W. F. Fischer, Jr., J. San Filippo, Jr., R. W. Bashe, and H. O. House, *J. Amer. Chem. Soc.*, 1969, **91,** 4871.
213. W. H. Mandeville and G. M. Whitesides, *J. Org. Chem.*, 1974, **39,** 400.
214. H. O. House and W. F. Fischer, Jr., *J. Org. Chem.*, 1968, **33,** 949.
215. J. Hooz and R. B. Layton, *Canad. J. Chem.*, 1970, **48,** 1626.
216. R. K. Boeckman, Jr., K. J. Bruza, J. E. Baldwin, and O. W. Lever, *J.C.S. Chem. Comm.*, 1975, 519.
217. C. G. Chavdarian and C. H. Heathcock, *J. Amer. Chem. Soc.*, 1975, **97,** 3822.
218. E. Piers and R. J. Keziere, *Canad. J. Chem.*, 1969, **47,** 137.
219. J. Cairns, C. L. Hewett, R. T. Logan, G. McGarry, D. F. M. Stevenson, and G. F. Woods, *J.C.S. Perkin I*, 1976, 1558.
220. H. O. House and W. F. Fischer, Jr., *J. Org. Chem.*, 1969, **34,** 3615.
221. S. A. Humphrey, J. L. Herrmann, and R. H. Schlessinger, *Chem. Comm.*, 1971, 1244.
222. C. P. Casey, D. F. Marten, and R. A. Boggs, *Tetrahedron Letters*, 1973, 2071.
223. G. H. Posner, C. E. Whitten, and J. J. Sterling, *J. Amer. Chem. Soc.*, 1973, **95,** 7788.
224. E. J. Corey and D. J. Beames, *J. Amer. Chem. Soc.*, 1972, **94,** 7210.
225. G. H. Posner, C. E. Whitten, J. J. Sterling, and D. J. Brunelle, *Tetrahedron Letters*, 1974, 2591.
226. E. J. Corey and R. H. Wollenberg, *J. Amer. Chem. Soc.*, 1974, **96,** 5581.
227. R. G. Pearson and C. D. Gregory, *J. Amer. Chem. Soc.*, 1976, **98,** 4098.
228. H. O. House and M. J. Umen, *J. Amer. Chem. Soc.*, 1972, **94,** 5495.
229. H. O. House, L. E. Huber, and M. J. Umen, *J. Amer. Chem. Soc.*, 1972, **94,** 8471.
230. G. M. Whitesides and P. E. Kendall, *J. Org. Chem.*, 1972, **37,** 3718.
231. G. H. Posner and D. J. Brunelle, *J.C.S. Chem. Comm.*, 1973, 907.
232. E. Piers and I. Nagakura, *J. Org. Chem.*, 1975, **40,** 2694.
233. R. K. Boeckman, Jr., *J. Org. Chem.*, 1973, **38,** 4450.
234. G. Stork, G. L. Nelson, F. Rouessac, and O. Gringore, *J. Amer. Chem. Soc.*, 1971, **93,** 3091.
235. H. C. Brown, M. W. Rathke, G. W. Kabalka, and M. M. Rogić, *J. Amer. Chem. Soc.*, 1968, **90,** 4166.
236. G. W. Kabalka, H. C. Brown, A. Suzuki, S. Honma, A. Arase, and M. Itoh, *J. Amer. Chem. Soc.*, 1970, **92,** 710; H. C. Brown and G. W. Kabalka, *ibid.*, pp. 712, 714.
237. P. Jacob, III, and H. C. Brown, *J. Amer. Chem. Soc.*, 1976, **98,** 7832; J. A. Sinclair, G. A. Molander, and H. C. Brown, *ibid.*, 1977, **99,** 954.
238. M. E. Jung, *Tetrahedron*, 1976, **32,** 3.
239. P. T. Lansbury, *Accounts Chem. Res.*, 1972, **5,** 311.
240. S. Ramachandran and M. S. Newman, *Org. Synth.*, 1961, **41,** 38.
241. T. A. Spencer, K. K. Schmiegel, and K. L. Williamson, *J. Amer. Chem. Soc.*, 1963, **85,** 3785.
242. J. S. Dutcher, J. G. Macmillan, and C. H. Heathcock, *J. Org. Chem.*, 1976, **41,** 2663.
243. D. J. Goldsmith and I. Sakano, *J. Org. Chem.*, 1976, **41,** 2095.
244. U. Eder, G. Sauer, and R. Wiechert, *Angew. Chem. Internat. Edn.*, 1971, **10,** 496.
245. J. A. Marshall and T. M. Warne, *J. Org. Chem.*, 1971, **36,** 178; J. A. Marshall and R. A. Ruden, *ibid.*, p. 594.
246. A. R. Pinder and A. K. Torrence, *J. Chem. Soc.* (*C*), 1971, 3410; C. Berger, M. Franck-Neumann, and G. Ourisson, *Tetrahedron Letters*, 1968, 3451.
247. J. A. Marshall and W. I. Fanta, *J. Org. Chem.*, 1964, **29,** 2501.
248. R. M. Coates and J. E. Shaw, *J. Amer. Chem. Soc.*, 1970, **92,** 5657.
249. J. E. Telschow and W. Reusch, *J. Org. Chem.*, 1975, **40,** 862.
250. G. R. Newkome, L. C. Roach, R. C. Montelaro, and R. K. Hill, *J. Org. Chem.*, 1972, **37,** 2098.
251. G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, 1963, **85,** 207.
252. S. Mukherjee, D. Mukherjee, M. Sharma, N. K. Basu, and P. C. Dutta, *J.C.S. Perkin I*, 1972, 1325.

253. P. A. Zoretic, B. Branchaud, and T. Maestrone, *Tetrahedron Letters*, 1975, 527.
254. E. Wenkert and D. A. Berges, *J. Amer. Chem. Soc.*, 1967, **89,** 2507; R. E. Ireland, D. R. Marshall, and J. W. Tilley, *ibid.*, 1970, **92,** 4754.
255. C. H. Heathcock and J. E. Ellis, *Chem. Comm.*, 1971, 1474; G. Stork and R. N. Guthikonda, *J. Amer. Chem. Soc.*, 1972, **94,** 5109.
256. R. B. Woodward and T. Singh, *J. Amer. Chem. Soc.*, 1950, **72,** 494.
257. G. Stork and B. Ganem, *J. Amer. Chem. Soc.*, 1973, **95,** 6152.
258. R. K. Boeckman, Jr., *J. Amer. Chem. Soc.*, 1973, **95,** 6867, and *ibid.*, 1974, **96,** 6179; G. Stork and J. Singh, *ibid.*, p. 6181.
259. A. Rosan and M. Rosenblum, *J. Org. Chem.*, 1975, **40,** 3621.
260. E. Brown, M. Ragault, and J. Touet, *Tetrahedron Letters*, 1971, 1043.
261. W. G. Dauben, G. Ahlgren, T. J. Leitereg, W. C. Schwarzel, and M. Yoshioko, *J. Amer. Chem. Soc.*, 1972, **94,** 8593.
261a. G. L. Buchanan, *Chem. Soc. Rev.*, 1974, **3,** 41.
262. D. Caine and F. N. Tuller, *J. Org. Chem.*, 1969, **34,** 222.
263. E. J. Corey and S. Nozoe, *J. Amer. Chem. Soc.*, 1965, **87,** 5728.
264. E. Piers, R. W. Britton, and W. de Waal, *Canad. J. Chem.*, 1969, **47,** 4307.
265. J. Weill-Raynal, *Synthesis*, 1969, 49.
266. (a) G. Stork, S. Danishefsky, and M. Ohashi, *J. Amer. Chem. Soc.*, 1967, **89,** 5459; (b) G. Stork and J. E. McMurry; *ibid.*, pp. 5463 and 5464.
267. W. L. Meyer, G. B. Clemans, and R. W. Huffman, *Tetrahedron Letters*, 1966, 4255.
268. U. Axen, J. E. Pike, and W. P. Schneider, in 'Total Synthesis of Natural Products,' ed. J. ApSimon, Wiley-Interscience, New York, 1973, vol. 1, pp. 81 *et seq.*
269. A. J. Birch and K. P. Dastur, *Tetrahedron Letters*, 1974, 1009.
270. V. Dave and J. S. Whitehurst, *J.C.S. Perkin I*, 1973, 393.
271. C. Casagrande, L. Canonica, and G. Severini-Ricca, *J.C.S. Perkin I*, 1975, 1652.
272. J. Colonge, J. Dreux, and M. Thiers, *Bull. Soc. chim. France*, 1959, 370.
273. J. Colonge, J. Dreux, and M. Thiers, *Bull Soc. chim. France*, 1959, 450; R. Chapurlat, J. Huet, and J. Dreux, *ibid.*, 1967, 2446.
274. C. Arnaud and J. Huet, *Bull. Soc. chim. France*, 1971, 4525.
275. W. G. Dauben, G. W. Shaffer, and N. D. Vietmeyer, *J. Org. Chem.*, 1968, **33,** 4060; R. L. N. Harris, F. Komitsky, Jr., and C. Djerassi, *J. Amer. Chem. Soc.*, 1967, **89,** 4765.
276. S. Yamada, K. Hiroi, and K. Achiwa, *Tetrahedron Letters*, 1969, 4233; S. Yamada and G. Otani, *ibid.*, p. 4237.
277. E. J. Corey, T. Ravindranathan, and S. Terashima, *J. Amer. Chem. Soc.*, 1971, **93,** 4326.
278. M. A. Qasseem, N. A. J. Rogers, and A. A. Othman, *Tetrahedron*, 1968, **24,** 4535.
279. M. F. Ansell and M. H. Palmer, *Quart. Rev.*, 1964, **18,** 211.
280. A. T. Blomquist, L. H. Liu, and J. C. Bohrer, *J. Amer. Chem. Soc.*, 1952, **74,** 3643; A. T. Blomquist, R. E. Burge, Jr., and A. C. Sucsy, *ibid.*, p. 3636; A. T. Blomquist and A. Goldstein, *Org. Synth. Coll. Vol. 4*, 1963, 838.
281. H. S. Verter, in Ref. 38, chapter 2.
282. K. B. Sharpless, R. F. Lauer, O. Repić, A. Y. Teranishi, and D. R. Williams, *J. Amer. Chem. Soc.*, 1971, **93,** 3303.
283. D. P. Bauer and R. S. Macomber, *J. Org. Chem.*, 1975, **40,** 1990.
284. N. Kornblum and H. W. Frazier, *J. Amer. Chem. Soc.*, 1966, **88,** 865.
285. J. Strating, S. Reiffers, and H. Wynberg, *Synthesis*, 1971, 209, 211.
286. H. H. Wasserman and J. L. Ives, *J. Amer. Chem. Soc.*, 1976, **98,** 7868.
287. H. Gopal and A. J. Gordon, *Tetrahedron Letters*, 1971, 2941.
288. D. G. Lee and M. van den Engh, in Ref. 128, part B, chapter 4.
289. J. A. Marshall and D. E. Seitz, *J. Org. Chem.*, 1974, **39,** 1814.
290. B. M. Trost, M. Preckel, and L. M. Leichter, *J. Amer. Chem. Soc.*, 1975, **97,** 2224.
291. F. Huet, M. Pellet, and J. M. Conia, *Tetrahedron Letters*, 1976, 3579.
292. J. Tsuji, H. Takahashi, and T. Kajimoto, *Tetrahedron Letters*, 1973, 4573.
293. C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, 1954, **8,** 59.
294. S. Boatman, T. M. Harris, and C. R. Hauser, *Org. Synth. Coll. Vol. 5*, 1973, 187.
295. S. M. Bloom, *J. Amer. Chem. Soc.*, 1958, **80,** 6280.
296. P. De Clerq, R. Coen, E. Van Hoof, and M. Vandewalle, *Tetrahedron*, 1976, **32,** 2747.
297. M. Gorodetsky, E. Levy, R. D. Youssefyeh, and Y. Mazur, *Tetrahedron*, 1966, **22,** 2039.
298. H. Gerlach and W. Müller, *Angew. Chem. Internat. Edn.*, 1972, **11,** 1030.
299. A. B. Mekler, S. Ramachandran, S. Swaminathan, and M. S. Newman, *Org. Synth. Coll. Vol. 5*, 1973, 743.
300. H. Stetter, in Ref. 181, vol. 2, 1963, pp. 51 *et seq.*
301. J. P. John, S. Swaminathan, and P. S. Venkataramani, *Org. Synth. Coll. Vol. 5*, 1973, 747.
302. T. M. Shepherd, *Chem. and Ind. (London)*, 1970, 567.
303. W. Cocker and D. H. Grayson, *J.C.S. Perkin I*, 1975, 1347.
304. D. T. Manning, H. A. Coleman, and R. A. Langdale-Smith, *J. Org. Chem.*, 1968, **33,** 4413.
305. E. C. Taylor and A. McKillop, *Accounts Chem. Res.*, 1970, **3,** 338.
306. M. T. Pizzorno and S. M. Albonico, *Chem. and Ind., (London)*, 1972, 425; J. M. McIntosh and P. M. Beaumier, *Canad. J. Chem.*, 1973, **51,** 843.

307. J. W. Pilkington and A. J. Waring, *J.C.S. Perkin II*, 1976, 1349.
308. P. Boldt and H. Militzer, *Tetrahedron Letters*, 1966, 3599.
309. T. M. Harris, G. P. Murphy, and A. J. Poje, *J. Amer. Chem. Soc.*, 1976, **98,** 7733.
310. K. G. Hampton and J. J. Christie, *J. Org. Chem.*, 1976, **41,** 2772.
311. M. L. Wolfrom and J. M. Bobbitt, *J. Amer. Chem. Soc.*, 1956, **78,** 2489.
312. R. H. Cornforth, J. W. Cornforth, and G. Popják, *Tetrahedron*, 1962, **18,** 1351.
313. S. Boatman and C. R. Hauser, *Org. Synth. Coll. Vol. 5*, 1973, 767.
314. M. F. Ansell, W. J. Hickinbottom, and P. G. Holton, *J. Chem. Soc.*, 1955, 349.
315. Y. Ito, T. Konoike, and T. Saegusa, *J. Amer. Chem. Soc.*, 1975, **97,** 2912.
316. J. E. McMurry and J. Melton, *J. Amer. Chem. Soc.*, 1971, **93,** 5309.
317. M. Miyashita, T. Yanami, and A. Yoshikoshi, *J. Amer. Chem. Soc.*, 1976, **98,** 4679.
318. R. M. Dessau and E. I. Heiba, *J. Org. Chem.*, 1974, **39,** 3457.
319. J. E. McMurry and T. E. Glass, *Tetrahedron Letters*, 1971, 2575.
320. G. Büchi and H. Wüest, *J. Org. Chem.*, 1966, **31,** 977.
321. W. S. Johnson, M. B. Gravestock, and B. E. McCarry, *J. Amer. Chem. Soc.*, 1971, **93,** 4332.
322. P. A. Grieco and C. S. Pogonowski, *J. Org. Chem.*, 1974, **39,** 732.
323. F. Duus, *Tetrahedron*, 1976, **32,** 2817.
324. M. S. Schechter, N. Green, and F. B. La Forge, *J. Amer. Chem. Soc.*, 1949, **71,** 3165.
325. E. Ritchie and W. C. Taylor, *Austral. J. Chem.*, 1971, **24,** 2137.
326. N. C. Deno, H. G. Richey, N. Friedman, J. D. Hodge, J. J. Houser, and C. U. Pittman, *J. Amer. Chem. Soc.*, 1963, **85,** 2991.
327. L. C. Crombie and M. Elliott, *Fortschr. Chem. org. Naturstoffe*, 1961, **19,** 120.
328. L. T. Scott and J. O. Naples, *Synthesis*, 1973, 209.
329. J. J. Bloomfield, D. C. Owsley, and J. M. Nelke, *Org. Reactions*, 1976, **23,** 259.
330. T. Wakamatsu, K. Akasaka, and Y. Ban, *Tetrahedron Letters*, 1974, 3879, 3883.
330a. J. A. Katzenellenbogen and S. B. Bowlus, *J. Org. Chem.*, 1973, **38,** 627.
331. J. A. Marshal and H. Roebke, *J. Org. Chem.*, 1969, **34,** 4188.
332. J. E. Baldwin, O. W. Lever, Jr., and N. R. Tzodikov, *J. Org. Chem.*, 1976, **41,** 2312.
333. E. J. Corey and C. U. Kim, *Tetrahedron Letters*, 1974, 287.
334. G. M. Rubottom, M. A. Vazquez, and D. R. Pelegrina, *Tetrahedron Letters*, 1974, 4319.
335. K. L. Williamson and W. S. Johnson, *J. Org. Chem.*, 1961, **26,** 4563.
336. J. A. Marshall and G. M. Cohen, *J. Org. Chem.*, 1971, **36,** 877.
337. R. B. Warneboldt and L. Weiler, *Tetrahedron Letters*, 1971, 3413.
338. A. J. Fry and J. J. O'Dea, *J. Org. Chem.*, 1975, **40,** 3625.
339. R. Criegee, in Ref. 340, pp. 277 *et seq.*
340. 'Oxidation in Organic Chemistry', ed. K. B. Wiberg, Academic, New York, 1965, part A.
341. M. E. Kuehne and T. J. Giacobbe, *J. Org. Chem.*, 1968, **33,** 3359.
342. R. J. Ouellette, in Ref. 128, chapter 3.
343. A. McKillop, O. H. Oldenziel, B. P. Swann, E. C. Taylor, and R. L. Robey, *J. Amer. Chem. Soc.*, 1971, **93,** 7331.
344. E. J. Corey and S. Knapp, *Tetrahedron Letters*, 1976, 4687.
345. J. N. Gardner, F. E. Carlon, and O. Gnoj, *J. Org. Chem.*, 1968, **33,** 3294.
346. E. J. Corey and D. E. Cane, *J. Org. Chem.*, 1971, **36,** 3070.
347. M. Fetizon, M. Golfier, and J.-M. Louis, *Chem. Comm.*, 1969, 1102.
348. P. Chamberlain and G. H. Whitham, *J. Chem. Soc. (B)*, 1969, 1131.
349. P. Chamberlain and G. H. Whitham, *J.C.S. Perkin II*, 1972, 130.
350. R. N. Ring, G. C. Tesoro, and D. R. Moore, *J. Org. Chem.*, 1967, **32,** 1091.
351. 'The Carbohydrates, Chemistry and Biochemistry,' ed. W. Pigman and D. Horton, Academic, New York, 1972, 2nd edn.
352. J. L. Herrmann, J. E. Richman, P. J. Wepplo, and R. H. Schlessinger, *Tetrahedron Letters*, 1973, 4707.
353. W. Franke, R. Kraft, and W. Kosswig, in Ref. 181, vol. 2, pp. 1 *et seq.*
354. J. L. Herrmann, G. R. Kieczykowski, R. F. Romanet, P. J. Wepplo, and R. H. Schlessinger, *Tetrahedron Letters*, 1973, 4711.
355. A. F. Thomas, in 'The Total Synthesis of Natural Products,' ed. J. ApSimon, Wiley-Interscience, New York, 1973, vol. 2, pp. 55, 56, 74, 87.
356. J. Colonge and G. Descotes in '1,4-Cycloaddition Reactions,' ed. J. Hamer, Academic, New York, 1967, chapter 9.
357. R. I. Katkevich and L. I. Vereshchagin, *Russ. Chem. Rev.* 1969, **38,** 900.
358. C. C. Beard, in Ref. 107, vol. 1, chapter 6.
359. H. J. Reich, I. L. Reich, and J. M. Renga, *J. Amer. Chem. Soc.*, 1973, **95,** 5813.
360. H. J. Reich, J. M. Renga, and I. L. Reich, *J. Org. Chem.*, 1974, **39,** 2133.
361. D. L. J. Clive, *J.C.S. Chem. Comm.*, 1973, 695.
362. K. B. Sharpless, R. F. Lauer, and A. Y. Teranishi, *J. Amer. Chem. Soc.*, 1973, **95,** 6137.
363. B. M. Trost, T. N. Salzmann, and K. Hiroi, *J. Amer. Chem. Soc.*, 1976, **98,** 4887.
364. N. Rabjohn, *Org. Reactions*, 1949, **5,** 331; 1976, **24,** 261.
365. E. N. Trachtenberg, in Ref. 366, vol. 1, 1969, chapter 3.
366. 'Oxidation,' ed. R. L. Augustine, Dekker, New York, 1969.
367. A. J. Waring, *Adv. Alicyclic Chem.*, 1966, **1,** 129.

368. E. J. Corey and J. P. Schaefer, *J. Amer. Chem. Soc.*, 1960, **82,** 918; R. A. Jerussi and D. Speyer, *J. Org. Chem.*, 1966, **31,** 3199.
369. M. Mühlstadt, L. Zach, and H. Becurar-Reinhardt, *J. prakt. Chem.*, 1964, **29,** [4], 158.
370. F. D. Gunstone and R. M. Heggie, *J. Chem. Soc.*, 1952, 1437.
371. B. Wesslen and L. O. Ryrfors, *Acta Chem. Scand.*, 1968, **22,** 2071; B. Wesslen, *ibid.*, p. 2085.
372. R. A. J. Smith and T. A. Spencer, *J. Org. Chem.*, 1970, **35,** 3220.
373. S. T. Young, J. R. Turner, and D. S. Tarbell, *J. Org. Chem*, 1963, **28,** 928.
374. J. K. Groves, *Chem. Soc. Rev.*, 1972, **1,** 73.
375. R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. McLamore, *J. Amer. Chem. Soc.*, 1952, **74,** 4223; E. M. McMahon, J. N. Roper, W. P. Utermohlen, R. H. Hasek, R. C. Harris, and J. H. Brant, *ibid.*, 1948, **70,** 2971.
376. H. C. Odom and A. R. Pinder, *Org. Synth.*, 1971, **51,** 115.
377. N. Jones and H. T. Taylor, *J. Chem. Soc.*, 1961, 1345.
378. M. F. Ansell and S. A. Mahmud, *J.C.S. Perkin I*, 1973, 2789.
379. J. C. Floyd, *Tetrahedron Letters*, 1974, 2877.
380. M. Bourgain and J. F. Normant, *Bull. Soc. chim. France*, 1973, 2137.
381. P. A. Grieco, D. Boxler, and C. S. Pogonowski, *J.C.S. Chem. Comm.*, 1974, 497.
382. G. M. Ksander and J. E. McMurry, *Tetrahedron Letters*, 1976, 4691.
383. A. E. Vanstone and J. S. Whitehurst, *J. Chem. Soc.* (*C*), 1966, 1972.
384. J. Le Gras, *Compt. rend.*, 1966, **263C,** 1460.
385. D. G. Lee, in Ref. 366, vol. 1, 1969, chapter 1.
386. J. G. Moffatt, in Ref. 366, vol. 2, 1971, chapter 1.
387. J. Colonge, G. Descotes, and R. Mugnier, *Bull. Soc. chim. France*, 1965, 2733.
388. J. J. Sims and L. H. Selman, *Tetrahedron Letters*, 1969, 561.
388a. E. H. White and J. N. Marx, *J. Amer. Chem. Soc.*, 1967, **89,** 5511.
389. W. G. Dauben, M. Lorber, and D. S. Fullerton, *J. Org. Chem.*, 1969, **34,** 3587.
390. J. E. Shaw and J. J. Sherry, *Tetrahedron Letters*, 1971, 4379.
391. K. H. Schulte-Elte, M. Gadola, and G. Ohloff, *Helv. Chim. Acta*, 1973, **56,** 2028.
392. A. J. Birch and G. Subba Rao in 'Advances in Organic Chemistry, Methods and Results,' ed. E. C. Taylor, Wiley-Interscience, New York, 1972, vol. 8.
393. F. J. Kakis, in Ref. 55, chapter 6.
394. E. A. Braude and J. A. Coles, *J. Chem. Soc.*, 1952, 1430; S. Hirano, T. Hiyama, and H. Nozaki, *Tetrahedron Letters*, 1974, 1429.
395. J. M. Conia and M. L. Leriverend, *Tetrahedron Letters*, 1968, 2101.
396. R. Noyori, K. Yokoyama, S. Makino, and Y. Hayakawa, *J. Amer. Chem. Soc.*, 1972, **94,** 1772.
397. R. L. Augustine, in Ref. 107, vol. 1, 1972, chapter 3.
398. M. J. F. Burman, D. R. Elliott, M. H. Gordon, R. G. Peck, and M. J. T. Robinson, *Tetrahedron Letters*, 1976, 1535.
399. D. Caine, *Org. Reactions*, 1976, **23,** 1.
400. H. L. Dryden, in Ref. 107, vol. 1, 1972, chapter 2.
401. J. E. Starr, in Ref. 55, chapter 7.
402. G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *J. Amer. Chem. Soc.*, 1965, **87,** 275.
403. G. Stork and S. D. Darling, *J. Amer. Chem. Soc.*, 1964, **86,** 1761.
404. D. M. S. Wheeler and M. M. Wheeler, in Ref. 107, vol. 1, 1972, chapter 2.
405. E. R. H. Walker, *Chem. Soc. Rev.*, 1976, **5,** 23.
406. M. N. Rerick, in Ref. 407, chapter 1.
407. 'Reduction', ed. R. L. Augustine, Arnold, London, and Dekker, New York, 1968.
408. E. C. Ashby and J. R. Boone, *J. Amer. Chem. Soc.*, 1976, **98,** 5524.
409. H. Haubenstock, *J. Org. Chem.*, 1972, **37,** 656.
410. W. R. Jackson and A. Zurqiyah, *J. Chem. Soc.*, 1965, 5280.
411. E. C. Ashby, J. J. Lin, and R. Kovar, *J. Org. Chem.*, 1976, **41,** 1939.
412. M. F. Semmelhack and R. D. Stauffer, *J. Org. Chem.*, 1975, **40,** 3619.
413. J. M. Fortunato and B. Ganem, *J. Org. Chem.*, 1976, **41,** 2194.
414. W. L. Dilling and R. A. Plepys, *J. Org. Chem.*, 1970, **35,** 2971.
415. I. Ghilezan, Sir E. R. H. Jones, G. D. Meakins, and J. O. Miners, *J.C.S. Perkin I*, 1976, 1350.
416. E. J. Corey, K. B. Becker, and R. K. Varma, *J. Amer. Chem. Soc.*, 1972, **94,** 8616.
417. K. E. Wilson, R. T. Seidner, and S. Masamune, *Chem. Comm.*, 1970, 213.
418. M. Stefanović and S. Lajšić, *Tetrahedron Letters*, 1967, 1777.
419. J. Dale, *J. Chem. Soc.*, 1961, 910.
420. W. Reusch, in Ref. 407, chapter 3.
421. E. Vedejs, *Org. Reactions*, 1975, **22,** 401.
422. J. G. St. C. Buchanan and P. D. Woodgate, *Quart. Rev.*, 1969, **23,** 522.
423. R. O. Hutchins, B. E. Maryanoff, and C. A. Milewski, *J. Amer. Chem. Soc.*, 1971, **93,** 1793.
424. (a) M. Sevrin, D. van Ende, and A. Krief, *Tetrahedron Letters*, 1976, 2643; (b) M. Sevrin, W. Dumont, L. Hevesi, and A. Krief, *ibid.*, p. 2647.
425. R. H. Shapiro, *Org. Reactions*, 1976, **23,** 405.
426. R. E. Ireland and G. Pfister, *Tetrahedron Letters*, 1969, 2145.

427. T. Akiyama, D. Pedder, J. V. Silverton, J. I. Seeman, and H. Ziffer, *J. Org. Chem.*, 1975, **40,** 3675.
428. J. W. Frankenfeld and W. E. Tyler, *J. Org. Chem.*, 1971, **36,** 2110.
429. M. Stiles and A. L. Longroy, *J. Org. Chem.*, 1967, **32,** 1095.
430. M. Smith, in Ref. 407, chapter 2.
431. Y. Ogata and A. Kawasaki, in Ref. 38, chapter 1.
432. W. P. Jencks, *Progr. Phys. Org. Chem.*, 1964, **2,** 63.
433. H. J. E. Loewenthal in 'Protective Groups in Organic Chemistry,' ed. J. F. W. McOmie, Plenum, London, 1973, chapter 9; R. Gardi and A. Ercoli, in Ref. 107, vol. 1, chapter 7.
434. J. L. Isidor and R. M. Carlson, *J. Org. Chem.*, 1973, **38,** 554.
435. E. J. Corey, E. J. Trybulski and J. W. Suggs, *Tetrahedron Letters*, 1976, 4577.
436. E. J. Corey and J. W. Suggs, *Tetrahedron Letters*, 1975, 3775.
437. E. J. Corey and R. A. Ruden, *J. Org. Chem.*, 1973, **38,** 834.
438. P. R. Heaton, J. M. Midgley, and W. B. Whalley, *Chem. Comm.*, 1971, 750.
439. W. F. J. Huurdeman, H. Wynberg, and D. W. Emerson, *Tetrahedron Letters*, 1971, 3449.
440. M. Fetizon and M. Jurion, *J.C.S. Chem. Comm.*, 1972, 382.
441. E. L. Eliel, V. S. Rao, and F. G. Riddell, *J. Amer. Chem. Soc.*, 1976, **98,** 3583.
442. S. R. Maynez, L. Pelavin, and G. Erker, *J. Org. Chem.*, 1975, **40,** 3302.
443. A. McKillop, J. D. Hunt, R. D. Naylor, and E. C. Taylor, *J. Amer. Chem. Soc.*, 1971, **93,** 4918.
444. J. E. McMurry and M. Silvestri, *J. Org. Chem.*, 1975, **40,** 1502.
445. S. H. Wilen, *Topics Stereochem.*, 1971, **6,** 107.
446. C. H. Rochester, 'Acidity Functions,' Academic, London, 1970.
447. E. M. Arnett and G. Scorrano, *Adv. Phys. Org. Chem.*, 1976, **13,** 83.
448. D. G. Lee, *Canad. J. Chem.*, 1970, **48,** 1919.
449. A. R. Butler, *J.C.S. Perkin II*, 1976, 959; A. R. Butler and H. A. Jones, *ibid.*, p. 963.
450. R. I. Zalewski, *Bull. Acad. polon. Sci. Sér. Sci. chim.*, 1971, **19,** 351.
451. J. W. Larsen and P. A. Bouis, *J. Amer. Chem. Soc.*, 1975, **97,** 6094.
452. G. A. Olah, A. M. White, and D. H. O'Brien, *Chem. Rev.*, 1970, **70,** 561.
453. G. A. Olah, Y. Halpern, Y. K. Mo, and G. Liang, *J. Amer. Chem. Soc.*, 1972, **94,** 3554.
454. J. N. Marx, *Tetrahedron Letters*, 1971, 4957.
455. R. D. Clark and C. H. Heathcock, *Tetrahedron Letters*, 1974, (a) 1713, (b) 2027.
456. K. W. Bentley, in Ref. 457, part 2, chapter 12.
457. 'Elucidation of Organic Structures by Physical and Chemical Methods; Techniques of Chemistry, Vol. IV,' 2nd edn., ed. K. W. Bentley and G. W. Kirby, Wiley-Interscience, New York, 1973.
458. B. M. Trost and M. J. Bogdanowicz, *J. Amer. Chem. Soc.*, 1973, **95,** 2038; B. M. Trost, *Fortschr. Chem. Forsch.*, 1973, **41,** 1.
459. P. G. Gassman, J. T. Lumb, and F. V. Zalar, *J. Amer. Chem. Soc.*, 1967, **89,** 946.
460. B. Sklarz, *Quart. Rev.*, 1967, **21,** 3.
461. C. J. Collins and J. F. Eastham, in Ref. 4, chapter 15.
462. A. Fry, in 'Mechanism of Molecular Migration,' ed. B. S. Thyagarajan, Wiley, London, 1971, vol. 4, p. 113.
463. C. D. Gutsche and D. Redmore,'Carbocyclic Ring Expansion Reactions,' Suppl. I to *Adv. Alicyclic Chem.*, Academic, New York, 1968.
464. P. A. S. Smith and D. R. Baer, *Org. Reactions*, 1960, **11,** 157.
465. U. Schöllkopf and P. Böhme, *Angew. Chem. Internat. Edn.*, 1971, **10,** 491.
466. M. St. Jacques, C. Vaziri, D. A. Frenette, A. Goursot, and S. Fliszár, *J. Amer. Chem. Soc.*, 1976, **98,** 5759.
467. H. Taguchi, H. Yamamoto, and H. Nozaki, *Tetrahedron Letters*, 1972, 4661.
468. D. Redmore and C. D. Gutsche, *Adv. Alicyclic Chem.*, 1971, **3,** 1.
469. S. Selman and J. F. Eastham, *Quart. Rev.*, 1960, **14,** 221.
470. A. S. Kende, *Org. Reactions*, 1960, **11,** 261.
471. N. J. Turro, *Accounts Chem. Res.*, 1969, **2,** 25.
472. J. E. Baldwin and J. H. I. Cardellina, *Chem. Comm.*, 1968, 558.
473. O. L. Chapman and D. S. Weiss, *Organic Photochem.*, 1973, **3,** 197.
474. K. Schaffner, *Adv. Photochem.*, 1966, **4,** 81.
475. D. R. Arnold, *Adv. Photochem.*, 1968, **6,** 301.
476. N. J. Turro, W. E. Farneth, and A. Devaquet, *J. Amer. Chem. Soc.*, 1976, **98,** 7425.
477. B. M. Monroe, *Adv. Photochem.*, 1971, **8,** 77.
478. L. J. Bellamy, 'The Infra-red Spectra of Complex Molecules,' 3rd edn., Chapman and Hall, London, 1975, chapter 9; L. J. Bellamy, 'Advances in Infrared Group Frequencies,' Chapman and Hall, London, 1975, chapter 5.
479. H. H. Jaffé and M. Orchin, 'Theory and Applications of Ultraviolet Spectroscopy,' Wiley, New York, 1962; A. I. Scott, 'Interpretation of the Ultraviolet Spectra of Natural Products,' Pergamon, Oxford, 1964; C. J. Timmons, in Ref. 457, part 1, chapter 2.
480. L. M. Jackman and S. Sternhell, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' 2nd edn., Pergamon, Oxford, 1969.
481. N. S. Bhacca and D. H. Williams, 'Applications of NMR Spectroscopy in Organic Chemistry,' Holden-Day, San Francisco, 1964.
482. B. C. Mayo, *Chem. Soc. Rev.*, 1973, **2,** 49.

483. J. B. Stothers, 'Carbon-13 NMR Spectroscopy,' Academic, New York, 1972; G. C. Levy and G. L. Nelson, 'Carbon-13 Nuclear Magnetic Resonance for Organic Chemists,' Wiley-Interscience, New York, 1972.
484. G. C. Barrett, in Ref. 457, part 1, chapter 8; P. Crabbé, 'ORD and CD in Chemistry and Biochemistry, an Introduction,' Academic, New York, 1972; 'Fundamental Aspects and Recent Developments in Optical Rotatory Dispersion and Circular Dichroism,' ed. F. Ciardelli and P. Salvadori, Heyden, London, 1973.
485. E. Erstbrunner, M. R. Giddings, and J. Hudec, *J.C.S. Chem. Comm.*, 1976, 953, and following papers.
486. S. Ueji and M. Nakamura, *Tetrahedron Letters*, 1976, 2549.
487. M. Fétizon, J. Goré, P. Laszlo, and B. Waegell, *J. Org. Chem.*, 1966, **31,** 4047.
488. A. Bienvenüe, *J. Amer. Chem. Soc.*, 1973, **95,** 7345.
489. F. H. Cottee and C. J. Timmons, *J. Chem. Soc.* (*B*), 1968, 326.
490. R. H. Levin and L. Weingarten, *Tetrahedron Letters*, 1975, 611.
491. J. Dabrowski and M. Tencer, *Tetrahedron*, 1976, **32,** 587.
492. A. F. Kluge and C. P. Lillya, *J. Org. Chem.*, 1971, **36,** 1977.
493. M. R. Morris and A. J. Waring, *J. Chem. Soc.* (*C*), 1971, (a) 3266, (b) 3269.
494. H. Hart and R. H. Schlosberg, *J. Amer. Chem. Soc.*, 1968, **90,** 5189.
495. T. A. Geissman and R. Mukherjee, *J. Org. Chem.*, 1968, **33,** 656.
496. Sir E. R. H. Jones, G. D. Meakins, J. O. Miners, J. H. Pragnell, and A. L. Wilkins, *J.C.S. Perkin I*, 1975, 1552.
497. H. Eggert and C. Djerassi, *J. Org. Chem.*, 1973, **38,** 3788.
498. Z. W. Wolkowski, *Tetrahedron Letters*, 1971, 821; K. L. Servis and D. J. Bowler, *J. Amer. Chem. Soc.*, 1975, **97,** 80.
499. R. F. Childs, E. F. Lund, A. G. Marshall, W. J. Morrisey, and C. V. Rogerson, *J. Amer. Chem. Soc.*, 1976, **98,** 5924.

5.3

Aromatic Aldehydes

T. LAIRD
Imperial Chemical Industries Ltd., Blackley, Manchester

5.3.1 INTRODUCTION 1105
5.3.2 SYNTHESIS OF AROMATIC ALDEHYDES 1108
5.3.2.1 Synthesis of aromatic aldehydes by oxidation of methyl aromatics 1108
5.3.2.2 Synthesis of aromatic aldehydes from halomethyl and aminomethyl compounds 1110
5.3.2.3 Synthesis of aromatic aldehydes by oxidation of hydroxymethyl aromatics 1114
5.3.2.4 Synthesis of aromatic aldehydes by hydrolysis of dihalomethyl aromatics 1114
5.3.2.5 Gattermann–Koch and related reactions 1114
5.3.2.6 Formylation using dichloromethyl alkyl ethers 1116
5.3.2.7 Gattermann reaction 1116
5.3.2.8 Vilsmeier–Haack formylation 1117
5.3.2.9 Duff reaction 1119
5.3.2.10 Reimer–Tiemann reaction 1119
5.3.2.11 Selective ortho *formylation of phenols* 1120
5.3.2.12 Synthesis of aromatic aldehydes from haloaromatics 1122
5.3.2.13 Synthesis of aromatic aldehydes by the reduction of acids, acid halides, esters, nitriles 1123
5.3.2.14 Synthesis of aromatic dialdehydes by the oxidation of polycyclic aromatic hydrocarbons 1126
5.3.3 ELECTROPHILIC SUBSTITUTIONS OF AROMATIC ALDEHYDES 1128
5.3.4 NUCLEOPHILIC ADDITION TO THE CARBONYL GROUP OF AROMATIC ALDEHYDES 1129
5.3.4.1 Aldol condensation and related reactions 1130
5.3.4.2 Darzens condensation 1133
5.3.5 OXIDATION OF AROMATIC ALDEHYDES 1134
5.3.6 REDUCTION OF AROMATIC ALDEHYDES 1136
5.3.6.1 Reductive coupling of aromatic aldehydes to olefins and oxirans 1138
5.3.7 CANNIZZARO REACTION 1140
5.3.8 BENZOIN CONDENSATION AND RELATED REACTIONS 1142
5.3.9 DECARBONYLATION OF AROMATIC ALDEHYDES 1147
5.3.10 PHOTOCHEMISTRY OF AROMATIC ALDEHYDES 1149
5.3.11 SPECIFIC ALDEHYDES 1153
5.3.11.1 Aralkyl aldehydes 1153
5.3.11.2 Aromatic dialdehydes 1154
5.3.11.3 o-Hydroxybenzaldehydes 1156

5.3.1 INTRODUCTION

The chemistry of aromatic aldehydes has many similarities to that of aliphatic aldehydes (see Chapter 5.1), but there are very important additional aspects that need to be

considered. The methods of introduction of the formyl group into the aromatic ring are numerous and are discussed in some detail in Section 5.3.2. The major differences between the types of reactions undergone by aliphatic and aromatic aldehydes arise in part from the fact that the latter cannot enolize and partly because the aromatic ring can to a limited extent stabilize an adjacent carbanion; these factors are important in the benzoin condensation and related reactions (Section 5.3.8). However, most of the chemistry of aromatic aldehydes, as with aliphatic aldehydes, results from nucleophilic attack on the carbonyl carbon atom. The addition of nucleophiles to aromatic carbonyls is in general less favourable than with aliphatic carbonyls owing to the greater loss in resonance energy in converting a trigonal carbon, where π-orbital overlap between the C=O group and the aromatic ring is important, to a tetrahedral species. If dehydration of the resultant intermediate to a double bond is possible, however, then the overall process may be exothermic, and under appropriate conditions the reaction can be driven to completion. The synthesis of derivatives such as oximes, hydrazones, semicarbazones, Schiff bases, *etc.*, and the condensations with active methylene groups, such as in the Perkin and Claisen–Schmidt reactions, are examples of these addition–dehydration processes.

Aromatic aldehydes are colourless or pale yellow, water-immiscible, liquids or solids with low melting points (Table 1) and are generally volatile in steam. Many members of the series have characteristic odours; benzaldehyde itself, which occurs in nature in the leaves and kernels of apricots and peaches, has a pleasant odour of bitter almonds. Phenolic aldehydes, such as salicylaldehyde (2-hydroxybenzaldehyde), and their ethers,

TABLE 1

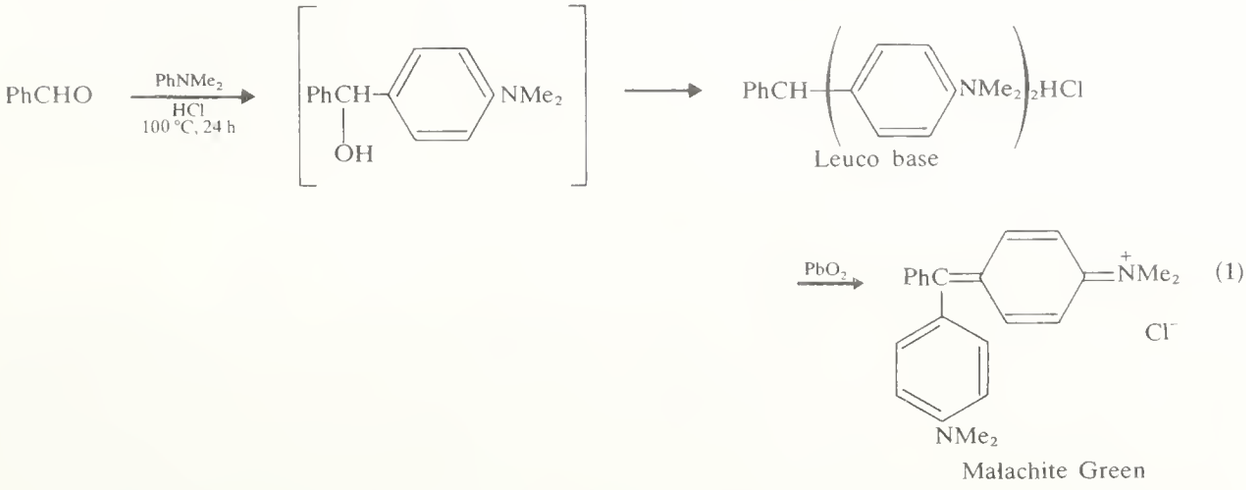
Physical Properties of Aromatic Aldehydes and Derivatives Used for Characterization[a]

	M.p. (°C)	*B.p.* (°C/760 mmHg)	*Semicarbazone* *M.p.* (°C)	2,4-*Dinitrophenylhydrazone* *M.p.* (°C)
Benzaldehyde	−26	178	222	237
4-Aminobenzaldehyde	71	—	153	—
4-Dimethylaminobenzaldehyde	74	—	222	325
4-Bromobenzaldehyde	57	—	228	128
2-Chlorobenzaldehyde	12	212	146	213
3-Chlorobenzaldehyde	17	213	228	248
4-Chlorobenzaldehyde	47	213	230	254
2-Hydroxybenzaldehyde[b]	−7	197	231	248
3-Hydroxybenzaldehyde	108	240	199	260
4-Hydroxybenzaldehyde	117	—	224	280
4-Hydroxy-3-methoxybenzaldehyde[c]	77	285	240	271
4-Methoxybenzaldehyde[d]	0	249	210	253
3,4-Methylenedioxybenzaldehyde[e]	37	263	237	266
3,4-Dimethoxybenzaldehyde[f]	44(58)	285	177	263
4-Nitrobenzaldehyde	106	sublimes	221	320
4-Formylbenzaldehyde[g]	116	—	245	—
4-Carboxybenzaldehyde	256	—	202	—
4-Phenylbenzaldehyde	60	—	243	239
Phenylacetaldehyde	33	194	163	121
1-Naphthaldehyde	34	292	221	—
2-Naphthaldehyde	60	150	245	270
1-Phenanthraldehyde	111	—	—	—
9-Anthraldehyde	105	—	219	—
Pyrene-1-carboxaldehyde	126	—	—	—

[a] 'Handbook of Chemistry and Physics', ed. R. C. Weast, Chemical Rubber Company, Cleveland, 51st edition, 1976; 'Handbook of Tables for Organic Compound Identification', ed. Z. Rappoport, Chemical Rubber Company, Cleveland, 3rd edition, 1967. [b] Salicylaldehyde. [c] Vanillin. [d] Anisaldehyde. [e] Piperonal. [f] Veratraldehyde. [g] Terephthalaldehyde.

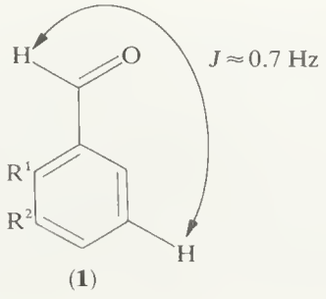
such as vanillin (3-methoxy-4-hydroxybenzaldehyde) and piperonal (3,4-methylenedioxybenzaldehyde), also have agreeable odours and are synthesized on a large scale for use in the flavouring and perfumery industries.

Benzaldehyde is also an important industrial material, being used in the food, beverage, and pharmaceutical industries as a flavouring and in the fine chemicals industry as an intermediate in the synthesis of other perfumery and flavouring chemicals (*e.g.* cinnamaldehydes, ArCH=CHCHO). Benzaldehyde and many other substituted benzaldehydes (*e.g.* *o*-chlorobenzaldehyde, *o*-formylbenzenesulphonic acid) are intermediates in the synthesis of triphenylmethane dyestuffs [*e.g.* Malachite Green (equation 1) and Crystal Violet] which are used extensively in the paper, printing, and synthetic fibre industries.

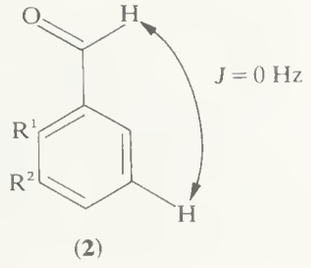


The spectroscopic properties of aromatic aldehydes differ in only minor aspects from those of aliphatic aldehydes. In vibrational spectra the carbonyl stretch changes from 5.75–5.80 μm for aliphatic aldehydes to 5.85–5.95 μm for aromatic aldehydes, being of longest wavelength when chelating *ortho* substituents (OH, NH_2) are present. In the infrared and Raman spectra of *ortho*- and *meta*-substituted aldehydes it is possible in some cases to detect two possible conformations (**1**) and (**2**) in solution at room temperature.[1] For steric reasons, *o*-bromobenzaldehyde exists entirely in the conformation (**1**; $R^1 = Br$, $R^2 = H$) at room temperature. The ultraviolet spectral differences between aliphatic and aromatic aldehydes markedly influence the photochemical reactivity. This topic is discussed in Section 5.3.10.

In the ^1H n.m.r. spectra of aromatic aldehydes the chemical shifts of the aldehydic proton is affected by two contrasting factors: (i) the deshielding effect of the aromatic ring and (ii) the conjugative shielding effect of an increase in electron density of the carbonyl carbon atom. The deshielding effect predominates so that aromatic aldehydic protons appear at lower fields (δ 9.65–11.5) than aliphatic ones; with polycyclic aromatic aldehydes, which have larger ring currents, the protons are even more deshielded.[2] Electron-withdrawing substituents on the aromatic ring enhance the deshielding. For *ortho*-substituted aldehydes the aldehydic proton appears at much lower field, possibly because the formyl group may be forced out of planarity and the conjugate shielding



(**1**)



(**2**)

effect is thus lowered. In *ortho*-disubstituted aromatic aldehydes and polycycles such as 9-anthraldehyde (δ_{CHO} 11.51), this effect is particularly marked.[2]

An interesting phenomenon is the long-range coupling of the aldehydic proton to the *meta*-proton on the ring.[3] This is observed only in conformation (**1**) and not in (**2**). Thus the coupling constant, which is an average of the values for the two conformations (**1**) and (**2**), can be used to determine the relative conformational preferences. With *ortho*-substituted aldehydes, conformation (**1**) is preferred except where hydrogen bonding is possible ($R^1 = OH$, NH_2), whereas in *meta*-substituted aldehydes the conformational equilibrium varies with substituents. When $R^1 = H$ and $R^2 = NO_2$, Cl, or Br, conformation (**1**) is preferred, whereas when $R^2 = OH$ or OMe, conformation (**2**) predominates.

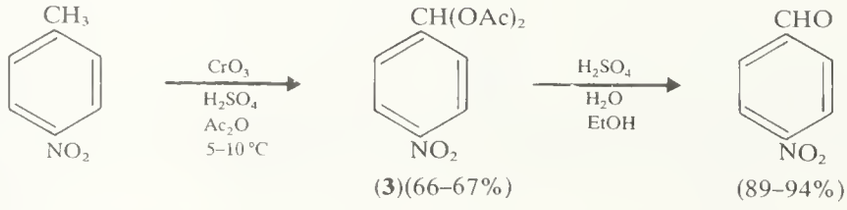
The mass spectra of aromatic aldehydes are usually very simple, giving abundant molecular ions ($ArCHO^{+\cdot}$) which break down by loss of a hydrogen atom giving the very stable ion ($ArCO^+$) or *via* loss of CO with hydrogen transfer, giving the radical cation, ($ArH^{+\cdot}$).

5.3.2 SYNTHESIS OF AROMATIC ALDEHYDES

5.3.2.1 Synthesis of aromatic aldehydes by oxidation of methyl aromatics

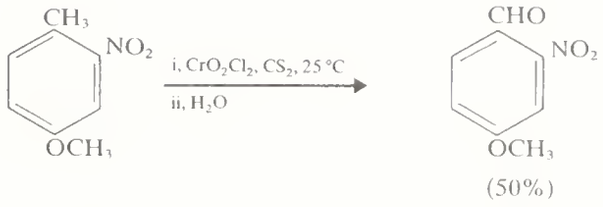
The direct oxidation of toluene is now the method of choice for the manufacture of benzaldehyde, gradually replacing the older method (hydrolysis of benzal chloride, $PhCHCl_2$) since it gives a chlorine-free product, more suitable for the food, beverage, and pharmaceutical industries. A typical process involves the passage of a mixture of air and toluene vapour (14:1 weight ratio) over a catalyst consisting of oxides of uranium and molybdenum (ratio 93:7), impregnated on a carrier at 500 °C. High temperatures and short contact times are essential to maximize yields, which are in the 30–50% range. The formation of the major by-product, maleic anhydride, can be reduced by the addition of small amounts of copper oxide to the catalyst. Other by-products include benzoic acid and anthraquinone. An alternative process, the liquid phase oxidation of toluene with manganese dioxide–sulphuric acid, which is related to laboratory methods, is suitable for small-scale manufacture.

In the laboratory the synthesis of aromatic aldehydes from the corresponding methyl-substituted aromatics is normally accomplished by oxidation using chromium or manganese compounds.[4,5] Chromium trioxide in acetic anhydride is an excellent reagent for the oxidation of nitro- or cyano-toluenes to the corresponding aldehydes. Further oxidation to the acid is prevented by the formation of the intermediate diacetate (**3**), which is stable to the reaction conditions. Hydrolysis in aqueous ethanol gives the aldehyde in good yield[4,5] (equation 2).



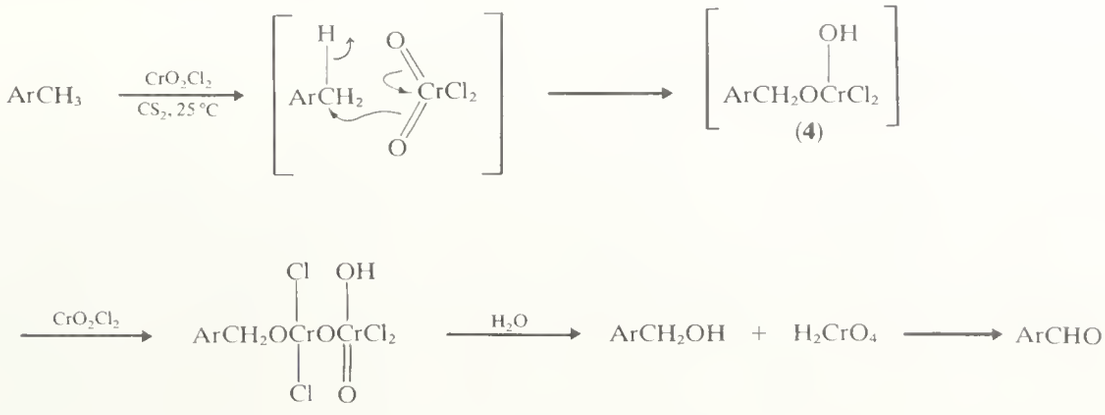
(**3**)(66–67%) (89–94%) (2)

A similar transformation, which can be accomplished using chromyl chloride as the oxidizing agent, is known as the Etard reaction.[6] The reaction is carried out using carbon disulphide, carbon tetrachloride, or chloroform as solvent and 2 moles of chromyl chloride. Initially, a precipitate which contains two chromium atoms per molecule of hydrocarbon is deposited; this yields the aldehyde on treatment with water.[7] The Etard reaction is applicable to the synthesis of aromatic aldehydes containing nitro, halogen, or alkyl subtituents, although alkyl groups other than methyl groups may be oxidized preferentially. In certain cases, alkoxy substituents can survive without being oxidized (equation 3).[8]



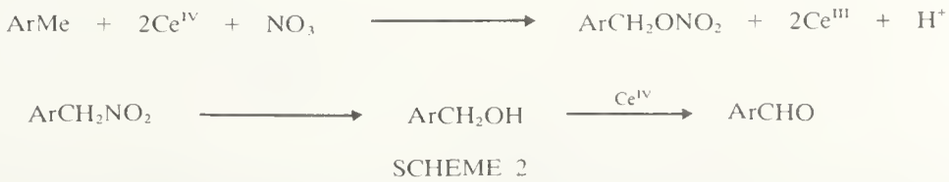
(3)

The detailed mechanism of the reaction has been the subject of much controversy,[9,10] but most of the data can be accommodated by that shown in Scheme 1. The rate-determining step has been shown by deuterium isotope studies[11] to be cleavage of the C—H bond, which occurs *via* a cyclic transition state. This slow step produces an intermediate (**4**) which reacts immediately with another molecule of chromyl chloride, yielding the 1:2 adduct. This complex precipitates out and can be isolated and examined spectroscopically.[12] The hydrolysis stage gives the alcohol which is immediately oxidized to the aldehyde in most cases; in the presence of sulphur dioxide as reducing agent the alcohol has occasionally been isolated.[13]



SCHEME 1

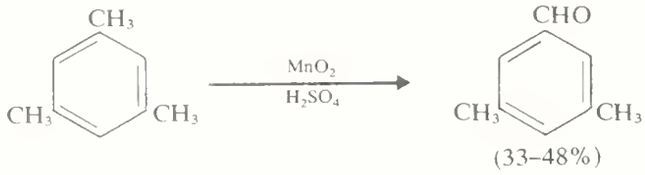
More recently the oxidizing agent ammonium cerium(IV) nitrate has been used to perform the transformation $ArCH_3 \rightarrow ArCHO$ under mild conditions (3.5N HNO_3, 40–80 °C, 1–2 h) in high yields (90–100%).[14] Although the exact details are unclear, the mechanism seems likely to be that shown in Scheme 2 involving the initial formation of a nitrate ester, hydrolysis of this to the alcohol, and oxidation by a second molecule of ammonium cerium(IV) nitrate;[15] the oxidation of benzylic alcohols to aldehydes using this reagent is well documented.[16] In certain cases the intermediate nitrate esters have been isolated.[17]



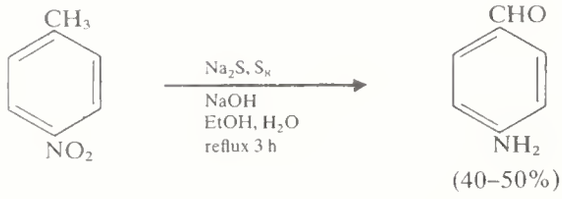
SCHEME 2

The use of manganese dioxide as oxidizing agent is limited to a few examples, one of which is illustrated in equation (4).[18] Selenium dioxide oxidation is seldom successful, except for methylnaphthalenes[19] and particularly methyl groups attached to heteroaromatics.[20] The reagent of choice for the synthesis of aminobenzaldehydes from nitrotoluenes is sodium polysulphide, which reduces the nitro group while simultaneously oxidizing the methyl group (equation 5).[21]

Indirect methods of converting aromatic methyl groups to aldehydes usually involve halogenation to give either the halomethyl or dihalomethyl compounds. The conversion of



(4)



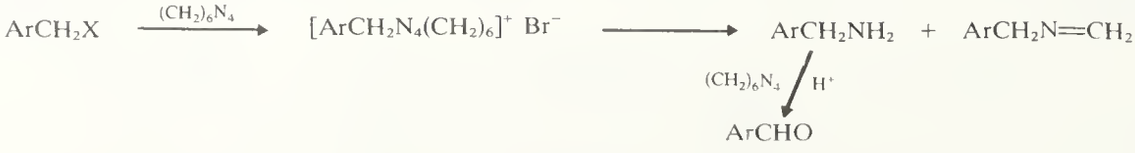
(5)

halomethyl compounds to aromatic aldehydes is discussed in the following section and the route *via* hydrolysis of dihalomethyl aromatics in Section 5.3.2.4.

5.3.2.2 Synthesis of aromatic aldehydes from halomethyl and aminomethyl compounds

This group of synthetic methods represents an important class of reactions since the halomethylated aromatics are readily available starting materials, formed either by the halogenation of methylaromatics (*e.g.* using *N*-halosuccinimides) or by direct halomethylation[22] (*e.g.* using formaldehyde–hydrogen chloride). The older methods of converting $CH_2X \rightarrow CHO$ such as the Sommelet[23] and Krohnke[24] processes are indirect but nevertheless give good overall yields. The practical advantage of these indirect methods is that there is no need to purify the lachrymatory, unstable, and often carcinogenic halomethyl starting materials since the first stage produces a highly crystalline salt (hexaminium or pyridinium, respectively) which is easier to purify. More recently, however, specific oxidizing reagents (*e.g.* Me_2SO, $Hg_2(NO_3)_2$, K_2CrO_4) have been used to effect the transformation $CH_2X \rightarrow CHO$.

The Sommelet reaction[23] is the process whereby aldehydes are formed from aralkyl halides by the action of hexamethylenetetramine (hexamine). The reaction proceeds *via* the hexaminium salt, which can be isolated if required. Normally, however, the salts are hydrolysed to aralkylamines, which under the conditions (excess of hexamine) are oxidized to imines; after acid hydrolysis the aldehydes are produced in good yields (Scheme 3).

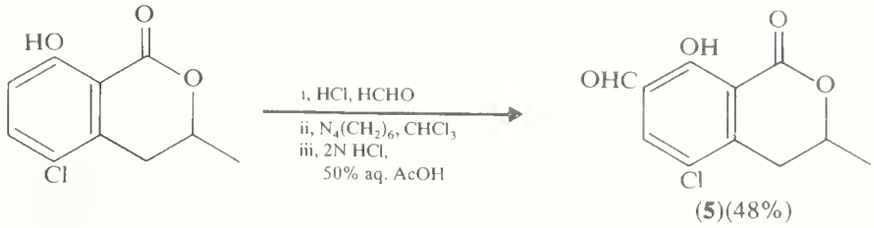


SCHEME 3

The oxidation stage has been examined in detail; at first, it was postulated that oxidation involved isomerization of the imine ($ArCH_2N{=}CH_2$) to the isomer ($ArCH{=}NMe$) which, on hydrolysis, would yield the aldehyde. It has been demonstrated, however, that the hexamine present functions as the methylene derivative of ammonia ($CH_2{=}NH$) and that this oxidizes the aralkylamine to imine and methylamine.

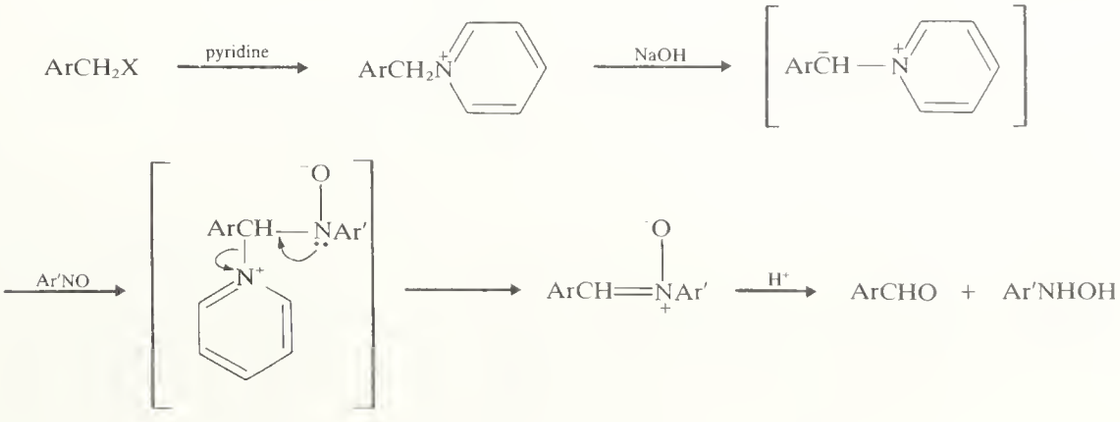
The Sommelet reaction is applicable to the synthesis of a variety of aromatic and heteroaromatic aldehydes, usually in yields of 50–80%. The limitations are that at least one *ortho* position must be vacant; the presence of two strongly electron-attracting substituents hinders the reaction; and phenolic aldehydes cannot normally be synthesized, unless electron-attracting substituents are present, *e.g.* nitrohydroxybenzaldehydes can be

prepared. Phenolic aldehydes, however, can be prepared *via* the Duff reaction (see Section 5.3.2.9). The Sommelet reaction has proved to be the best method of synthesis of vinylbenzaldehydes[25] for polymerization studies, for the dihydrocoumarin (**5**) (equation 6), which is an important intermediate in the synthesis of the mycotoxin Ochratoxin A,[26] and for 1-naphthaldehyde.[27]



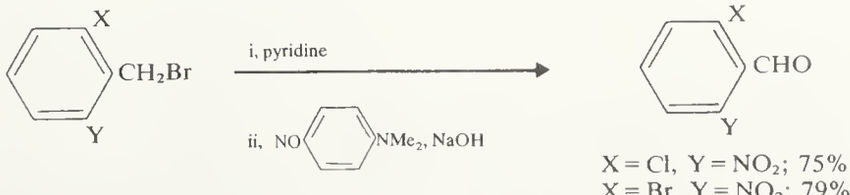
(**5**)(48%) (6)

The Krohnke reaction[24] involves quaternization of the halomethyl derivative with pyridine, followed by base-catalysed condensation with nitrosodimethylaniline which leads to a nitrone; subsequently, hydrolysis with aqueous acid gives the aldehyde (Scheme 4).



SCHEME 4

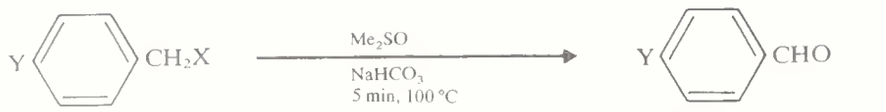
Although this may seem a long route, in practice it is very convenient, uses very mild conditions, gives good yields (50–80%), and is widely applicable, not only to the synthesis of aromatic aldehydes, but also unsaturated aldehydes and α-ketoacids. It is suitable for the synthesis of *ortho*-disubstituted aldehydes, (equation 7),[28] aromatic aldehydes bearing nitro groups (equation 7),[29] and sensitive aldehydes.



X = Cl, Y = NO_2; 75%
X = Br, Y = NO_2; 79%
X = Y = NO_2; 58%
X = Y = Cl; 50%
X = H, Y = NO_2; 53% (7)

The reaction of halides and toluene-*p*-sulphonates with dipolar compounds containing nucleophilic oxygen atoms leads to unstable intermediate salts which, in the presence of mild base, break down to aldehydes. The Kornblum oxidation[30] using dimethyl sulphoxide gives excellent results with benzylic bromides and toluene-*p*-sulphonates (equation 8).

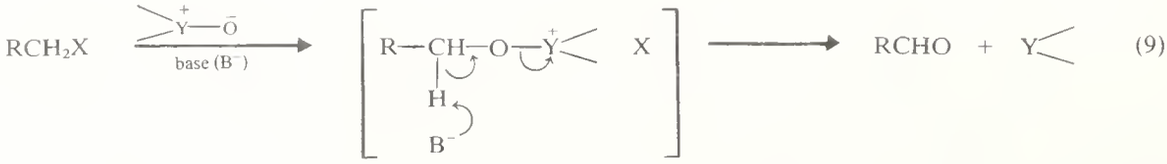
Unhindered aliphatic aldehydes can also be synthesized using this method, although the use of silver tetrafluoroborate–dimethyl sulphoxide reagent enables even hindered aldehydes to be oxidized.[31] Pyridine[32] or trimethylamine *N*-oxides[33] have also been used as



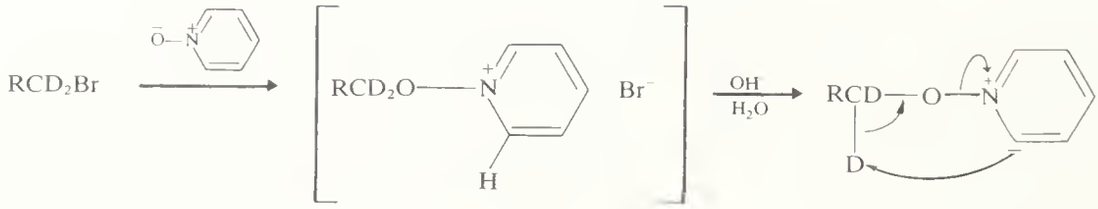
(8)

X = Br, Y = Br; 76%
X = Br, Y = Me; 65%
X = Br, Y = NO_2; 76%
X = OTs, Y = Br; 65%
X = OTs, Y = Me; 74%
X = OTs, Y = NO_2; 84%

oxidants. The mechanisms of all these processes are very similar (equation 9); in the case of the pyridine *N*-oxide oxidations, however, the elimination stage has been shown by deuterium-labelling studies to occur *via* the cyclic process depicted in Scheme 5. It is possible, therefore, that the Kornblum oxidation may also involve a cyclic elimination step.



(9)

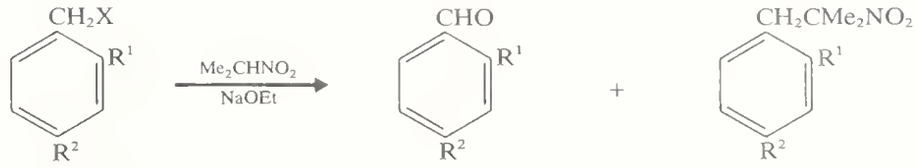


SCHEME 5

The oxidation of halomethyl aromatics to aromatic aldehydes using the sodium salt of 2-nitropropane is sometimes called the Hass reaction.[34] The sodium salt, obtained by treating 2-nitropropane with sodium ethoxide, reacts smoothly with halomethyl aromatics at room temperature to give good yields of aldehydes. The mechanism of the reaction is similar to that of the Kornblum oxidation; in some cases, however, usually when a nitro group is present in the aromatic ring (Table 2), *C*-alkylation rather than *O*-alkylation takes place, and it has been postulated[35] that this process takes place *via* a different mechanism. From the examples in Table 2 it can be seen that other electron-attracting substituents do not have the same effect as the *p*-nitro group. It was also found that the *C*-alkylation reactions proceeded *ca.* 100 times faster than when *O*-alkylation predominated and that the addition of other nitro compounds (e.g. *p*-dinitrobenzene) inhibited the *C*-alkylation process.[35] These results are best explained by invoking initial electron transfer forming the radical ion (**6**), which has been detected by e.s.r. spectroscopy. The radical ion breaks down by elimination of the benzylic substituent; the resultant benzyl radical then reacts in a chain process (Scheme 6) which regenerates the radical ion (**6**).

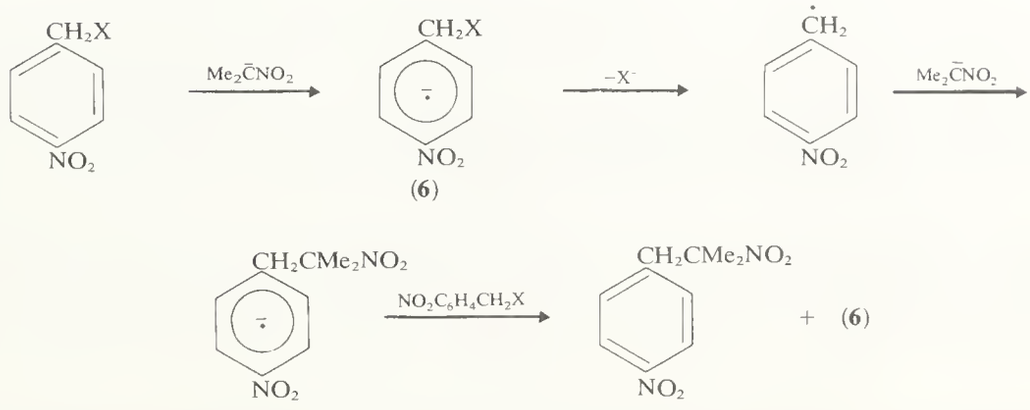
TABLE 2

Reaction of Aralkyl Compounds with Sodium 2-Nitropropanide[a]



X	R^1	R^2	*Yields (%)* O-*Alkylation*	C-*Alkylation*
Br	Me	H	75	—
Cl	H	H	82	—
Br	H	CO_2Me	72	—
Br	H	CN	70	—
Br	H	CF_3	77	—
Br	H	NO_2	65	17
I	H	NO_2	81	7
OTs	H	NO_2	32	40
Cl	H	NO_2	6	92
$C_6Cl_5CO_2$	H	NO_2	—	93
$\overset{+}{N}Me_3\ Cl^-$	H	NO_2	—	93

[a] Ref 35.

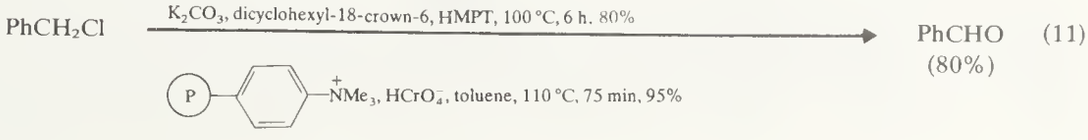


SCHEME 6

Mercuric nitrate and silver nitrate react in a mechanistically very similar fashion to the Kornblum and Hass oxidations, giving the intermediate nitrates which are cleaved by base (equation 10).[36]

$$ArCH_2Br \xrightarrow[MeOCH_2CH_2OMe]{Hg(ONO_2)_2} ArCH_2ONO_2 \xrightarrow[EtOH]{EtONa} \underset{(54\text{–}94\%)}{ArCHO} \qquad (10)$$

One of the problems associated with the use of chromium reagents for aldehyde synthesis has now been overcome.[37] Potassium chromate, which is virtually insoluble in all organic solvents, can be dissolved in hexamethylphosphoric triamide (HMPT) in the presence of crown ethers which complex the potassium ion; this reagent has been used to oxidize allylic and benzylic halides directly to aldehydes (equation 11). Even better results have been obtained by using a chromate reagent supported on a quaternary ammonium polymer.[37]



(11)

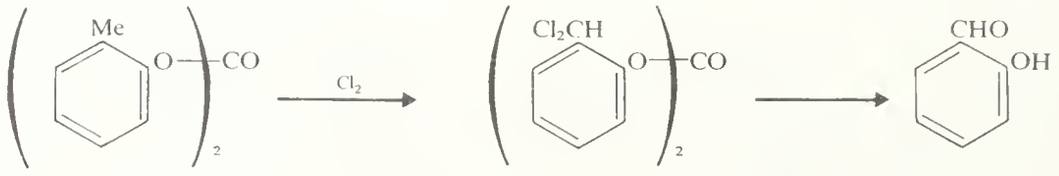
5.3.2.3 Synthesis of aromatic aldehydes by oxidation of hydroxymethyl aromatics

Aromatic aldehydes are also readily prepared by the oxidation of aralkyl alcohols ($ArCH_2OH$), but since the latter are only available from the corresponding halides ($ArCH_2Cl$) or esters ($ArCO_2R$) the method has limited synthetic value. A vast number of oxidizing agents will perform the transformation, the most efficient being Collins reagent (chromium trioxide–pyridine complex),[38] dichlorodicyanobenzoquinone (DDQ),[39] and several inorganic reagents adsorbed on insoluble supports. These include silver carbonate on celite,[40] chromic acid on ion exchange resins[41] or on graphite,[42] and potassium permanganate on molecular sieves[43] — this is in contrast to aqueous potassium permanganate which yields the carboxylic acid. In all cases, high yields (>80%) of aldehydes were obtained with very little acid as by-product.

5.3.2.4 Synthesis of aromatic aldehydes by hydrolysis of dihalomethyl aromatics

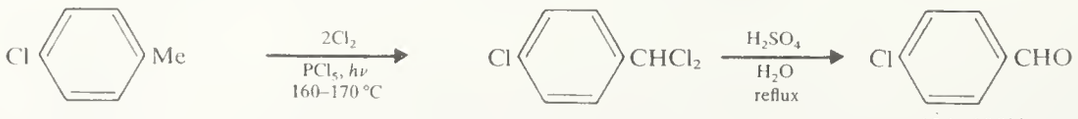
This synthetic route is mainly of industrial importance for the manufacture of benzaldehyde, although it is gradually being superseded by the method of direct vapour-phase oxidation of toluene. Toluene is readily chlorinated in the side chain at elevated temperatures using u.v. light to initiate the radical process, and the reaction can be terminated after 2 moles of chlorine have been used. The by-products are benzyl chloride ($PhCH_2Cl$) and benzotrichloride ($PhCCl_3$). The major product, benzal chloride ($PhCHCl_2$), is readily hydrolysed to benzaldehyde using either aqueous alkali or sulphuric acid.

In the manufacture of 2-hydroxybenzaldehyde (salicylaldehyde) by the Raschig process, carbonate or phosphate esters of *o*-cresol are chlorinated at high temperatures and the resultant tetrachloride on hydrolysis gives good yields of the aldehyde (equation 12). The aldehyde manufactured by this route, however, has a slightly disagreeable odour and is unsuitable for use in perfumery without further purification.



(12)

Although similar methods have been used on the laboratory scale (equation 13),[44] bromination using 2 moles of bromine or *N*-bromosuccinimide (NBS) is often more convenient; for reactive aromatic nuclei such as polycyclic aromatics or heterocyclics, which undergo nuclear substitution with molecular halogens, the use of NBS is the method of choice. Hydrolysis with aqueous silver nitrate,[45] calcium carbonate, or potassium oxalate[46] gives high yields of the aldehydes.



(54–60%)

(13)

5.3.2.5 Gattermann–Koch and related reactions[47–49]

The Gattermann–Koch reaction is a method of inserting carbon monoxide into an aromatic C—H bond using hydrogen chloride and typical Friedel–Crafts catalysts, such as aluminium chloride. High yields can be obtained particularly if the carbon monoxide is used at high pressure (100–250 atmospheres), or at atmospheric pressure with aluminium

chloride or bromide as catalyst and cuprous chloride as promoter. The reaction is applicable to simple alkyl and halo aromatics, but not to phenols, phenol ethers, anilines, naphthalenes and other polycyclic aromatic hydrocarbons (Table 3). Naphthalenes, however, are formylated if a modified catalyst, hydrogen fluoride and boron trifluoride, is used. The reaction has found industrial applications for the synthesis of simple aromatic aldehydes.

TABLE 3

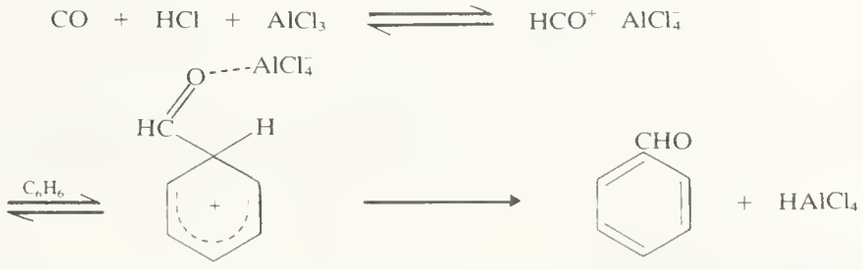
Aromatic Aldehydes Prepared by the Gattermann–Koch Reaction

Reactant	*Conditions*	*Product*	*Yield (%)*	*Ref.*
Benzene	CO, HCl, $AlCl_3$	Benzaldehyde	85	a
Toluene	SbF_5, HF	4-Methylbenzaldehyde	90	b
o-Xylene	CO, HCl, $AlCl_3$, $CuCl_2$	3,4-Dimethylbenzaldehyde	58	c
Mesitylene	CO, HCl, $AlCl_3$, $CuCl_2$	2,4,6-Trimethylbenzaldehyde	80	c
Biphenyl	CO, HCl, $AlCl_3$, $CuCl_2$	4-Phenylbenzaldehyde	73	c
Naphthalene	CO, HF, BF_3	1-Naphthaldehyde	73	d

[a] Ger. Pat. 281 212/1913. [b] Brit. Pat. 1 128 966/1968 (*Chem. Abs.*, 1969, **70**, 37 472). [c] L. Gattermann, *Annalen*, 1906, **347**, 347. [d] U.S. Pat. 2 485 237/1946.

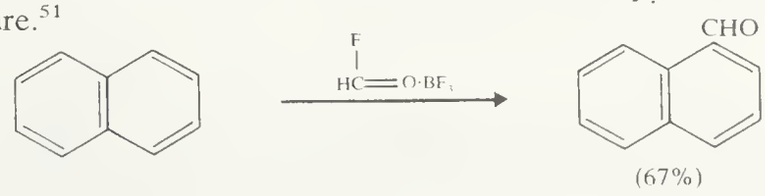
One of the limitations of the high-pressure reactions is that, under the vigorous conditions used, alkyl aromatics isomerize or disproportionate; thus *p*-xylene gives 2,4-dimethylbenzaldehyde. Normally, almost exclusive *para* substitution is observed with simple monoalkylbenzenes.

The mechanism of the reaction is similar to that of the Friedel–Crafts acylation, except that a formyl carbenium ion or its equivalent is the reactive species (Scheme 7). The formylating agent can only be produced in the presence of significant amounts of carbon monoxide. This can be provided by carrying out the reaction under pressure or by using a promoter such as cuprous chloride, which, in the presence of aluminium chloride, absorbs appreciable quantities of carbon monoxide. The aromatic aldehydes formed complex with any Lewis acid present, and this is an important driving force for the reaction.



SCHEME 7

A reaction related to the Gattermann–Koch synthesis is the direct formylation of aromatics using formyl fluoride, the only known stable acyl halide of formic acid.[50] In the presence of boron trifluoride a 1 : 1 complex is formed, which directly formylates the aromatic compound (equation 14). A characteristic of this method is the relatively high proportion of *ortho* isomers which are obtained in the formylation of alkylbenzenes at room temperature.[51]



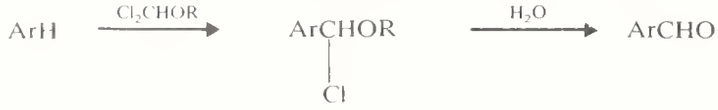
(14)

5.3.2.6 Formylation using dichloromethyl alkyl ethers

This is one of the best methods for the introduction of the aldehyde group into an aromatic ring. It was discovered by Fischer in 1934,[52] but it was not used widely until the potential was demonstrated by Rieche *et al.* in 1960.[53] A wide variety of aromatics can be formylated by this method (Table 4).

TABLE 4

Formylations using Dichloromethyl Alkyl Ethers[a]



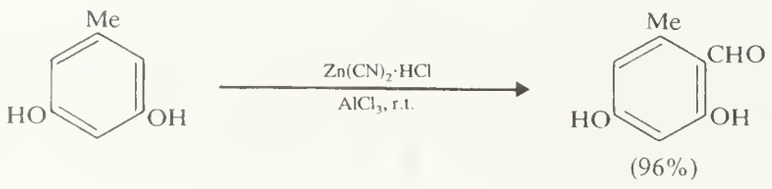
Substrate	*Reagent*	*Catalyst*	*Product*	*Yield (%)*
Benzene	Cl_2CHOCH_3	$TiCl_4$	Benzaldehyde	80
1,2-Dimethoxybenzene	$Cl_2CHOC_4H_9$	$SnCl_4$	3,4-Dimethoxybenzaldehyde	77
Resorcinol	Cl_2CHOCH_3	$SnCl_4$	2,4-Dihydroxybenzaldehyde	68
Biphenyl	Cl_2CHOCH_3	$SnCl_4$	4-Phenylbenzaldehyde	80
Naphthalene	$Cl_2CHOC_4H_9$	$TiCl_4$	1-Formylnaphthalene	79
Fluorene	Cl_2CHOCH_3	$SnCl_4$	2-Formylfluorene	92
Anthracene	$Cl_2CHOC_4H_9$	$TiCl_4$	9-Formylanthracene	86
Pyrene	$Cl_2CHOC_4H_9$	$TiCl_4$	1-Formylpyrene	88
2-Naphthol	Cl_2CHOCH_3	$SnCl_4$	2-Hydroxy-1-formylnaphthalene	82

[a] See Ref. 53.

Dichloromethyl alkyl ethers, in the presence of a Friedel–Crafts catalyst ($TiCl_4$ is often preferred) react with aromatic compounds in 10–15 minutes at room temperature, yielding α-alkoxybenzyl chlorides, which, on heating or hydrolysis, give aldehydes in very good yields. The mechanism of the reaction is assumed to be a normal Friedel–Crafts alkylation. This method has much more scope than any other aromatic formylation method and, in view of its experimental simplicity, it has been used widely since its introduction. The major disadvantage is that the regioselectivity is not as high as in the Gattermann–Koch reaction. For example, whereas in the Gattermann–Koch reaction the formylation of toluene yields 2- and 4-methyl-benzaldehydes (7% and 93%), in the dichloromethyl methyl ether formylation method the corresponding yields are 36% and 60%.[51] Since steric factors are unlikely to be significant in formylations, the different ratios must be due to the position of the transition state along the reaction pathway. In a transition state which resembles an arenium ion (σ complex), a *para* methyl is more stabilizing than an *ortho*. However, if an 'early' (reactant-like) transition state is involved, the stabilizing effect is diminished and a higher *ortho–para* ratio results.

5.3.2.7 Gattermann reaction[54]

Since the Gattermann–Koch reaction fails with phenols and phenol ethers, Gattermann developed a second formylation method, involving the reaction of the aromatic substrate with HCN and HCl, usually in the presence of a Lewis acid. Adams modified the conditions by using zinc cyanide and HCl, to avoid using anhydrous HCN. These procedures gave good yields of aldehyde with phenols and phenol ethers at room temperature (equation 15) and with less reactive aromatics such as toluene at higher temperatures.[55]

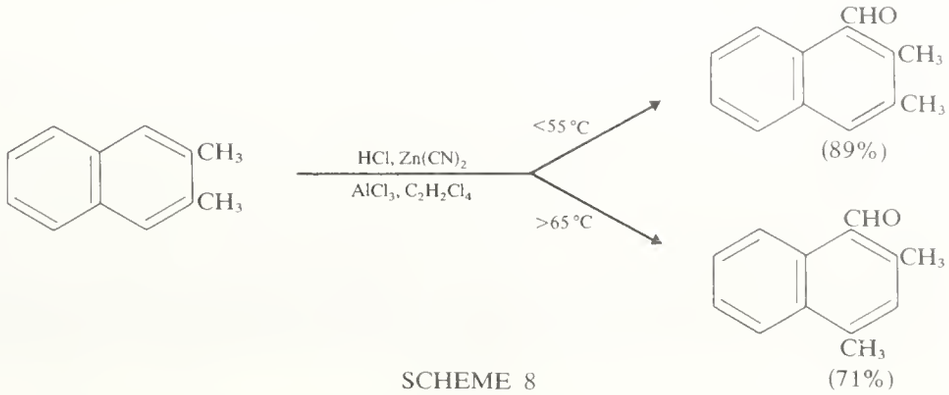


(96%) (15)

The mechanism of the reaction depends upon the conditions used and the particular reagent. In the presence of aluminium chloride, the intermediate (**7**) is probably formed, and this reacts with the aromatic to produce a methylene formamidine salt (**8**) which is subsequently hydrolysed to an aldehyde (equation 16). In the absence of Lewis acids, or at low temperatures, other species (*e.g.* $HC{\equiv}NH^+\ HCl_2^-$) may be involved.[54]

$$ArH + \underset{(7)}{HN{=}CH{-}N{=}CHCl} \xrightarrow{AlCl_3} \underset{(8)}{ArCH{=}\overset{+}{N}CH{=}NH_2} \xrightarrow{H_2O} ArCHO \quad (16)$$

In the formylation of alkyl aromatics, strict control of temperature is necessary otherwise acid-catalysed isomerization of the starting materials may take place. An excellent example of this is in the Gattermann reaction of 2,3-dimethyl naphthalene which, at temperatures below 55 °C, yields 2,3-dimethylnaphthaldehyde whereas above 65 °C the 2,4-dimethyl isomer is formed (Scheme 8).[56]



SCHEME 8

A recent modification of the Gattermann reaction involves the use of *sym*-triazine (**9**) instead of a cyanide; good yields of a wide variety of aldehydes, including alkylbenzenes, phenols and phenol ethers, polycyclic aromatics, and heterocyclics, have been reported (Table 5).[57]

TABLE 5

Gattermann Aldehyde Synthesis using *sym*-Triazine[a]

$$ArH \xrightarrow[\text{(9)}]{HCl} ArCH{=}\overset{+}{N}H_2\,Cl^- \xrightarrow{H_2O} ArCHO + NH_4Cl$$

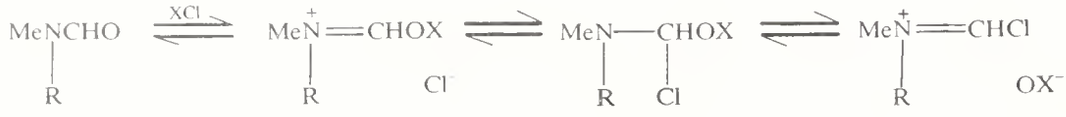
Reactant	*Catalyst*	*Solvent*	*Product*	*Yield* (%)
Benzene	$AlCl_3$	Benzene	Benzaldehyde	31
Toluene	$AlCl_3$	Toluene	4-Methylbenzaldehyde	81
Biphenyl	$AlCl_3$	Tetrachloroethane	4-Phenylbenzaldehyde	63
m-Xylene	$AlCl_3$	*m*-Xylene	2,4-Dimethylbenzaldehyde	89
Resorcinol	None	Ether	2,4-Dihydroxybenzaldehyde	77
Anisole	$AlCl_3$	Anisole	4-Methoxybenzaldehyde	67
Diphenyl ether	$AlCl_3$	Benzene	4-Phenoxybenzaldehyde	78
Naphthalene	$AlCl_3$	Chlorobenzene	1-Formylnaphthalene	55
Anthracene	$AlCl_3$	Chlorobenzene	9-Formylanthracene	55
Fluorene	$AlCl_3$	Chlorobenzene	2-Formylfluorene	64
2,4-Dimethylpyrrole	None	Ether	2,4-Dimethyl-5-formylpyrrole	86

[a] See Ref. 57.

5.3.2.8 Vilsmeier–Haack formylation[58–62]

The reaction between tertiary amides, such as *N*-methylformanilide (MFA) and *N*,*N*-dimethylformamide (DMF), and phosphorus oxychloride ($POCl_3$) leading to a 1 : 1 complex, which formylates a variety of substrates, was first recognized by Vilsmeier.[63] It was

established later that other reactive halides such as thionyl chloride ($SOCl_2$) and phosgene ($COCl_2$) also react with formamide derivatives and it has recently been shown[64] that the active formylating species is similar in each case (Scheme 9). With $POCl_3$ and DMF or MFA the equilibria favour formation of iminium salt (**10**),[64] whereas with $SOCl_2$ the stable compound (**11**) can be isolated.[65] When $COCl_2$ reacts with DMF, elimination of CO_2 takes place giving the iminium salt $R\overset{+}{N}(Me)=CHCl\ Cl^-$.[66]



(**10**) (**11**) (**12**)

R = Me, Ph; X = $OPCl_2$, OSCl, OCCl

SCHEME 9

The chloroiminium salts (**12**) react with electron-rich aromatics *via* a second-order electrophilic substitution reaction leading to a second iminium salt which gives the aldehyde on hydrolysis (Scheme 10). The position of substitution is *ortho* or *para*, as in other electrophilic substitutions.[67] The reaction is applicable to a variety of substituted benzenes, usually containing hydroxy, alkoxy, or dialkylamino substituents (see Table 6). Unsubstituted polycyclic aromatics, apart from naphthalene, phenanthrene, and chrysene, react with Vilsmeier reagents giving good yields of aldehydes (Table 6), and often this is the method of choice for their synthesis since practically it is a simple reaction to perform.

TABLE 6

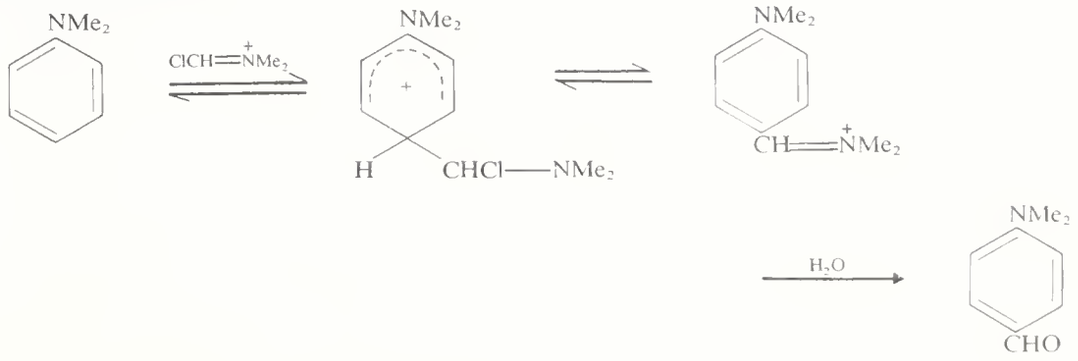
Formylation of Aromatics *via* the Vilsmeier–Haack Method

Reactant	*Conditions*[a]	*Product*	*Yield* (%)	*Ref.*
HOC_6H_5	DMF, $POCl_3$	4-HOC_6H_4CHO	85	b
1,3-$(HO)_2C_6H_4$	F, $POCl_3$	2,4-$(HO)_2C_6H_3CHO$	60	c
$MeOC_6H_5$	FP, $POCl_3$	4-$MeOC_6H_4CHO$	21	d
3-$Bu^tC_6H_4OMe$	MFA	2-MeO-4-$Bu^tC_6H_3CHO$	95	e
$Me_2NC_6H_5$	DMF	4-$Me_2NC_6H_4CHO$	85	f
2-PhC_6H_4OMe	DMF	3-MeO-4-PhC_6H_3CHO	79	b
1-$MeOC_{10}H_7$	DMF, $POCl_3$	4-MeO-1-$CHOC_{10}H_6$	90	g
2-$MeOC_{10}H_7$	DMF, $POCl_3$	2-MeO-1-$CHOC_{10}H_6$	90	h
Anthracene	DMF, $POCl_3$	9-Anthraldehyde	63	i
Anthracene	MFA, $POCl_3$	9-Anthraldehyde	84	j
Pyrene	MFA, $POCl_3$	Pyrene-1-carboxaldehyde	54	k

[a] DMF, *N,N*-dimethylformamide; MFA, *N*-methylformanilide; F, formanilide; FP, *N*-formylpiperidine. [b] N. P. Buu-Hoï, N. D. Xuong, M. Sy, G. Lejeune, and N. B. Tien, *Bull. Soc. chim. France*, 1955, 1594. [c] O. Dimroth and R. Zoeppritz, *Ber.*, 1902, **35,** 993. [d] S. Akabori and Y. Senoh, *Bull. Chem. Soc. Japan*, 1939, **14,** 166. [e] M. Iwata and S. Emoto, *Bull. Chem. Soc. Japan*, 1974, **47,** 1687. [f] E. Campaigne and W. L. Archer, *Org. Synth. Coll. Vol.* 4, 1963, 331. [g] N. P. Buu-Hoï and D. Lavit, *J. Chem. Soc.*, 1955, 2776. [h] N. P. Buu-Hoï, N. Hoan, and M. R. Khenissi, *J. Chem. Soc.*, 1951, 2307. [i] E. Campaigne and W. L. Archer, *J. Amer. Chem. Soc.*, 1953, **75,** 989. [j] L. F. Fieser, J. L. Hartwell and J. E. Jones, *Org. Synth. Coll. Vol.* 3, 1955, 98. [k] A. D. Mosnaim, M. E. Wolf, I. Saavedra, A. M. Amaro, G. Cordano, and D. C. Nonhebel, *Tetrahedron Letters*, 1973, 1491.

When the reaction was first discovered, MFA was the preferred reagent, *o*-dichlorobenzene being used as co-solvent. More recently, however, it has been realised that most reactions can be carried out using the cheaper and more volatile DMF, although yields are somewhat lower (Table 6). The main practical advantage is that excess of DMF can be used as solvent, and since DMF is miscible with water the product can be hydrolysed by pouring the reaction mixture into aqueous sodium acetate. With MFA as

the reagent, a time-consuming evaporation or steam distillation of MFA and *o*-dichlorobenzene is involved.

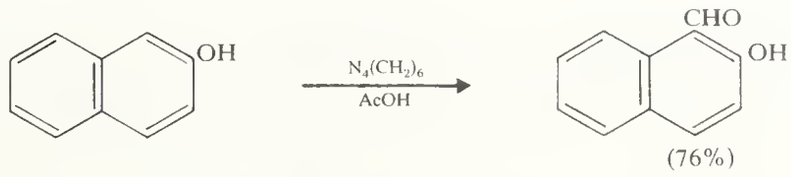


SCHEME 10

The Vilsmeier reaction is one of the most important methods for the formylation of heterocyclic compounds, particularly pyrroles, furans, and thiophens.[58–62]

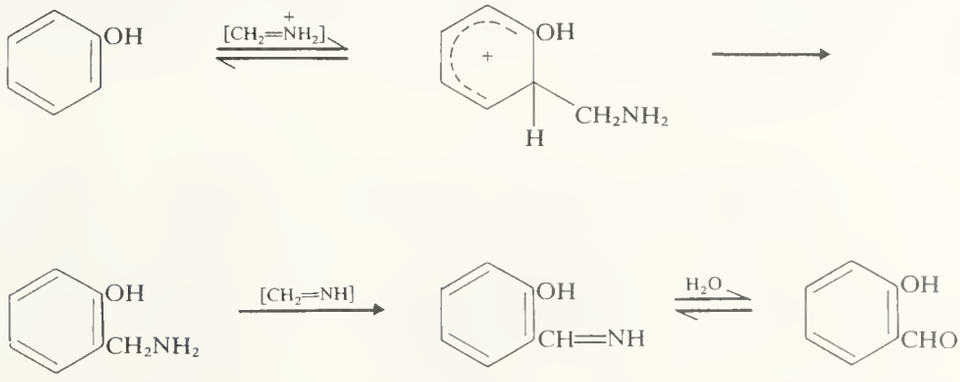
5.3.2.9 Duff reaction[68]

The Duff reaction is a formylation method, normally used for electron-rich aromatics such as phenols and aromatic amines, in which the formylating agent is hexamethylenetetramine in the presence of glycerol or acetic acid. Yields are only moderate, but the main value is that mainly *ortho* substitution occurs (equation 17).[69] A modern adaptation



(17)

uses trifluoroacetic acid as the catalyst; this allows simple aromatics such as toluene and xylene to be formylated, but under these conditions the reaction becomes *para* selective, even for phenols.[70] The mechanism involves fast aminomethylation followed by a rate-determining dehydrogenation to the imine similar to that observed in the Sommelet reaction; hydrolysis then gives the aldehyde (Scheme 11).[71]

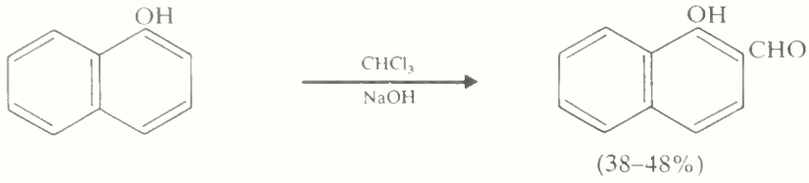


SCHEME 11

5.3.2.10 Reimer–Tiemann reaction[72]

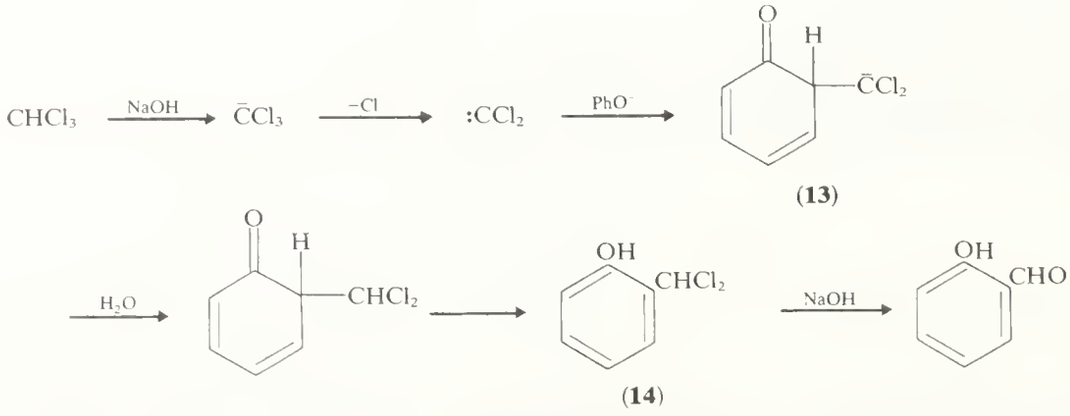
Formylation of electron-rich aromatics and heteroaromatics, such as phenols, using chloroform and alkali is known as the Reimer–Tiemann reaction. The reaction is carried

out by heating the substrate with 10% aqueous alkali and excess of chloroform at temperatures above 50 °C. The main preparative value is that a comparatively high ratio of *ortho*- to *para*-substituted products is obtained. The yields are not high, but isolation of the *o*-hydroxyaldehydes can be easily effected by steam distillation (equation 18).[73] The reaction has been used in the manufacture of *o*-hydroxybenzaldehydes from phenols.



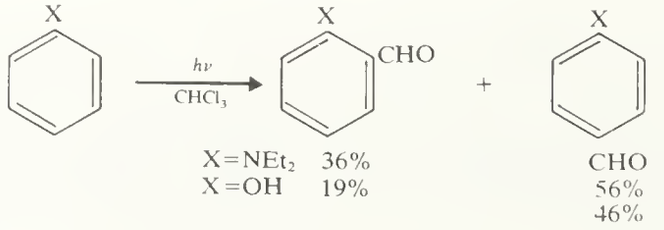
(18)

The reaction is of mechanistic interest since it was demonstrated[74] in 1959 that the active species, generated from chloroform and base, is dichlorocarbene ($:CCl_2$). The carbene reacts with, for example, phenolate ions as shown in Scheme 12. When the reaction was performed in D_2O, >97% deuterium was incorporated into the formyl group of salicylaldehyde. This demonstrates that the conversion **(13)** → **(14)** in Scheme 12 does not proceed *via* an intramolecular 1,2-shift.



SCHEME 12

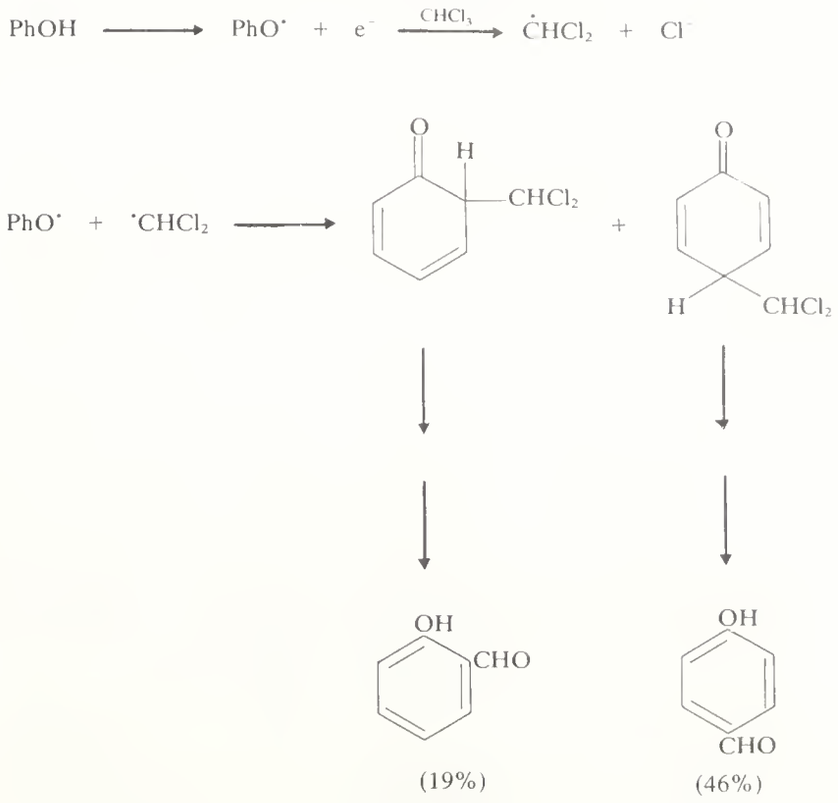
A recent development is the photochemical Reimer–Tiemann reaction.[75] Phenols and *N*,*N*-disubstituted anilines on irradiation in chloroform are converted to the corresponding 2- and 4-substituted benzaldehydes (equation 19) by a mechanism involving attack by the dichloromethyl radical (Scheme 13). Photolysis in deuteriochloroform yields products containing the deuterioformyl group.[76]



(19)

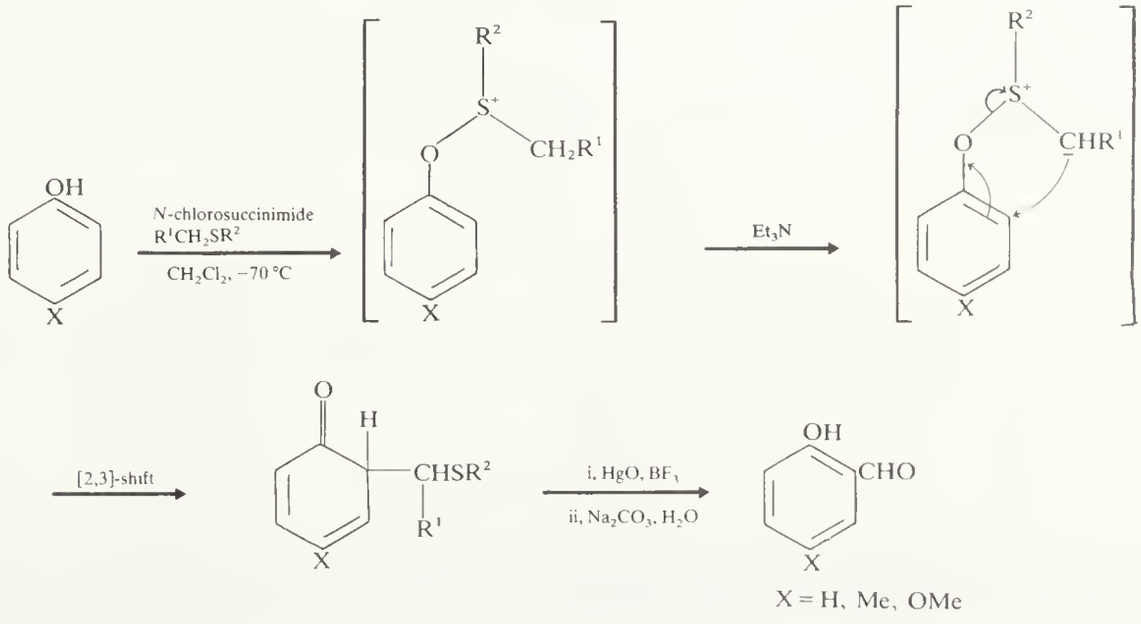
5.3.2.11 Selective *ortho* formylation of phenols

Two methods for the introduction of a formyl group *ortho* to a phenol have been introduced by Gassman and Amick.[77] Both methods are similar to the Sommelet–Hauser rearrangement[78] in that a [2,3]-sigmatropic shift is used to form the new carbon–carbon bond (Scheme 14). Although the yields are only moderate (20–45%), the reactions are



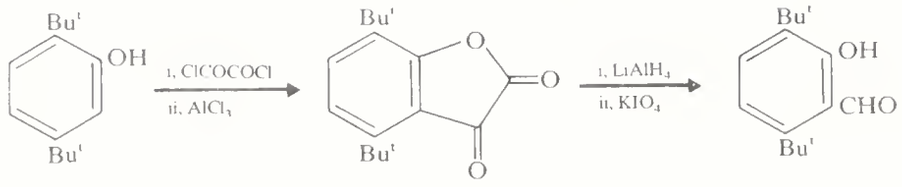
SCHEME 13

unusual in producing exclusive *ortho* substitution. Similar methods have also been introduced for the *ortho* formylation of aromatic and heteroaromatic amines.[79]



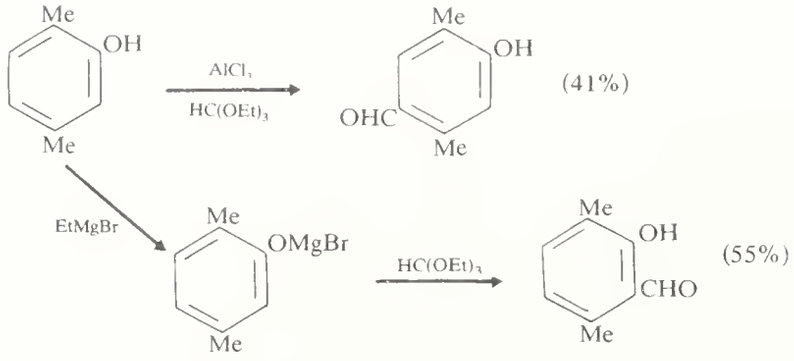
SCHEME 14

A further method, which is useful since it is applicable to phenols containing bulky substituents, is shown in equation (20).[80] Although the procedure involves three stages, yields are high at each stage, and overall yields of up to 65% were obtained, even with di-t-butyl-phenols. The older method of regioselective *ortho* formylation, the reaction of phenoxymagnesium halides with orthoformates, gives moderate yields (30–55%) with simple alkyl phenols, but yields are very low when bulky alkyl groups, halo, nitro, or



(20)

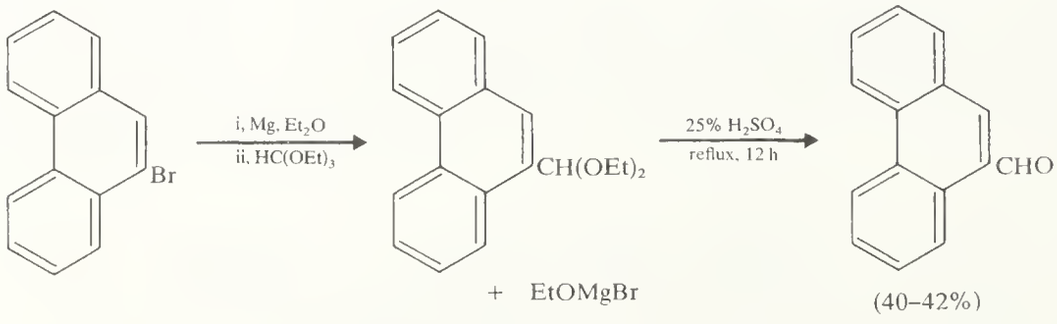
carboxy substituents are present (Scheme 15).[81] In contrast, formylation of free phenols with aluminium chloride–triethylorthoformate yields the *para*-isomer (Scheme 15).[82]



SCHEME 15

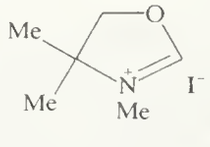
5.3.2.12 Synthesis of aromatic aldehydes from haloaromatics

Although there are several ways of performing the transformation ArBr → ArCHO, most involve the initial formation of an organometallic such as an aryl-lithium or magnesium halide, followed by reaction with a formylating agent such as ethyl formate, triethyl orthoformate (equation 21),[83] *N*,*N*-dimethylformamide, oxazoline methiodide (**15**),[84] or ethoxymethyleneaniline.[85] In a comparative study, the last reagent gave the best yields of aldehydes. These methods are analogous to those used for the synthesis of aliphatic aldehydes (see Section 5.1.2.8).

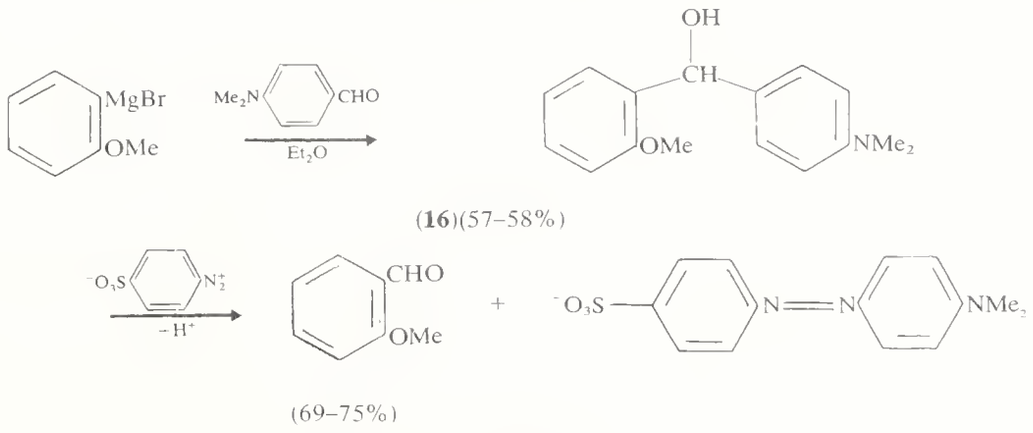


(21)

An interesting method, which is longer yet gives moderate yields, involves the transfer of a formyl group from one aldehyde to another (Scheme 16) *via* the intermediate alcohol (**16**); the latter is regioselectively cleaved by a diazonium salt, yielding the aldehyde.[86]

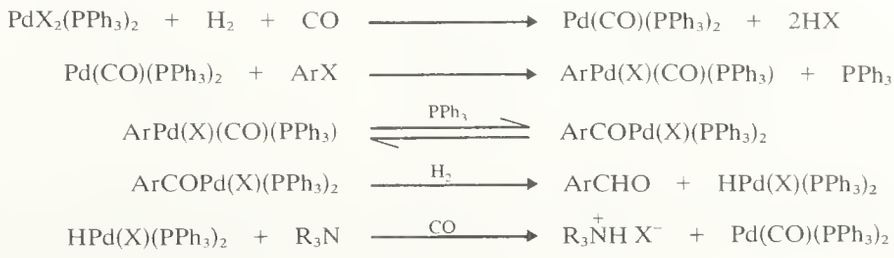


(**15**)



SCHEME 16

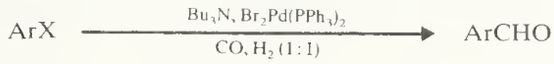
A more recent method specific for aromatic and heteroaromatic aldehydes involves the reaction of an aryl halide with carbon monoxide and hydrogen under pressure in the presence of dihalo(triphenylphosphine)palladium(II) catalyst and a base.[87] The process is widely applicable, failing only with *o*-dibromobenzene which gives benzaldehyde under the conditions used (Table 7). A mechanistic rationale is shown in Scheme 17.



SCHEME 17

TABLE 7

Palladium-catalysed Formylation of Aryl Halides[a]



Aryl halide	*Initial pressure* (p.s.i.)	*Temp.* (°C)	*Time* (h)	*Yield* (%)
C_6H_5Br	1350	125	24	94
C_6H_5I[b]	1500	125	9	95
4-$MeOC_6H_4Br$[c]	1450	150	10	84
4-NCC_6H_4Br[d]	1475	150	24	76
1,4-$Br_2C_6H_4$	1375	140	24	83
1,2-$Br_2C_6H_4$	1190	140	41	66[e]
1-$C_{10}H_7Br$	1225	125	24	82

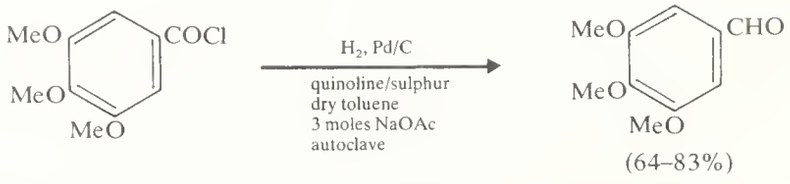
[a] Ref. 87. [b] Catalyst was $I_2Pd(PPh_3)_2$. [c] $CO:H_2$ ratio, 1:2. [d] Et_3N as base. [e] Product was benzaldehyde, not *o*-phthalaldehyde.

5.3.2.13 Synthesis of aromatic aldehydes by the reduction of acids, acid halides, esters, nitriles

An early review (1954)[88] on this subject discussed seven methods for the conversion of acids or their derivatives into aldehydes, but these methods have largely been superseded

by reductions using complex metal hydrides which are selective and experimentally easier to carry out. These early methods will therefore be discussed very briefly.

In the Rosenmund reduction,[89] which is applicable to both aromatic and aliphatic aldehydes, hydrogen is passed through a heated (typically 150 °C) mixture of the acid chloride (in a solvent) and the catalyst. The progress of the reaction is monitored by the amount of hydrogen chloride evolved. The catalyst, usually palladium on barium sulphate, is 'poisoned' with a suitable additive, *e.g.* quinoline–sulphur, to reduce the activity of the catalyst to try to prevent over-reduction. The yields of aldehydes are generally in the range 50–80%. The disadvantages of this procedure are that the use of a continuous stream of hydrogen is not only wasteful but hazardous when the high temperatures involved are considered. Generally, high catalyst to substrate ratios are required. A more efficient procedure, developed by scientists at Hoffmann-La Roche[90] is to use a closed system at low pressure, with sodium acetate present as the HCl acceptor; this method then gives excellent results for aromatic aldehydes (equation 22). Aromatic amines have also been used as HCl acceptors;[91,92] in some cases they also act as the catalyst poison, *e.g.* 2,6-dimethylpyridine,[93] yet allow sufficient catalyst activity for the reductions to be carried out in 1–2 h at room temperature in a closed system. When deuterium is used in place of hydrogen, the corresponding deuterioaldehydes (RCDO) are formed.[94]



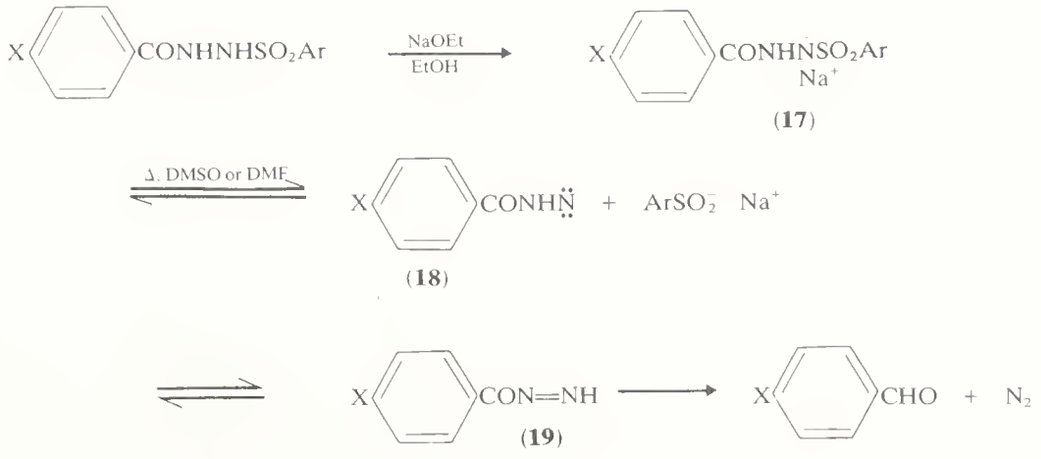
(22)

Indirect methods for converting aromatic acid chlorides to aldehydes include the hydrolysis of 'Reisserts' compounds,[88] the reductive desulphurization of thiol esters using Raney nickel,[88] the Sonn–Muller method *via* imidoyl chlorides,[88] and the McFadyen–Stevens reaction.[88] The latter procedure involves the synthesis of 1-acyl-2-arylsulphonylhydrazines either from acid chlorides or esters. Alkaline hydrolysis of these hydrazine derivatives yields aldehydes (equation 23).

(23)

The McFadyen–Stevens reaction is applicable to the synthesis of aromatic and heteroaromatic aldehydes, containing a variety of substituents (OH, OMe, F, Cl, Br). Aliphatic aldehydes can be synthesized only if excess of base is avoided in the decomposition of the sulphonylhydrazine; excess of base removes the α-hydrogen atom of aliphatic aldehydes, leading to further reactions, *e.g.* aldol condensation. The mechanism of the McFadyen–Stevens reaction has recently been re-investigated.[95] The first step in the base-induced decomposition of arylsulphonylhydrazines is removal of a proton, giving the stable salt (**17**). Thermolysis then leads to the aldehyde with elimination of arylsulphinate anion and nitrogen, and intramolecular hydrogen transfer (Scheme 18). The intramolecularity was demonstrated by using deuteriated derivatives. Coincidentally, this produced a convenient method for synthesizing 1-deuterioaldehydes.[95]

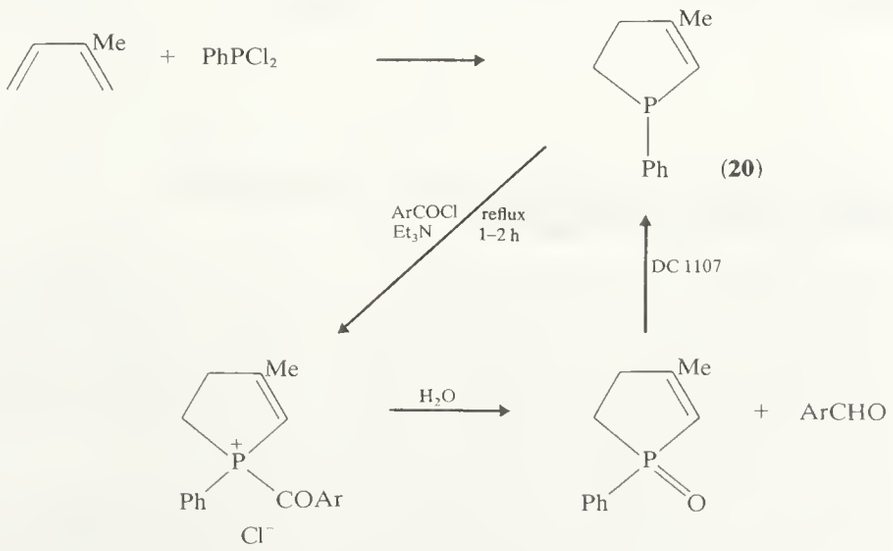
On the basis of a kinetic study using aroylsulphonylhydrazines substituted in the aromatic ring, the mechanism in Scheme 18 has been postulated. The reaction is accelerated by electron-donating groups and retarded by electron-attracting substituents, implying that hydride transfer to the carbonyl is unlikely. Fast elimination of arylsulphinate anion from the salt (**17**) leads to the arylaminonitrene (**18**) which, after proton (or aroyl) migration, gives the imide (**19**); elimination of nitrogen, with intramolecular hydrogen transfer, produces the aldehyde. The rate of reaction changes remarkably little with solvent and this is consistent with the intermediacy of the nitrene (**18**).[95]



SCHEME 18

The older methods discussed previously have largely been replaced by reduction using metal hydrides. Lithium tetrahydridoaluminate cannot be used to reduce acid chlorides directly to aldehydes, since further reduction to the alcohol usually takes place. Brown and Subba Rao[96] introduced a less-reactive hydride, lithium (tri-t-butoxy)hydridoaluminate [$LiAl(OBu^t)_3H$], as a useful reagent for the reduction of both aliphatic and aromatic acid chlorides to aldehydes in diglyme at −78 °C. *ortho*-Substituted aromatics give rather low yields, hindering the approach of the bulky reagent. Functional groups such as CN, CO_2R, NO_2, and certain heterocyclic groups are not reduced by the reagent, although lithium tetrahydridoaluminate reduces all of them.

An alternative reagent which is suitable only for the synthesis of aromatic and heteroaromatic aldehydes is the phospholene (**20**), readily prepared from isoprene and dichlorophenylphosphine.[97] Reaction of (**20**) with aroyl chlorides in the presence of triethylamine generates a salt which is hydrolysed by water to give the aldehydes in good yields (Scheme 19). The reagent (**20**) can be regenerated from the by-product by reduction with the polymethyl hydrogen siloxane (DC 1107).[97] Iron carbonyl reagents, *e.g.* $Fe(CO)_5$, $NaHFe(CO)_4$, and $(Me_4N)^+HFe(CO)_4^-$, have also been used to convert acid chlorides into aldehydes.[98]

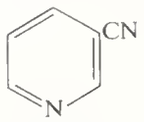


SCHEME 19

The transformation of aromatic nitriles to aldehydes can be carried out by a variety of methods,[99] but undoubtedly the most versatile are partial reductions using lithium triethoxyhydridoaluminate[100] (Table 8) or di-isobutylhydridoaluminate.[101] An alternative, direct procedure uses nickel–aluminium alloy or Raney nickel in formic acid solution (Table 8); ketones, esters, amides, and acids are inert, but nitro compounds are reduced by the reagent to formamide derivatives.[102]

TABLE 8

Reduction of Nitriles to Aldehydes

Nitrile	*Yields (%) of aldehyde using* $LiAl(OEt)_3H$[a]	Ni–Al[b]	$SnCl_2$–HCl[a,c]
C_6H_5CN	96	97	97
$2\text{-}MeC_6H_4CN$	87	—	9
$2\text{-}ClC_6H_4CN$	87	—	100
$4\text{-}ClC_6H_4CN$	92	100	100
$4\text{-}MeOC_6H_4CN$	81	93	—
$4\text{-}NH_2SO_2C_6H_4CN$	—	69	—
$4\text{-}MeO_2CC_6H_4CN$	—	—	90
$\alpha\text{-}C_{10}H_7CN$	80	—	7
	58	—	—
$PhCH_2CN$	0	—	—

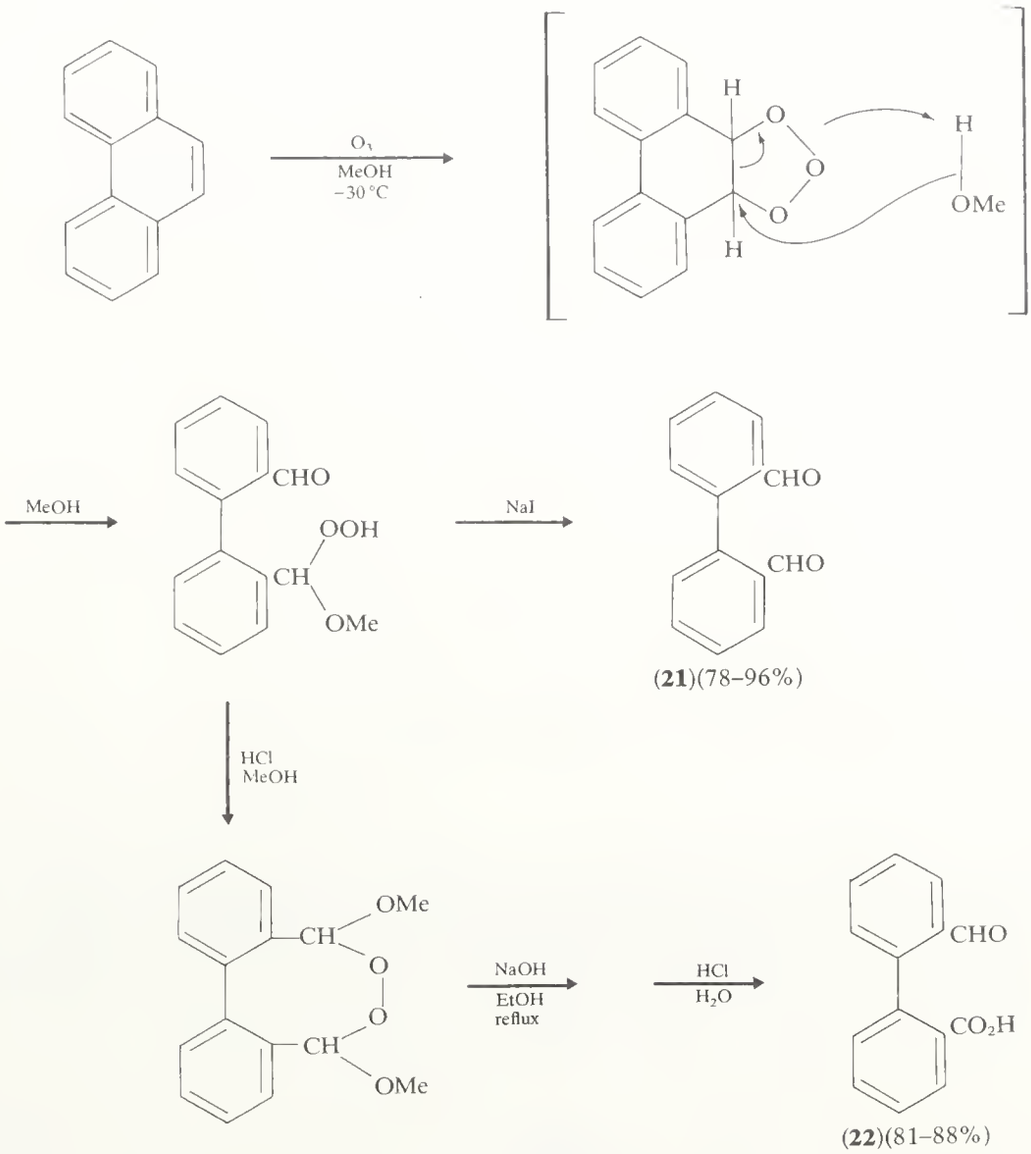
[a] Ref. 100. [b] HCO_2H solvent, reflux 1 h; see Ref. 102. [c] Ether solvent; intermediate complex hydrolysed with boiling water; see Ref. 88.

In the method devised by Stephen,[88] the nitrile is reduced with stannous chloride and hydrogen chloride. The nitrile initially combines with HCl to form an imidochloride [RC(Cl)=NH·HCl], which on reduction yields an aldimine; hydrolysis of the aldimine produces the aldehyde. The method gives excellent results using aromatic nitriles as starting materials but aliphatic nitriles normally give low yields of aldehydes (Table 8). In many cases the intermediate aldimine separates out as a crystalline complex, $(RCH{=}NH{\cdot}HCl)_2SnCl_4$, which can be isolated and hydrolysed with boiling water (Table 8).

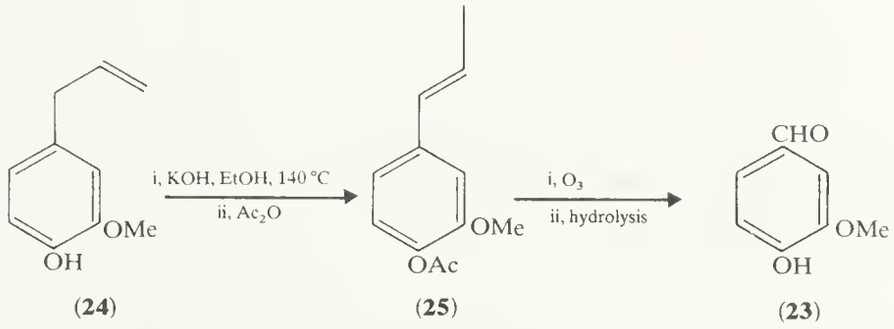
5.3.2.14 Synthesis of aromatic dialdehydes by the oxidation of polycyclic aromatic hydrocarbons

One of the best methods of synthesizing aromatic di-, tri- and tetra-aldehydes is by the oxidative cleavage of readily available polycyclic aromatic hydrocarbons; usually, ozonolysis followed by reduction of the intermediate ozonide[103] is the preferred method for the synthesis of aldehydes. A well-known example is the oxidation of phenanthrene, which gives high yields of either the dialdehyde (**21**) or the aldehyde-acid (**22**) according to the conditions;[104] the mechanism is shown in Scheme 20.[104]

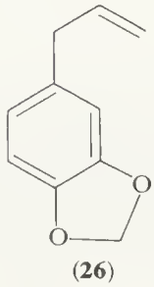
The oxidation of arylethenes also gives good yields of aldehydes. The method is mainly of interest for the manufacture of vanillin (**23**); the readily available eugenol (**24**) is isomerized by base to the isomer (**25**), which, after acetylation, is oxidized by ozone or dichromate to the aldehyde (**23**) (equation 24).[105] Piperonal (3,4-methylenedioxybenzaldehyde) is manufactured similarly from safrole (**26**).



SCHEME 20



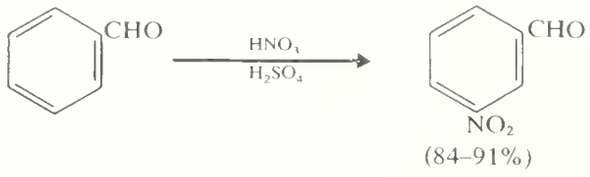
(24)



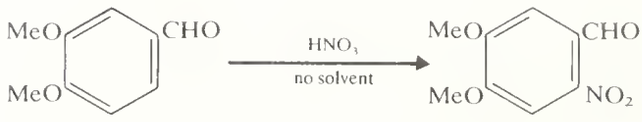
(26)

5.3.3 ELECTROPHILIC SUBSTITUTIONS OF AROMATIC ALDEHYDES

Electrophilic substitutions of aromatic aldehydes are relatively unimportant owing to the deactivating effect of the aldehyde group. Nitration of benzaldehyde takes place readily in strong acid media, giving mainly the anticipated *meta* isomer (equation 25), the proportion of *meta* product increasing with increasing acid strength.[106] Nitration with acetyl nitrate, however, leads to a large proportion of *p*-nitrobenzaldehyde owing to prior formation of the diacetate, $PhCH(OAc)_2$, before nitration.[107] The position of nitration of substituted benzaldehydes is often determined by the substituent rather than the aldehyde group, particularly if activating substituents are present[108] (equation 26).

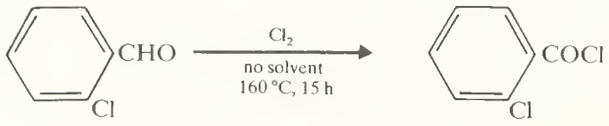


(84–91%) (25)

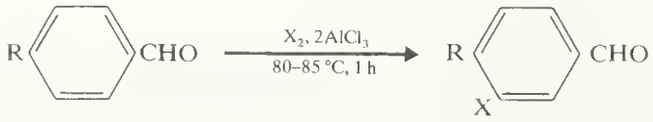


(73–79%) (26)

Although aromatic aldehydes are readily converted to aroyl halides on treatment with halogens (equation 27),[109] nuclear halogenation can be accomplished in moderate yield without oxidation of the aldehyde provided that the aldehyde is complexed with aluminium chloride before addition of halogen, that no solvent is used, and that sufficient aluminium chloride is present to complex with the halogen (equation 28).[110]



(70–72%) (27)



(28)

R = H, X = Br; 59%
R = H, X = Cl; 43%
R = Me, X = Br; 44%

Surprisingly, only aluminium chloride (or bromide) or antimony pentachloride act as 'catalysts'; no other Lewis acid effected the nuclear halogenation. The reason is not readily apparent; the purpose of the catalyst must be to complex the aldehyde, the complex being more susceptible to electrophilic attack in the nucleus than the parent aldehyde. The additional mole of 'catalyst' complexes and presumably activates the halogen in electrophilic substitution. In agreement with this, an increase in the amount of 'catalyst' increases the rate of reaction.

5.3.4 NUCLEOPHILIC ADDITION TO THE CARBONYL GROUP OF AROMATIC ALDEHYDES

The rate of addition of nucleophiles to aromatic carbonyl groups is slower than with aliphatic carbonyl groups owing to both steric and electronic factors.[111] The aromatic ring reduces the electron deficiency of the carbonyl carbon atom, particularly if electron-releasing substituents are present in the nucleus. With simple nucleophiles HX (X = OR, NHR, SR, CN, *etc.*), addition occurs under general acid or general base catalysis, leading to ArCH(OH)X. The addition is usually reversible if X is a stable anion or nucleophile but irreversible if X is unstable, *e.g.* H^-, R^- (from Grignard reagent).[111]

Hydration is thus readily reversible[112] and, in ^{18}O-enriched water, exchange takes place.[113] This provides an accurate method for estimating relative rates of hydration and, using this technique, the following times for equilibration (0.001N HCl, tetrahydrofuran) have been measured:[113] acetaldehyde (immediate), benzaldehyde (20 min), 2-naphthaldehyde (25 min), 1-naphthaldehyde (35 min), 9-anthraldehyde (45 min), and 9-phenanthraldehyde (55 min). The figures reflect the ability of the nucleus to delocalize the partial positive charge on the carbonyl carbon atom after protonation on oxygen ($ArCH{=}\overset{+}{O}H \leftrightarrow Ar\overset{+}{C}H{-}OH$), the polycyclic aromatics dispersing the charge more effectively and in consequence being less reactive.

Hemiacetal formation is unfavourable with aromatic aldehydes except when strongly electron-attracting groups are present, although acetals are formed readily.[114] Aromatic cyanohydrins can be easily prepared but they are much less stable than their aliphatic counterparts.[115] Bisulphite addition to aromatic aldehydes is also very much slower than with aliphatic aldehydes.[116]

The reaction of benzaldehyde with ammonia proceeds in a different manner from that with aliphatic aldehydes giving, initially, the imine (**27**; R = H) which reacts immediately with a second molecule of aldehyde to yield the product (**28**) (Scheme 21). The condensations with hydroxylamine, semicarbazide, and aniline, however, occur in the normal manner in two stages (Scheme 21), the rate-determining step at pH 7 being the dehydration stage.[117] At low pH, however, nucleophilic attack on the carbonyl is rate limiting. The reason for this change is that the dehydration stage is acid catalysed so that at low pH it becomes so fast that the formation of the intermediate [ArCH(OH)NHR] can no longer keep up with the rate of dehydration; the rate of nucleophilic attack then becomes the limiting factor. Thus the effect of substituents on these two stage reactions becomes complex, depending on the pH, electron-releasing or -attracting ability of the substituent, and the nucleophilicity of the amine (oxime or hydrazine). The rate of semicarbazone ($ArC{=}NNHCONH_2$) formation at neutral pH is relatively independent of aromatic substituents. At pH 3.9, however, there is a break in the structure–reactivity correlation since the attack step, having a large dependence on structure, is rate-determining for aldehydes with electron-donating substituents, whereas the dehydration stage is rate limiting for aldehydes with electron-withdrawing substituents, which undergo nucleophilic attack relatively rapidly. At pH 1.75 a linear plot of rate *versus* Hammett σ values is obtained ($\rho = 0.91$), the rate increasing with increasing electron-attracting substituents.[117]

$$ArCHO + NH_2R \rightleftharpoons \underset{\underset{OH}{|}}{ArCHNHR} \rightleftharpoons \underset{\textbf{(27)}}{ArCH{=}NR} + H_2O$$

R = H only:

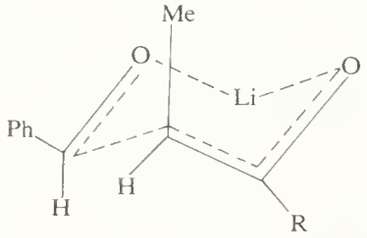
$$2ArCH{=}NH + ArCHO \rightleftharpoons \underset{\textbf{(28)}}{(ArCH{=}N)_2CHAr} + H_2O$$

SCHEME 21

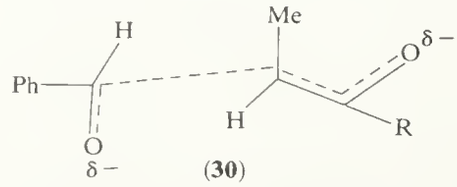
5.3.4.1 Aldol condensation and related reactions[118]

The condensation reactions of aromatic aldehydes are in many aspects similar to those of aliphatic aldehydes and ketones (Sections 5.1.5.2 and 5.2.7.1) and only factors which, in the author's opinion, are significantly different from aliphatic carbonyl chemistry will be mentioned. This has inevitably meant that important reactions such as the Reformatsky, and condensations with sulphur and phosphorus ylides, have not been dealt with and it should be assumed that in most cases the chemistry is similar to that of aliphatic aldehydes. Thus only certain aspects of the aldol condensation, Claisen–Schmidt, Knoevenagel, and Perkin reactions have been included.

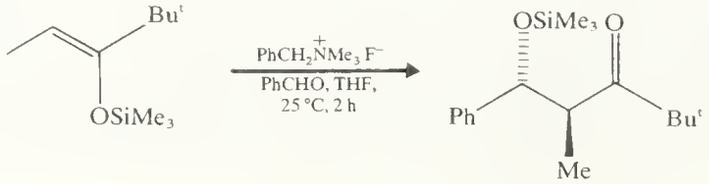
The aldol condensation,[118] *i.e.* the addition of an enol or enolate anion to the carbonyl group of an aldehyde or ketone, has been discussed in detail for aliphatic aldehydes in Section 5.1.5.2. Only factors peculiar to aromatic aldehydes will therefore be mentioned in this section. With aliphatic aldehydes the aldol condensation product can usually be isolated, whereas with aromatic aldehydes, dehydration to the α,β-unsaturated carbonyl compound normally takes place under conditions employing excess of base or acid catalysts. Recently, however, several groups have devised methods for the generation of enols and enolate anions in the absence of excess of base.[119–123] Condensation with aromatic aldehydes then proceeds to give the aldol product in good yield, whereas, previously, side reactions such as self condensation (of the enol) or polyaldol condensations gave rise to complex product mixtures, especially with aliphatic substrates. Using preformed enolate and low temperatures, aldol condensations exhibiting high stereoselectivity were observed when bulky substituents were present (Scheme 22); with small groups, however, the selectivity diminished or disappeared altogether.[122] The high selectivity can be explained by invoking the transition state (**29**) in which the two oxygen atoms of the carbonyl components are chelated by the metal cation. In support of this proposal is the observation that when the cation had no chelating ability, *e.g.* $R_4\overset{+}{N}$, the products had the opposite stereochemistry (equation 29); in this case the transition state (**30**) which minimizes electrostatic interactions seems likely to be involved.[122]



(**29**)

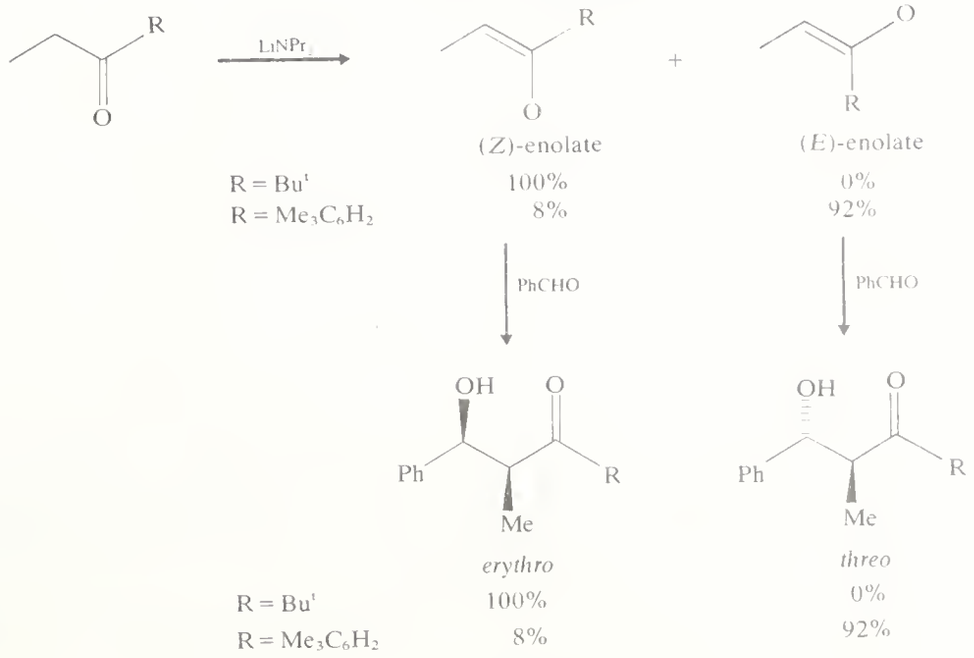


(**30**)



(52%) (100% *threo*) (29)

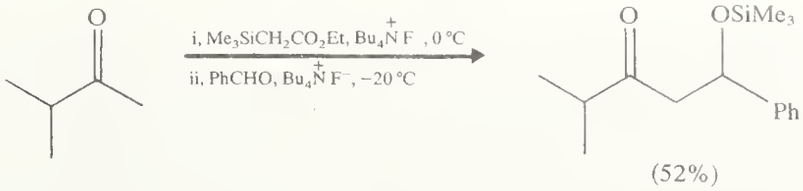
These fluoride ion catalysed reactions of silyl ethers show great promise for improving the synthetic utility of the aldol condensation.[121] In the past, the synthetic promise of a fast method of carbon–carbon bond formation has been limited when more than one mode of condensation existed and inseparable mixtures of products arose. The aldol intermediates are less stable than starting materials, so that methods such as dehydration of the aldol to an α,β-unsaturated carbonyl were required to displace the unfavourable equilibria. The fluoride ion catalysed reactions of silyl ethers generate 'naked' enols, not bound to any metal, and therefore very reactive. The aldol products are presumably stabilized by immediate formation of the silyl ether. When the enol is generated in the



SCHEME 22

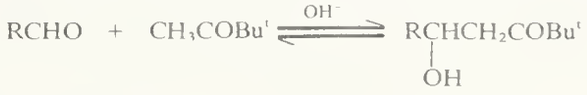
presence of metal ions the lower reactivity of the metal enolate diminishes the selectivity, but the metal ion chelates with the aldol product, displacing the equilibrium favourably towards product formation.

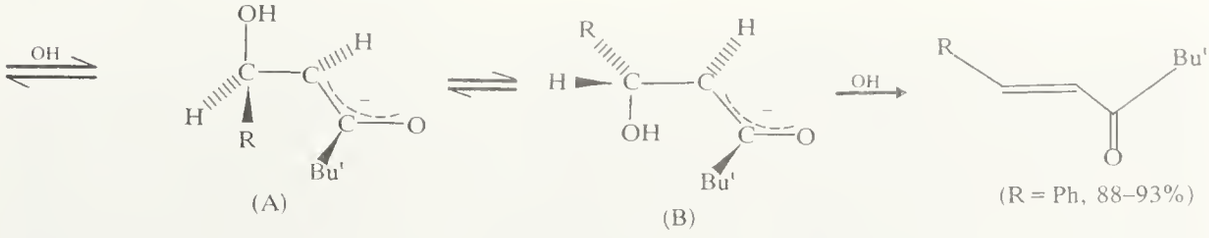
The silyl enol method also displays high chemoselectivity, the reaction taking place only with aldehydes. A one-pot procedure recently developed enables the enol silyl ether of a ketone to be generated and immediately reacted with an aldehyde (equation 30).[121] A similar reaction takes place using vinyloxyboranes.[123]



(30)

In the presence of strong acids or bases the aldol condensation products often dehydrate to give α,β-unsaturated carbonyl compounds.[124] The base-catalysed dehydration proceeds *via* an enolate anion (Scheme 23), but when R is a primary or secondary

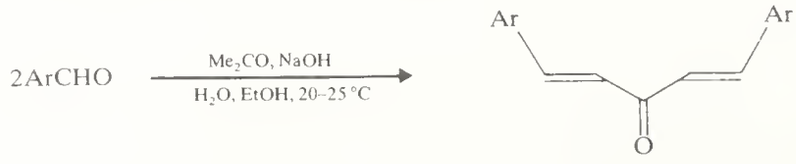




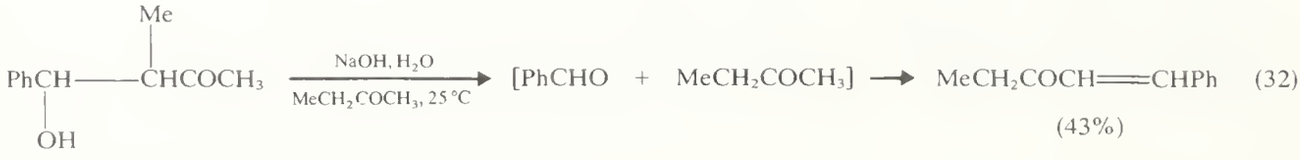
SCHEME 23

alkyl group, further base-catalysed aldol condensations may take place. The dehydration forces the reversible aldol condensation to completion and is especially useful for the synthesis of aromatic α,β-unsaturated carbonyl compounds; this is known as the Claisen–Schmidt reaction.[118] It is favoured by the presence of electron-withdrawing groups in the aromatic ring of the aldehyde. The products, α,β-unsaturated aldehydes or ketones, usually have the carbonyl group *trans* to the larger substituent on the β carbon atom. The stereoselectivity depends on the preferential dehydration of enolate in conformation B (Scheme 23) in which steric interaction between the enolate anion and the β-substituent is minimized.[124]

The condensation of 2 moles of aromatic aldehydes with acetone and cyclic ketones gives bis adducts (equation 31),[125] but this is very rarely the case with other acyclic ketones. The reaction with methyl alkyl ketones under basic conditions usually gives rise to the α,β-unsaturated ketone derived by condensation at the methyl group. Although formation of the aldol product may occur at the more highly substituted alkyl group, the reverse reaction usually predominates over the dehydration stage, allowing competition from the alternative aldol process to take place (equation 32).[126]

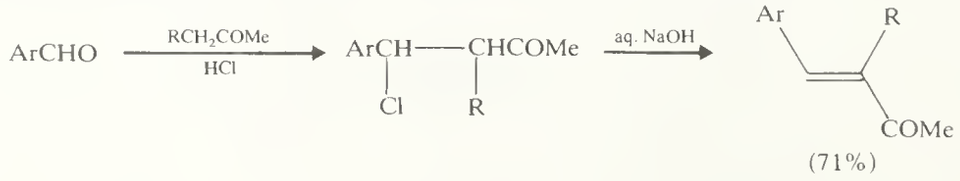


(90–94%) (31)



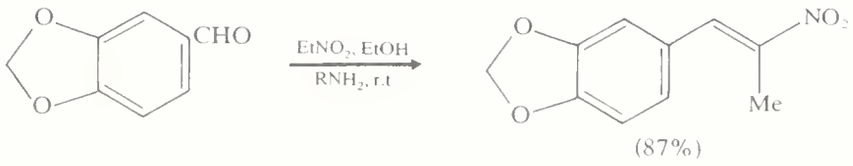
(43%) (32)

Condensation at the more hindered carbon atom, however, can be effected under acidic conditions since the more highly substituted enol is more stable. Dehydration of the aldol to the α,β-unsaturated carbonyl compound may occur in the presence of excess acid, but a useful alternative is to convert the aldol to a β-chloroketone using dry HCl gas. This pushes the equilibrium in favour of the product in the same manner as dehydration; the β-chloroketone can then be dehydrochlorinated in a separate stage (equation 33).[127] With ketones of the type $MeCOCHR^1R^2$, where dehydration cannot occur, condensation at the methyl group takes place under both acidic and basic conditions.[118]

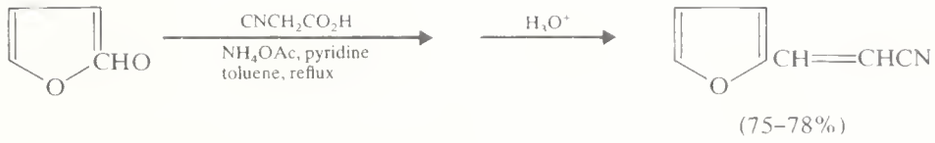


(71%) (33)

The condensation of aldehydes — and ketones — with active methylene compounds using catalytic amounts of basic, *e.g.* amines, and acid catalysts, known as the Knoevenagel condensation,[118,128] gives excellent results and proceeds well with aromatic aldehydes. Condensations with very active methylene groups (CH_2XY, where X, Y = CN, CO_2R, COMe) occur readily with aliphatic (see Section 5.1.5.2) and aromatic aldehydes, whereas the less reactive ketones and nitro compounds react only with aromatic aldehydes (equation 34).[129] The mechanism has been discussed earlier. When the reactions are run in pyridine solution, condensation of aldehydes and ketones with malonic acid derivatives is accompanied by decarboxylation of the intermediate; this procedure, known as the Doebner modification, gives the same product as the Perkin condensation but yields are usually better for the former (equation 35).[130]

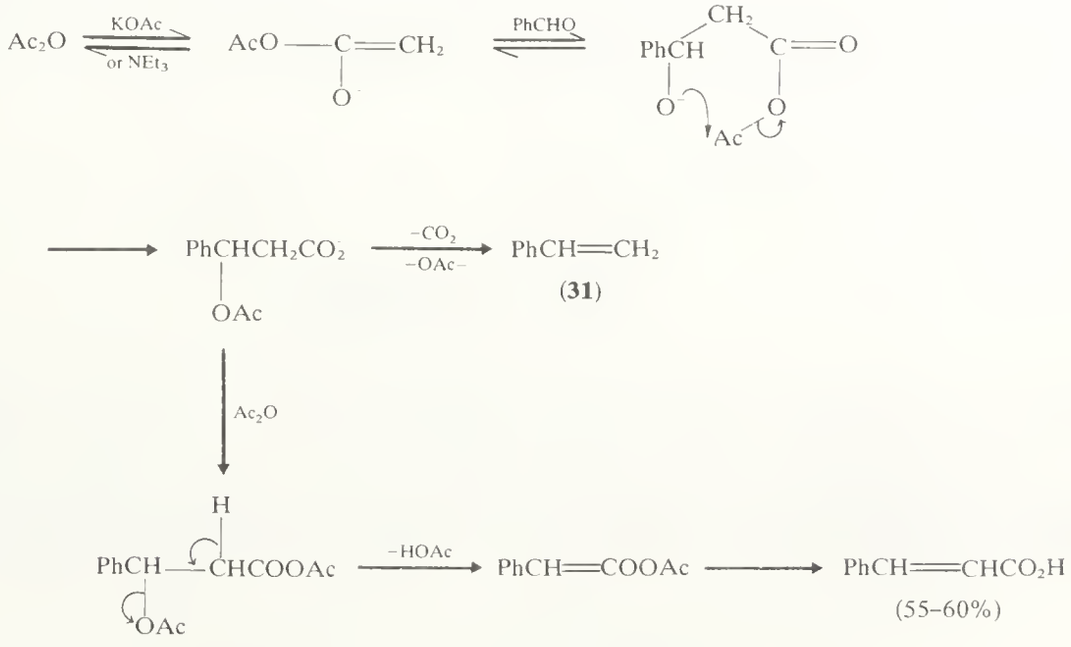


(34)



(35)

In the Perkin reaction,[131] which is applicable only to aromatic aldehydes, a mixture of the aldehyde, an anhydride, and a weak base are heated at temperatures of 150–200 °C. The mechanism of the reaction is shown in Scheme 24; the by-product, the decarboxylative elimination product (**31**), may become the major product when a suitable activating substituent is present.[131]

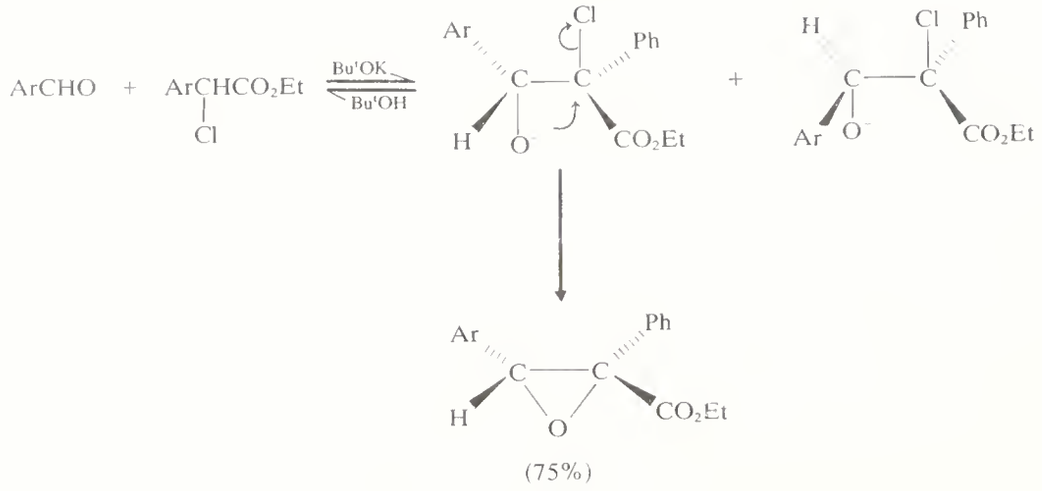


SCHEME 24

5.3.4.2 Darzens condensation[132]

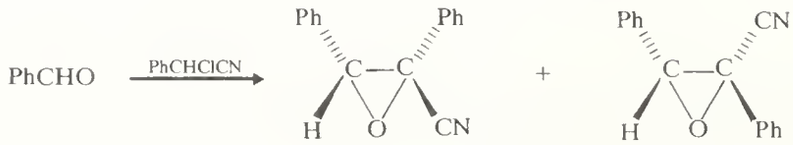
The reaction of an α-haloester or α-haloketone with a ketone or aromatic aldehyde in the presence of strong base is known as the Darzens condensation.[132] The product, an α,β-epoxy carbonyl compound, is formed by ring closure of the intermediate aldol condensation product (Scheme 25).[133] The stereochemistry of the product depends on the relative rates of the aldol condensation and ring closure steps. If the latter is the slower, equilibration of the aldol intermediates takes place, giving only the product with the carbonyl function *trans* to the larger β substituent (Scheme 25).[134] Factors which slow down the rate of aldol condensation (bulky substituents, non-polar solvents)[135,136] make this the rate-limiting step, and the product ratio then depends solely on the rate of formation of the aldol intermediates.

The scope of the Darzens condensation has been greatly widened over the past few



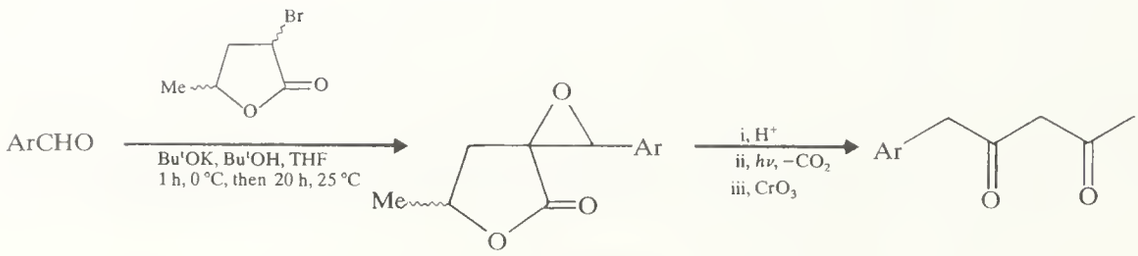
SCHEME 25

years and recent examples include the condensation of aromatic aldehydes with α-halonitriles[136] (equation 36), *p*-nitrobenzyl halides,[137] α-halothioesters,[138] and α-halolactones.[139] The latter reaction has been used in the synthesis of polyketides, for biosynthetic studies (equation 37). The vinylogous Darzens reaction also proceeds in good yield, giving a mixture of isomeric γ,δ-epoxy-α,β-unsaturated esters.[140]



(36)

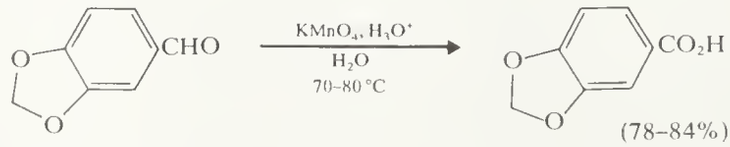
Bu'ONa, HMPA, 95%, ratio 2:98
Bu'ONa, benzene 55%, ratio 85:15



(37)

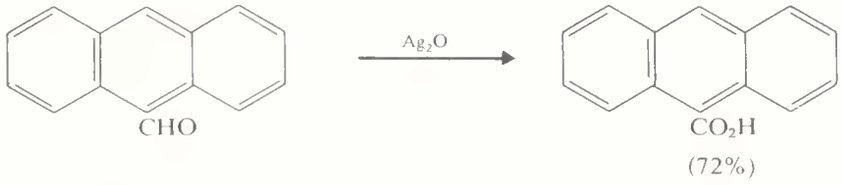
5.3.5 OXIDATION OF AROMATIC ALDEHYDES

Aromatic aldehydes oxidize readily in air at room temperature to carboxylic acids, the process (autoxidation) being promoted by light (see Section 5.3.10), metal ion catalysts, or peroxides.[141] Synthetically, aromatic aldehydes can be converted to carboxylic acids using permanganate[142] (equation 38)[143] or chromium(VI) oxide.[144] Silver oxide, however, is the preferred reagent for the oxidation of polycyclic aromatic aldehydes (equation 39)[145] since other reagents often cleave the aromatic ring.



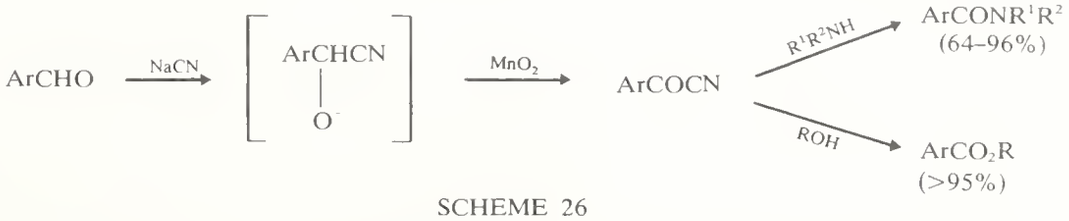
(38)

The direct oxidation of aldehydes to esters (or amides) proceeds using manganese dioxide in the presence of sodium cyanide and an alcohol (or amine).[146] Excellent results



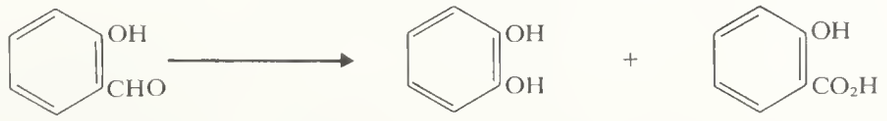
(39)

are obtained with aromatic aldehydes (Scheme 26). The reactions take place *via* oxidation of the aldehyde cyanohydrin to an aroyl cyanide, which reacts with alcohols or amines. Caro acid (peroxymonosulphuric acid, H_2SO_5) and nitrobenzene have also been used to oxidize aldehydes directly to esters[147] and nickel peroxide to oxidize aldehydes to amides and/or nitriles.[148]



SCHEME 26

The oxidation of aromatic aldehydes with peroxides or peroxy acids can lead to either oxidation to the carboxylic acid or rearrangement (Baeyer–Villager oxidation) to the phenolic ester, which is often hydrolysed to the phenol. Thus oxidation of salicylaldehyde with hydrogen peroxide under neutral conditions gave salicyclic acid, whereas in either acidic or basic media, catechol or its monoester were formed (equation 40).[149]



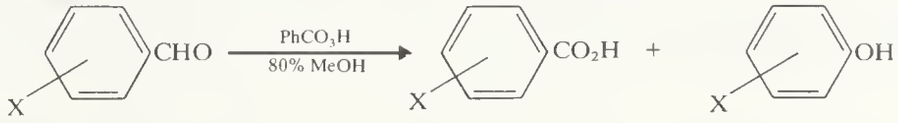
$NaOH, H_2O_2$	100%	—
$AcOH, H_2O_2$	100%	—
Neutral H_2O_2	—	70%

(40)

Both processes involve (see Scheme 27) the intermediate perester (**32**), which gives products *via* aryl or hydrogen migration, but the relative rates of these two pathways depend upon both pH and the substitutents on the aryl group (Table 9).[150] The Baeyer–Villager pathway is only observed when electron-releasing substituents are present in the *ortho* or *para* positions of the aromatic ring, and is favoured in acidic media. It is an excellent method for the specific synthesis of poly(alkoxy)phenols,[151] useful in the

TABLE 9

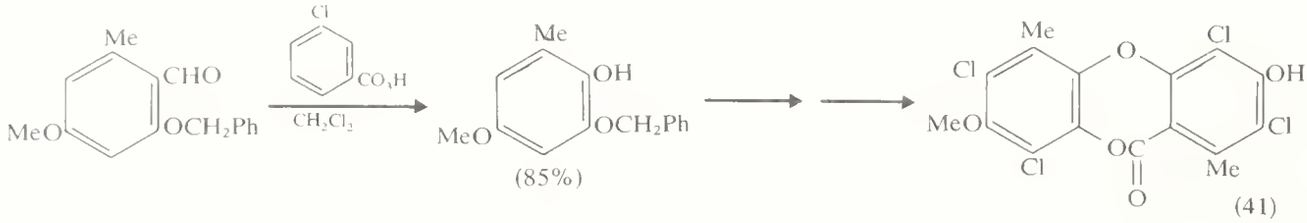
Oxidation of Aromatic Aldehydes using Peroxy Acids[a]



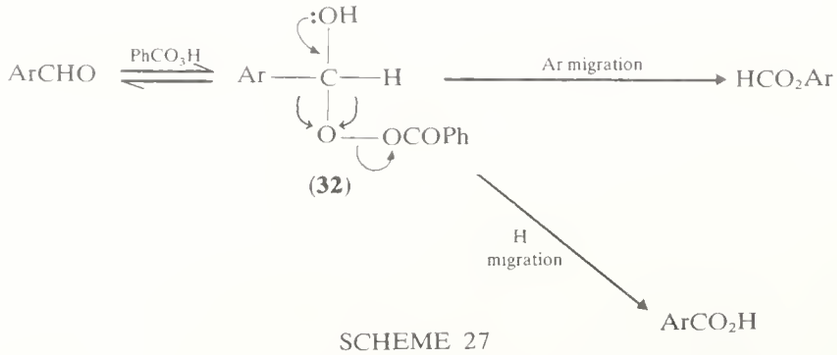
X	*Alkaline* Yield of CO_2H(%)	OH(%)	*Neutral* Yield of CO_2H(%)	OH(%)	*Acidic* Yield of CO_2H(%)	OH(%)
p-OH	0	94	0	92	0	91
o-OH	0	99	0	95	0	98
m-OH	65	2.1	—	—	—	—
p-OMe	69	4.7	17	40	19	73
o-OMe	39	37	1	68	—	—
H	100	0	90	0	90	0
p-Cl	93	0	97	0	—	—
p-NO_2	100	0	98	0	—	—
m-NO_2	98	0	—	—	—	—

[a] Ref. 150.

synthesis of natural products such as the lichen metabolites, depsidones (equation 41).[152] The reactions of aromatic aldehydes with alkaline hydrogen peroxide (Dakin reaction) give similar products.[153]



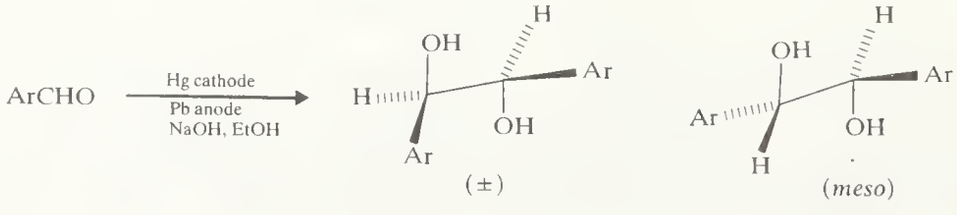
(41)



SCHEME 27

5.3.6 REDUCTION OF AROMATIC ALDEHYDES

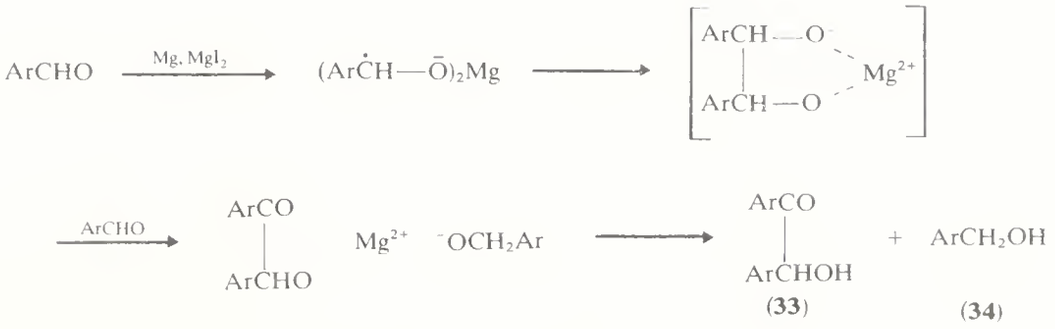
A vast number of methods are available for the reduction of aromatic aldehydes to aralkyl alcohols. Most of these methods (*e.g.* catalytic hydrogenation, Meerwein–Ponndorf–Verley reduction, sodium–ethanol reduction) have been discussed in relation to aliphatic aldehydes (Section 5.1.4.2) and no further comment is required here. In dissolving metal reductions the intermediate radical anion has appreciable lifetime in the absence of a proton donor, especially if stabilizing substituents such as aromatic groups are present. Reduction of carbonyl compounds with magnesium, zinc, and aluminium or their amalgams usually leads to pinacols, formed by dimerization of the radical anion, as major products.[154] With aromatic aldehydes, however, the products are the benzoin (**33**) and an aralkyl alcohol (**34**), formed by the exchange reaction shown in Scheme 28. High yields of pinacols can be obtained by reduction using acidic chromium(II) ions,[155] or *via* photochemical[156] or electrolytic[157] reduction in alkaline solution. In the latter method, an approximately 1 : 1 mixture of (±)- and *meso*-isomers is normally obtained, although the proportion of racemate may increase to 70% at higher pH. With phenolic aldehydes in basic solution, however, very high yields of *meso*-pinacols have been obtained, presumably owing to unfavourable electrostatic repulsions in the transition state for racemic pinacol formation (equation 42).[158]



(42)

Ar = 4-MeC_6H_4 or 4-$MeOC_6H_4$ ratio 1 : 1
Ar = 4-HOC_6H_4 or 2-MeO, 3-HOC_6H_3 ratio ≤1 : 10

Using the low-valent titanium species Mg(Hg)/$TiCl_3$, Corey *et al.*[159] have found that aromatic aldehydes yield pinacols in high yield, although the diastereoisomeric ratio was not reported. More importantly, the reagent gave good yields of mixed pinacols in both inter- and intra-molecular reactions where the classical reducing agents were ineffective.[160] In a similar manner to aliphatic aldehydes (Section 5.1.4.2), aromatic aldehydes

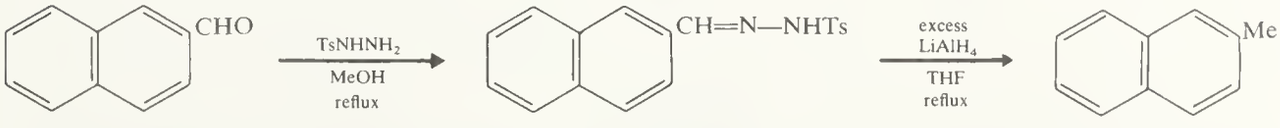


SCHEME 28

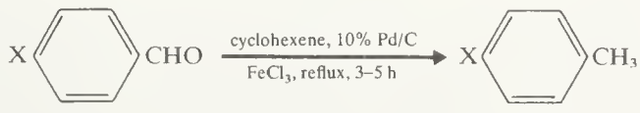
are also reduced to aralkyl alcohols by most of the common complex hydride reducing agents.[161,162] The factors which determine the choice of reagent are the solvent required to dissolve the substrate and reagent and whether reduction of additional functional groups must be avoided. Reduction of aldehydes is faster than with most other functionalities, so that selective reduction can often be accomplished by correct choice of reagents. Reduction of aldehydes in the presence of esters, acids, amides, nitriles, non-conjugated olefins, and nitro groups can be effected using $NaBH_4$ or $NaBH_3CN$ (acid solution), in the presence of acid halides by $NaBH_2S_3$, and in the presence of alkyl or aryl halides by $NaBH_4$; many other reagents have similar selectivities[162] (see Section 5.1.4.2).

The reduction of benzaldehyde with sodium tetrahydridoborate proceeds more slowly than with aliphatic aldehydes but is approximately 400 times faster than with acetophenone. It is possible, therefore, to reduce aromatic aldehydes in the presence of aromatic ketones using $NaBH_4$[163] or a variety of other reagents {$Li(Bu^tO)_3AlH$,[163] Me_2CHOH/Al_2O_3,[164] $NaBH_4/RSH$,[165] $NaBH(OAc)_3$,[166] or lithium dibutyl-9-borabicyclo[3,3,1]nonane[167]}. Many of these reagents discriminate between aldehydes and ketones partly on steric grounds and partly owing to electronic factors. Reduction with nucleophilic hydride reagents (*e.g.* BH_4^-) is generally faster when the carbonyl carbon atom is more electron deficient, although many other factors (solvent, cation, complexation) may reverse this trend.

The reduction of aromatic aldehydes to hydrocarbons can be effected either by catalytic hydrogenation over platinum,[168] Wolff–Kishner reduction and the related arylsulphonylhydrazine method[169] (equation 43), or Clemmenson reduction[170] in a manner analogous to that employed with ketones and aliphatic aldehydes (see Section 5.1.4.2). An interesting method which has so far been successful only with aromatic aldehydes and ketones is catalytic transfer hydrogenation.[171] The method is experimentally simpler and safer than catalytic hydrogentaion; a mixture of the carbonyl compound, catalyst, and a large excess of donor (*e.g.* cyclohexene) is refluxed for 3–5 hours (equation 44). The major side-reaction is decarbonylation or, with *o*-carboxybenzaldehyde, lactone formation; this demonstrates that the reduction proceeds *via* benzylic alcohol intermediates. Reduction of benzaldehyde in the presence of acetic anhydride gave benzyl acetate (72%).[171]



(43)

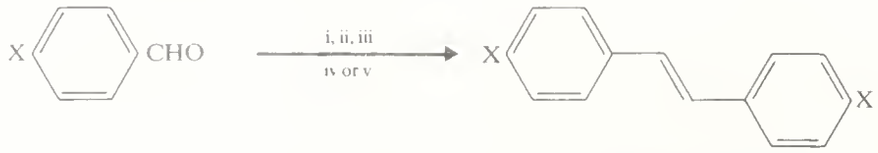


(44)

X = H, 80%
X = OMe, 80%
X = NMe_2, 75%

5.3.6.1 Reductive coupling of aromatic aldehydes to olefins and oxirans

One of the most useful classes of inorganic reducing agents to be introduced recently for organic synthesis is low-valent titanium species generated by treatment of the titanium(III) or titanium(IV) chloride with a reducing agent.[172] The reagent $TiCl_3/LiAlH_4$[173] has been shown to reduce both aliphatic and aromatic aldehydes (and ketones) directly to constitutionally symmetrical olefins in high yield, whereas less active reagents, formed from $TiCl_4/Zn$[174] or $TiCl_4/Mg$[175] will only reduce aromatic aldehydes (and ketones) at elevated temperatures (equation 45). Similarly, the use of low-valent tungsten complexes allows only aromatic carbonyl compounds to be reductively coupled (equation 45).[176] In contrast, the reagents $TiCl_4/Mg$ and $TiCl_4/Zn$ have been shown to reduce aldehydes to pinacols at 0 °C.[159]

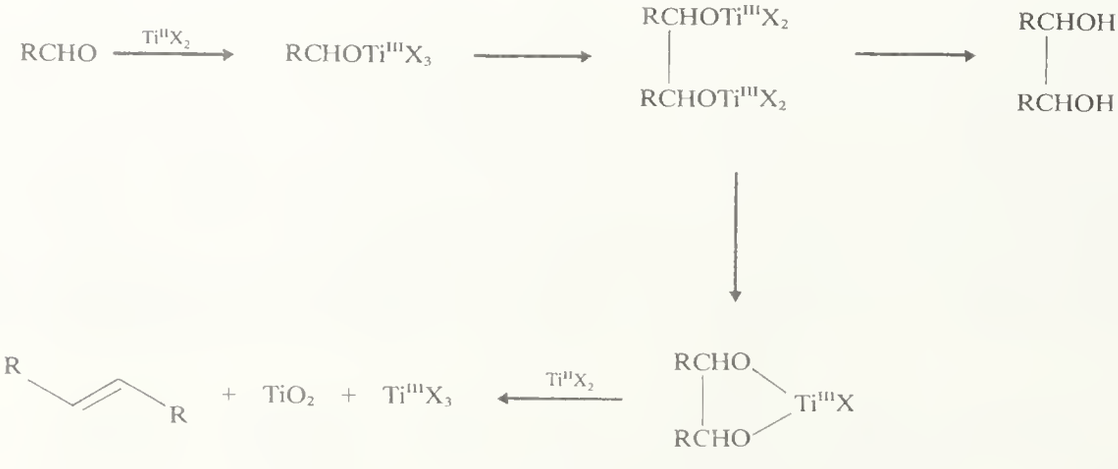


(45)

(>99% *trans*)

i, $TiCl_3/LiAlH_4$, THF, r.t., (85%); ii, $TiCl_4/Zn$, dioxan, reflux, 4 h, (98%); iii, $WCl_6/2BuLi$, THF, r.t., 6 h, (47–76%); iv, $NaPO(OEt)_2$, benzene, 80–140 °C, 5–14 h, (60–85%); v, $NaPOPh_2$, benzene, 200 °C, 5 h, (56–83%).

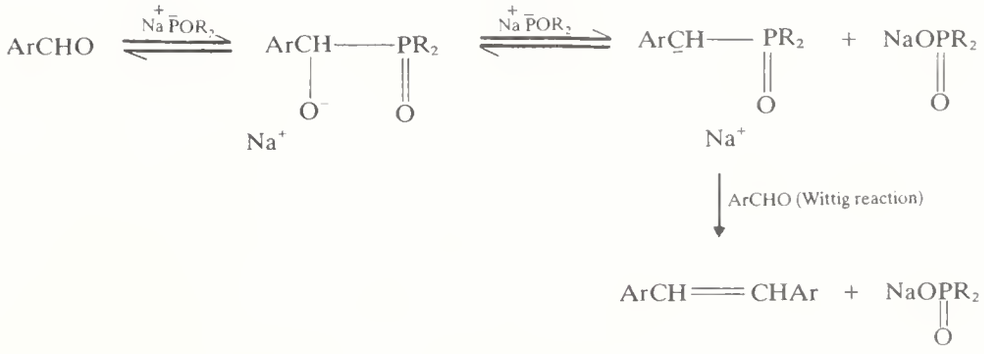
These interesting transformations can be readily accounted for if low-valent metal ions such as Ti(II) are involved. Such a strong reducing agent ($Ti^{2+} \rightarrow Ti^{3+} + e^-$; $E° \approx 0.37$ V) could effect reduction to the pinacol *via* the radical anion which, after complexing with Ti(II) and loss of TiO_2, gives the olefin (Scheme 29). In support of this mechanism it has been shown that pinacols are reduced by $TiCl_3/LiAlH_4$ to olefins in high yields. The reductive coupling can formally be regarded as the reverse of the well-known oxidation of olefins to carbonyl compounds using metal oxides.



SCHEME 29

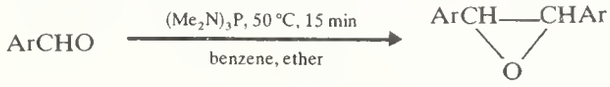
Similar transformations, however, can be effected using phosphorus reagents, but entirely different mechanisms are involved. Thus treatment of aromatic aldehydes with the sodium salt of an alkyldiarylphosphine oxide (or dialkylphosphonate) gives constitutionally symmetrical olefins in good yield (equation 45);[177,178] aliphatic aldehydes do not undergo this transformation, presumably owing to competing aldol condensations. A possible mechanism of olefin formation is depicted in Scheme 30.

In contrast, reaction of aromatic aldehydes with tris(dimethylamino)phosphine affords a mixture of *cis*- and *trans*-oxirans (usually in a 1:1 ratio) in good yields (equation 46).



SCHEME 30

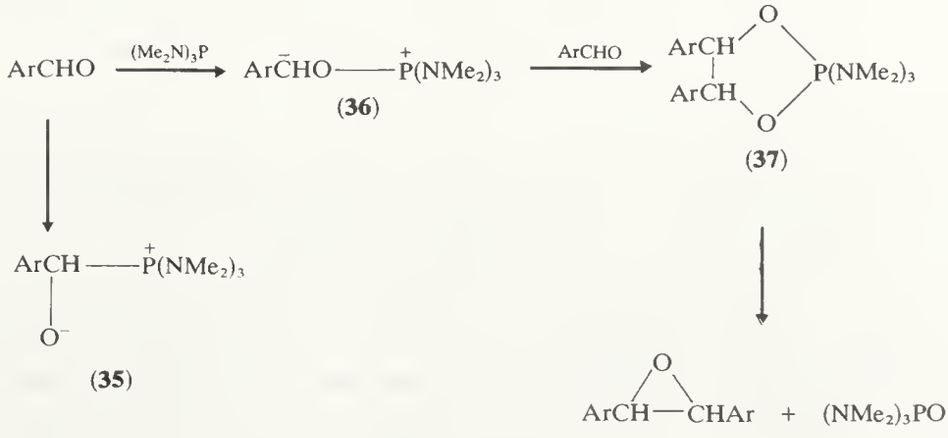
Again nucleophilic attack on the aldehyde gives an isolable 1:1 adduct (**35**); when the carbonyl group is a relatively poor acceptor of the nucleophile (aliphatic aldehydes, benzaldehyde, electron-rich aromatics, and some heteroaromatics) the reaction stops at this stage. In the presence of excess of aromatic aldehyde (containing electron-



(46)

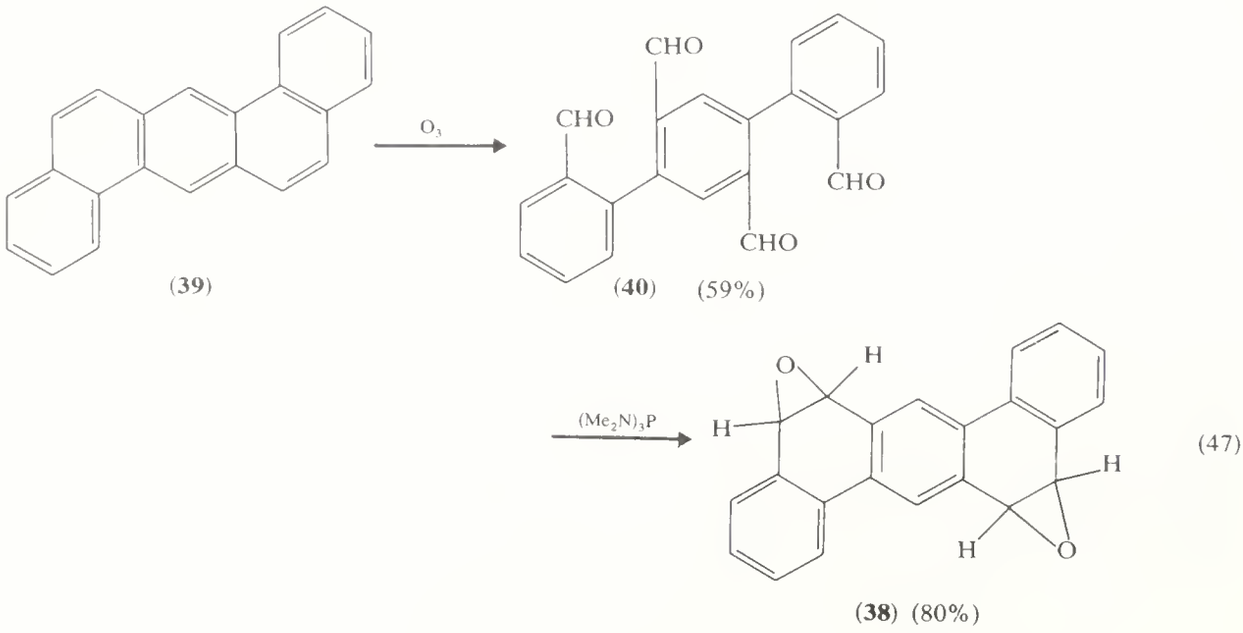
Ar=2-BrC_6H_4, 90–95%
Ar = 1-naphthyl, 83–87%
Ar = 4-CNC_6H_4, 90–95%
Ar = 2-pyridyl, 85–90%

withdrawing substituents, especially in the *ortho* position), further reaction takes place leading to the oxirans, possibly *via* the mechanism shown in Scheme 31. It seems likely that the intermediate (**35**) is not involved in the reaction and that the mechanism proceeds *via* initial P—O bond formation to give the betaine (**36**) which would be stabilized by electron-withdrawing substituents. This explains the high yields with *o*-substituted aldehydes since in these cases attack at the carbonyl carbon atom would be hindered. Cycloaddition of the betaine (**36**) to the aldehyde could then give intermediate (**37**) which, after phosphine oxide elimination, would lead to oxiran (Scheme 31).[179]



SCHEME 31

Although the reaction has mostly been applied to the synthesis of constitutionally symmetrical oxirans, the intramolecular reaction of aromatic dialdehydes with tris(dimethylamino)phosphine is applicable to constitutionally unsymmetrical precursors. Thus the dioxiran of dibenz[*a*,*h*]anthracene (**38**) has been synthesized by ozonolysis of (**39**) to tetra-aldehyde (**40**) followed by ring closure with tris(dimethylamino)phosphine (equation 47); oxirans of aromatic hydrocarbons are important in studies of the metabolism and mechanism of action of carcinogenic hydrocarbons such as (**39**).[180]



(39) (40) (59%) (47)

(38) (80%)

5.3.7 CANNIZZARO REACTION

The Cannizzaro reaction,[181] discovered over 100 years ago, is a base-induced disproportionation of two moles of a non-enolizable aldehyde into the corresponding acid and alcohol.[182] For example, benzaldehyde on treatment with 50% aqueous or alcoholic potassium hydroxide in the absence of solvent at room temperature,[182] or with solid potassium hydroxide using methylene chloride as solvent,[183] yields benzoic acid (85–90%) and benzyl alcohol (75–90%) (equation 48). The 'crossed' Cannizzaro reaction involves a mixture of two aldehydes, one of which is often formaldehyde; reduction of an aromatic aldehyde to an alcohol can be carried out in high yields by this method (equation 49).

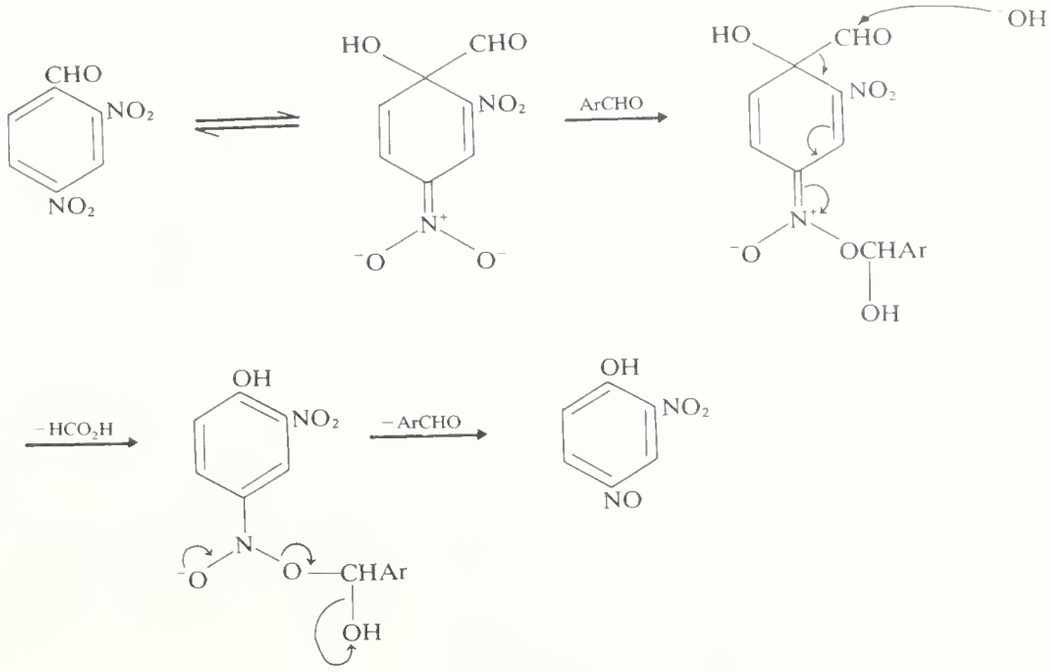
$$2ArCHO \xrightarrow{NaOH} ArCO_2Na + ArCH_2OH \quad (48)$$

$$CH_2O + ArCHO \xrightarrow{NaOH} HCO_2Na + ArCH_2OH \quad (49)$$

The Cannizzaro reaction is applicable to non-enolizable aldehydes, especially aromatic and heteroaromatic aldehydes. Exceptions are *ortho*-disubstituted benzaldehydes, which undergo decarboxylation,[184] *o*- and *p*-hydroxybenzaldehydes, which only react in the presence of metallic silver,[185] and 2,4-dinitrobenzaldehyde, which gives 2-nitro-4-nitrosophenol *via* the mechanism shown in Scheme 32.[186] Aldehydes with α-hydrogen atoms preferentially undergo the aldol condensation; cyclopropanecarboxaldehyde, however, is an exception giving good yields (>80%) of the corresponding alcohol and acid.[187]

The mechanism of the Cannizzaro reaction has been the subject of much discussion. The reaction is generally second order in aldehyde and first order in base;[182] electron-withdrawing substituents increase the rate of reaction whereas electron-donating substituents decrease it.[182] An intramolecular hydride transfer has been shown to be involved; when the reaction was performed in deuterium oxide, no deuterium was incorporated into the products.[188] Furthermore, when deuteriobenzaldehyde was used as the substrate, the product was dideuteriobenzyl alcohol ($C_6H_5CD_2OH$).[188] The hydride transfer appears to be the rate-determining step since a deuterium isotope effect (k_H/k_D) of 1.8 was determined in the above reaction.[189]

In a small number of cases, esters have been isolated from reactions using aqueous base, particularly when high temperatures and excess of base are avoided.[190] The reaction

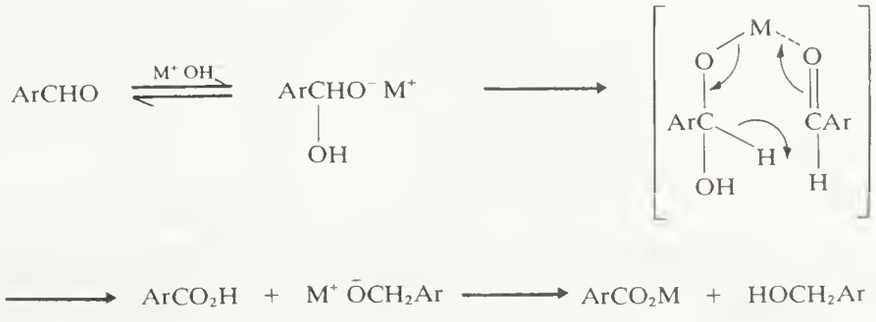


SCHEME 32

of benzaldehyde with aluminium ethoxide or sodium in THF, leading to benzyl benzoate ($PhCH_2OCOPh$) is known as the Tischenko reaction (equation 50).[191] More recent work,

$$PhCHO \xrightarrow[\text{benzene, 20 °C}]{Al(OBu^t)_3} PhCH_2OCOPh \quad (75\text{–}90\%) \qquad (50)$$

however, shows that an ester intermediate in the Cannizzaro reaction is unlikely. The rate of reaction varies with the metal hydroxide used[192] and, in one case, an intermediate complex, containing two moles of aldehyde and one of metal hydroxide, has been isolated.[193] The mechanism can thus be envisaged as proceeding by a hydride transfer through a cyclic six-membered transition state (Scheme 33).



SCHEME 33

When the alkali metal is complexed using 18-crown-6, so that it can no longer exert a coordinating role, the yield of alcohol drops drastically.[183] Moreover, if the reaction is performed using the solid hydroxide–methylene chloride method, the reaction is inhibited by the presence of a phase-transfer catalyst, benzyl triethylammonium bromide.[183] The effective base in the organic solvent is the quaternary ammonium hydroxide which cannot coordinate with the aldehydes to enable hydride transfer to take place.

5.3.8 BENZOIN CONDENSATION AND RELATED REACTIONS

The benzoin condensation[194] is the condensation of two moles of an aromatic or heterocyclic aldehyde in the presence of cyanide ion leading to an aromatic α-hydroxyketone, often called a benzoin[194] (see Table 10). By the use of one mole of two different aldehydes, mixed benzoins can be obtained, often in very good yields (see Table 11). The reaction is reversible and treatment of a benzoin with potassium cyanide in the presence of a second aldehyde also leads to a mixed benzoin (equation 51).

TABLE 10

'Symmetrical' Benzoins *via* the Benzoin Condensation

$$\text{RCHO} \xrightarrow[\text{EtOH}]{\text{KCN}} \text{RCH(OH)COR}$$

R	*Yield* (%)	*Ref.*
Phenyl	90	a
1-Naphthyl	12	b
9-Phenanthryl	93	c
4-Biphenylyl	90	d
3,5-Dimethylphenyl	80	e
2-Chlorophenyl	40	f
4-Methoxyphenyl	44	g
2,5-Dimethoxyphenyl	100	h
2-Quinolyl	90	i

[a] R. Adams and C. S. Marvel, *Org. Synth. Coll. Vol. 1*, 1941, 94. [b] M. Gomberg and F. J. van Natta, *J. Amer. Chem. Soc.*, 1929, **51,** 2238. [c] R. N. Jones, *J. Amer. Chem. Soc.*, 1945, **67,** 1956. [d] E. E. Baroni, K. A. Kovyrzina, and T. A. Tsvetkova, *Zhur. org. Khim.*, 1965, **1,** 506. [e] M. Weiler, *Ber.*, 1900, **33,** 334. [f] H. H. Hodgson and W. Rosenberg, *J. Chem. Soc.*, 1930, 14. [g] G. Sumrell, J. I. Stevens, and G. E. Goheen, *J. Org. Chem.*, 1957, **22,** 39. [h] J. L. Hartwell and S. R. L. Kornberg, *J. Amer. Chem. Soc.*, 1945, **67,** 1606. [i] C. A. Buehler and J. O. Harris, *J. Amer. Chem. Soc.*, 1950, **72,** 5015.

TABLE 11

'Unsymmetrical' Benzoins *via* the Benzoin Condensation

$$\text{R}^1\text{CHO} + \text{R}^2\text{CHO} \xrightarrow[\text{EtOH}]{\text{KCN}} \text{R}^1\text{CH(OH)COR}^2$$

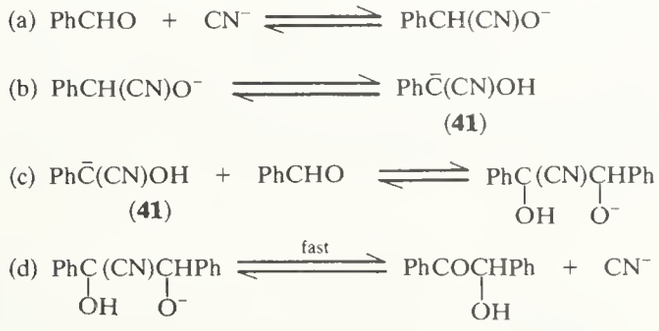
R^1	R^2	*Yield* (%)	*Ref.*
Phenyl	4-Dimethylaminophenyl	86	a
Phenyl	4-Methoxyphenyl	45	b
2-Chlorophenyl	4-Methoxyphenyl	60	c
2-Methoxyphenyl	4-Methoxyphenyl	77	d
3-Chlorophenyl	4-Dimethylaminophenyl	45	c
3-Pyridyl	4-Dimethylaminophenyl	92	e

[a] J. S. Buck and W. S. Ide, *J. Amer. Chem. Soc.*, 1931, **53,** 2350. [b] C. R. Kinney, *J. Amer. Chem. Soc.*, 1929, **51,** 1592. [c] J. S. Buck and W. S. Ide, *J. Amer. Chem. Soc.*, 1930, **52,** 4107. [d] M. Tiffaneau and J. Levy, *Bull. Soc. chim. France*, 1931, **49,** 725. [e] P. Bergmann and H. Paul, *Z. Chem.*, 1966, **6,** 339.

$$\text{ArCH(OH)COAr} + \text{Ar'CHO} \xrightarrow{\text{KCN}} \text{ArCH(OH)COAr'} \qquad (51)$$

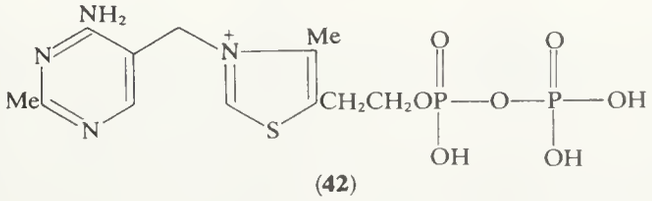
There has been much discussion surrounding the mechanism of the reaction and it is only recently[195] that the matter has been resolved. The mechanism originally proposed by Lapworth[196] was based on evidence that cyanohydrin formation was rapid relative to the condensation and that the reaction was first order in cyanide and second order in

aldehyde[194] (Scheme 34). The rate-determining step was regarded as stage (c). This mechanism satisfied the kinetics, and also explained why the catalyst is restricted to cyanide (or thiazolium ions)[197] since a successful catalyst must possess not only nucleophilic activity (stage a) but also catalyse proton transfer (stage b) and be able to stabilize an adjacent negative charge in an active aldehyde intermediate (**41**). In 1954, Wiberg[198] cast doubt on this mechanism after studying the reaction in deuteriated solvent and also using deuteriobenzaldehyde in non-deuteriated solvent. The Lapworth mechanism indicates that the intermediate carbanion should exchange with solvent faster than reacting with a second molecule of benzaldehyde, yet Wiberg found that the rates were approximately the same. More recent evidence[195] from an extremely thorough study of the mechanism shows that Lapworth's ideas were correct. Kuebrich *et al.*[195] examined the various stages of the Lapworth mechanism step by step and deduced the reaction parameters for each stage by a combination of spectroscopic and isotopic studies in pure methanol solution. The results showed that the active anion intermediate (**41**) is not a steady-state intermediate, but builds up in appreciable amounts. Furthermore, the stages (b) and (c) (Scheme 34) are not completely rate-determining. Wiberg's[198] deductions were based on data using partially deuteriated and mixed aqueous ethanolic solvents. In these circumstances, however, it is now known that linear extrapolation to 100% deuterium levels may not hold true, and this led to false conclusions being drawn.

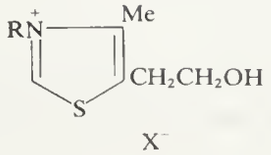


SCHEME 34

The benzoin condensation has been of interest to biochemists as a model for certain carbon–carbon bond-forming reactions in which the catalyst is the thiazolium moiety of thiamine pyrophosphate (**42**).[199] This coenzyme catalyses a number of important reactions, including decarboxylation of pyruvic acid to acetaldehyde and the conversion of pyruvic acid to acetoin. The common feature of these reactions is that they involve the formation of an acyl anion (RCO^-) or its stabilized equivalent. This analogy has led several workers to examine the use of thiazolium ion catalysts (**43**)–(**45**) on the benzoin

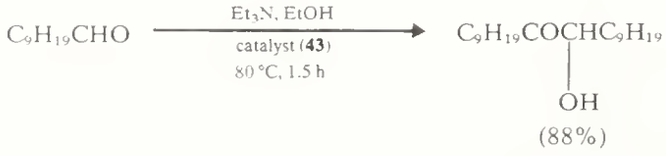


(**42**)



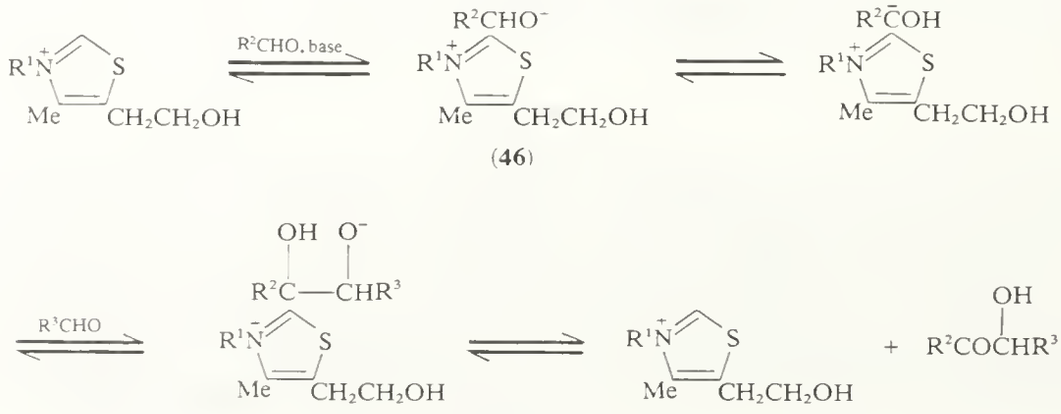
(**43**) R = CH_2Ph, X = Cl
(**44**) R = Et, X = Br
(**45**) R = Me, X = I

condensation (Scheme 35).[197] Like cyanide, the zwitterion, formed by reaction of thiazolium salts with base, is nucleophilic and reacts at the carbonyl group of aldehydes. The resultant intermediate can undergo base-catalysed proton transfer to give a carbanion which is stabilized by the thiazolium ring. In fact, the use of the thiazolium ion catalyst (**43**) increases the versatility of the reaction, allowing aliphatic aldehydes to be converted to α-hydroxyketones in high yield (equation 52).[200] The mechanism of action of these thiazolium catalysts is similar to that of cyanide. Occasionally the intermediate (**46**) can be isolated after protonation (Scheme 35).[199]



(52)

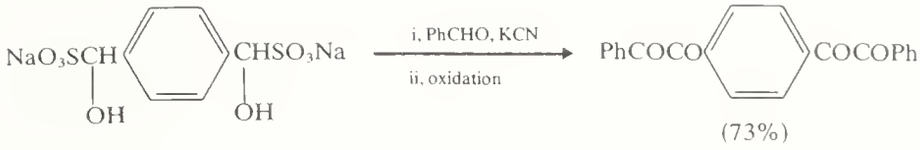
Until recently, the benzoin condensation has always been performed in aqueous alcohol as solvent with cyanide as catalyst by heating for periods up to 1–3 hours. The use of the thiazolium ion catalyst (**44**) enables the condensation of aromatic and heteroaromatic aldehydes to proceed at room temperature.[200] Alternatively, the reaction can be performed in water or benzene if a phase-transfer catalyst, such as *N*-laurylthiazolium bromide,[201–203] is used or if a crown ether is added to complex the potassium cyanide catalyst.[204] A further improvement has been to use a dipolar aprotic solvent, a mixture of DMF and DMSO giving the best results.[205] Aldehydes which normally give poor yields of benzoins in aqueous alcohol react in DMF–DMSO to give good yields of benzoins, especially if tetrabutylammonium cyanide is used as base.[201,202,205] Under these conditions the cyanide ion is free of solvation and becomes more nucleophilic and basic; the reactions are often complete in a few hours at room temperature.



SCHEME 35

Many substituted benzaldehydes usually containing electron-donating substituents fail to undergo the benzoin condensation, presumably because the active anion intermediate is not formed.[194] However, they will often undergo mixed condensations with other aldehydes and the reaction is of preparative value.[206] For example, 4-dimethylaminobenzaldehyde, unreactive in the simple benzoin condensation, reacts with benzaldehyde to give 4-dimethylaminobenzoin (86%, see Table 11). In theory, two 'symmetrical' and two 'unsymmetrical' benzoins could be formed; in practice, only one 'unsymmetrical' benzoin is isolated, since the two 'unsymmetrical' isomers normally equilibrate under the reaction conditions to the more stable product in which the carbonyl group is adjacent to the phenyl group with the more electron-donating substituent (equation 53).[194] The mixed benzoin condensation can also be performed by using the sodium bisulphite adduct of one of the aldehydes (equation 54).[207]

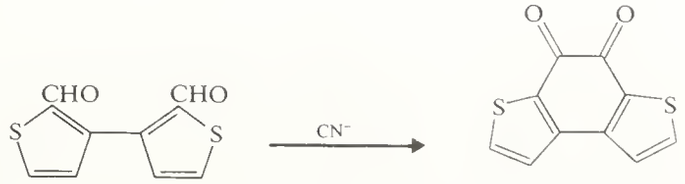
(53)



(54)

(73%)

Quite often the products of the benzoin condensation are unstable to oxygen and α-diketones[206,208] are obtained in many cases. This is often the case in intramolecular condensations since the initial product, an *o*-quinol, is easily oxidized to the quinone (equation 55).[209]



(55)

(50%)

Although the mixed benzoin condensation, which can be envisaged as the generation of a 'masked' acyl carbanion followed by reaction with a second carbonyl component, has been known for more than 50 years, it is rather surprising that the synthetic potential has only recently been realised.[210] Thus the 'masked' acyl carbanion (**41**) (Scheme 34), generated from an aldehyde by reaction with cyanide or thiazolium salts in the presence of base, has been found to add to a wide variety of compounds other than aldehydes, if dipolar aprotic solvents such as DMF are used. The Michael additions with α,β-unsaturated compounds proceed in excellent yields (Table 12).[210]

Since benzoin formation is reversible and precedes the Michael addition, use of the benzoin instead of aldehyde as starting material leads to identical products. In general,

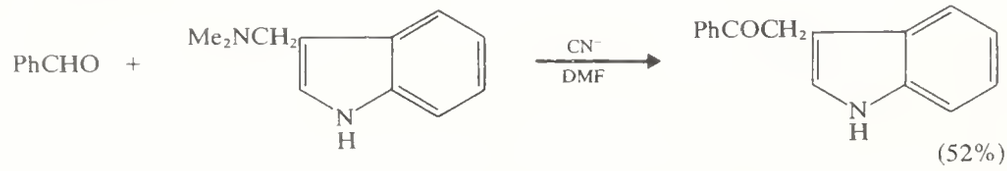
TABLE 12

1,4-Diketones, 4-Oxonitriles, and 4-Oxocarboxylic Esters from Aldehydes and Unsaturated Ketones, Nitriles, and Esters[a]

R^1	R^2	R^3	X	*Catalyst*	*Yield* (%)
Ph	H	H	COMe[b]	CN^-	82
Ph	Ph	H	COPh	CN^-	93
Ph	H	H	$COCH{=}CH_2$	CN^-	55[c]
4-ClC_6H_4	H	H	COMe[b]	CN^-	98
4-$MeOC_6H_4$	H	H	COMe[b]	(**44**)	42[d]
1-$C_{10}H_7$	H	H	COPh[b]	(**44**)	79
2-Pyridyl	Ph	H	COPh	CN^-	91
Ph	H	H	CN	CN^-	80
Ph	H	Me	CN	CN^-	73
Ph	Ph	H	CN	CN^-	80
Ph	H	H	CO_2Et	CN^-	55
Ph	Me	H	CO_2Bu^t	CN^-	52
4-ClC_6H_4	Ph	H	CO_2Bu^t	CN^-	60
2-Thienyl	Me	H	CO_2Et	CN^-	54

[a] Ref. 210. [b] The precursor $Me_2NCH_2CH_2COR$ can also be used to give the same products in 45–65% yield. [c] Product was $PhCOCH_2CH_2COCH_2CH_2COPh$. [d] EtOH solvent.

cyanide ion is the best catalyst for the addition of aromatic aldehydes to α,β-unsaturated carbonyl compounds, whereas thiazolium ion catalysts are preferred for aliphatic or *ortho*-substituted aromatic aldehydes. The examples in equation (56) and Tables 12 and 13 illustrate the variety of substrates which can be used and the synthetic potential of the reaction.[210] The significance of this new approach is twofold: firstly, that the products, 1,4-diketones, 4-oxonitriles, and 4-oxoesters, are starting materials for the synthesis of a wide variety of heterocyclic compounds; secondly, that the reaction generates a protected carbonyl anion, which acylates the substrate and is deprotected all under the same reaction conditions.[210]

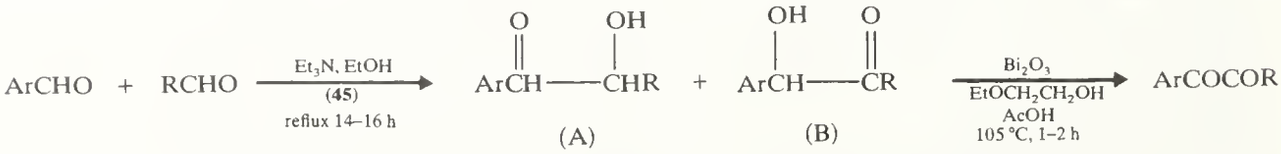


(56)

Finally, the method has recently been applied to the mixed benzoin condensation between an aromatic and an aliphatic aldehyde, yielding a mixture of 'unsymmetrical' benzoins (Table 13).[211] Although the method is not always useful for the synthesis of α-hydroxyketones, since the relative ratio of isomers is unpredictable, it represents an excellent method of obtaining 'unsymmetrical' α-diketones from a mixture of an aromatic and an aliphatic aldehyde, by subsequent oxidation of the mixture of α-hydroxyketones with bismuth oxide (Table 13).[211]

TABLE 13

1,2-Diketones from a Mixture of Aromatic and Aliphatic Aldehydes[a]

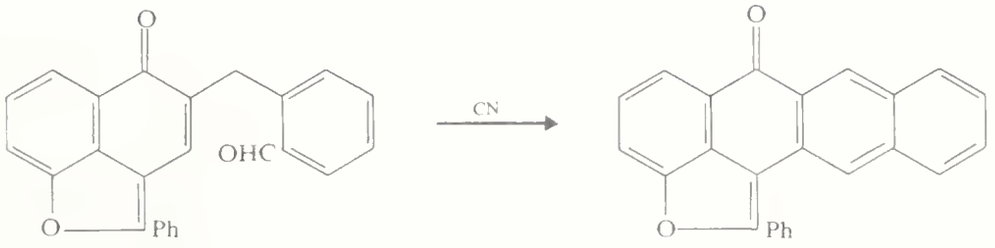


Ar	R	*Yield* (A + B) (%)	*Ratio* (A : B)	*Yield* (ArCOCOR) (%)
C_6H_5	Me_2CH	56	35:65	75
C_6H_5	$C_3H_7CH(Me)$	61	40:60	94
2-ClC_6H_4	Me_2CH	81	100:0	85
2-ClC_6H_4	$C_3H_7CH(Me)$	85	100:0	91
2-ClC_6H_4	Me	52	0:100	72
4-ClC_6H_4	Me_2CH	75	45:55	78
2-Furyl	Me_2CH	88	95:5	77

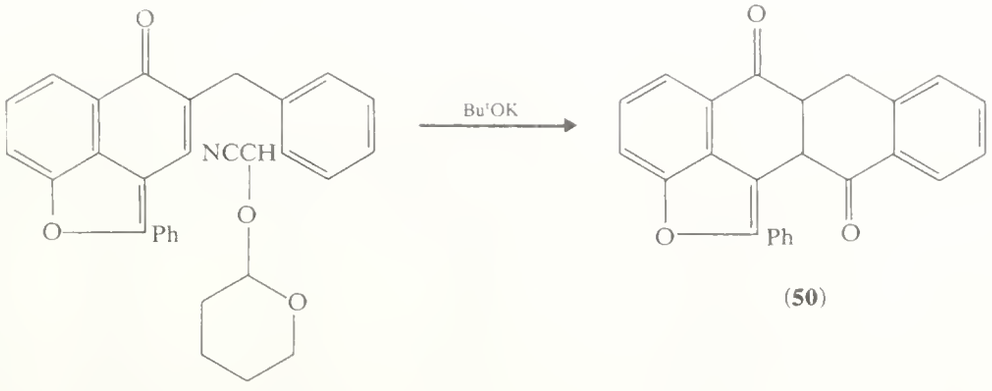
[a] Ref. 211.

The importance of carbonyl anion equivalents which react by nucleophilic acylation has only been realised over the last decade.[212] Several groups have recognized that the benzoin condensation falls into this category, and have generated the carbonyl anion equivalent by protection of the cyanohydrin followed by deprotonation. Barton *et al.*[213] used this approach in models for the synthesis of the important antibiotic tetracycline. The desired transformation, (**47**)→(**50**), could not be accomplished by reaction of the aldehyde (**47**) with cyanide ion since dehydration to (**48**) took place (equation 57). However, if the aldehyde was converted to the cyanohydrin and then protected as the tetrahydropyranyl ether (**49**), the desired diketone (**50**) could be obtained by treatment with potassium t-butoxide (equation 58). The tetrahydropyranyl ether of acetaldehyde cyanohydrin could not be alkylated under similar conditions; an aryl group is necessary to stabilize the carbanion intermediate.[213]

Stork and Maldonado[214] have discovered that by reacting cyanohydrins with ethyl vinyl ether, the resultant adducts are readily deprotonated using lithium di-isopropylamide or hexamethyldisilazane. Alkylation with a variety of alkyl halides then leads to ketones after

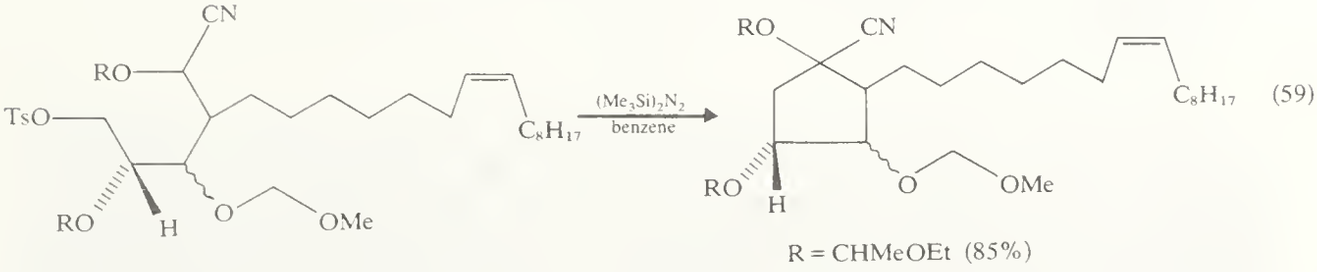


(47) (48) (57)



(49) (50) (58)

hydrolysis.[214] An intramolecular alkylation of a protected cyanohydrin anion has been used as the key stage in a chiral prostaglandin synthesis (equation 59).[215]



R = CHMeOEt (85%) (59)

The previous examples demonstrate that, although the benzoin condensation — and related reactions — had limited synthetic potential for over a century, they should now be regarded as but one of a general class of masked acyl carbanion reactions. The progress in this area over the last few years has been made possible by research aimed at understanding in detail the mechanism of the condensation and shows the importance of mechanistic studies in synthetic organic chemistry.[195,210]

5.3.9 DECARBONYLATION OF AROMATIC ALDEHYDES

The decarbonylation of aldehydes to hydrocarbons proceeds readily in the presence of transition metal catalysts.[216] The process probably proceeds *via* the reverse of carbonylation reactions, the first stage being a coordination of the aldehyde to the metal with formation of an acyl–metal bond (equation 60). Rearrangement of the acyl–metal complex to an aryl– or alkyl–metal complex with carbon–carbon bond cleavage is the important stage, the carbon monoxide remaining coordinated to the metal, but easily removed by heating in the absence of excess of carbon monoxide (equation 60).

$$RCHO \xrightarrow{M} RCO{-}M{-}H \longrightarrow R{-}\overset{\displaystyle CO}{\underset{|}{M}}{-}H \longrightarrow RH + M + CO \qquad (60)$$

Using palladium on charcoal catalyst the decarbonylation of aromatic aldehydes to hydrocarbons proceeds readily (Table 14), but the method is inappropriate for low-boiling aliphatic aldehydes, which give mixtures of alkane and alkene.[217] It is not clear why 2-naphthaldehyde should be so unreactive under these conditions, when a similar reaction proceeds using rhodium complex catalysts (Table 14).[218] The latter catalysts are also effective for aromatic aldehydes at high temperatures, but side reactions, such as aldol condensations, occur with aliphatics.[218]

TABLE 14

Catalytic Decarbonylation of Aromatic Aldehydes

ArCHO → ArH

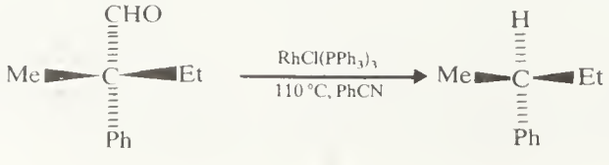
Ar	*Catalyst*	*Temp.* (°C)	*Time* (h)	*Yield* (%)	*Ref.*
Ph	5% Pd/C	179	1.0	78	a
4-MeC_6H_4	5% Pd/C	179	0.5	88	a
2-$MeOC_6H_4$	5% Pd/C	243	1.0	94	a
3-$NO_2C_6H_4$	5% Pd/C	205	1.75	86	a
4-$NO_2C_6H_4$	5% Pd/C	205	0.5	79	a
4-ClC_6H_4	$RhCl(CO)(PPh_3)_3$	220	9.0	77	b
2-HOC_6H_4	5% Pd/C	210	8.5	80	b
2-Pyridyl	5% Pd/C	180	1.0	68	a
1-Naphthyl	5% Pd/C	220	0.5	80	a
1-Naphthyl	$RhCl(PPh_3)_3$	—	2	88	c
2-Naphthyl	5% Pd/C	250	0.5	0	a
2-Naphthyl	$RhCl(PPh_3)_3$	—	2.5	77	c
9-Anthryl	5% Pd/C	240	0.5	84	a

[a] Ref. 217. [b] Ref. 218. [c] Ref. 219.

Decarbonylation can also be effected under very mild conditions by using a stoichiometric quantity of the rhodium complex $RhCl(PPh_3)_3$, which is soluble in benzene or methylene chloride. The reaction proceeds homogeneously at room temperature for primary aliphatic aldehydes, but aromatic or secondary aldehydes usually require heating to 80–100 °C for a few hours.[219] When heated to very high temperatures the rhodium complex is converted to a dimeric species, $(Ph_3P)_2RhCl_2Rh(PPh_3)_2$, which stops the decarbonylation; if nitriles are used as solvents, however, the complex $RhCl(PPh_3)_3$ is solvated, and decomposition does not occur.[219]

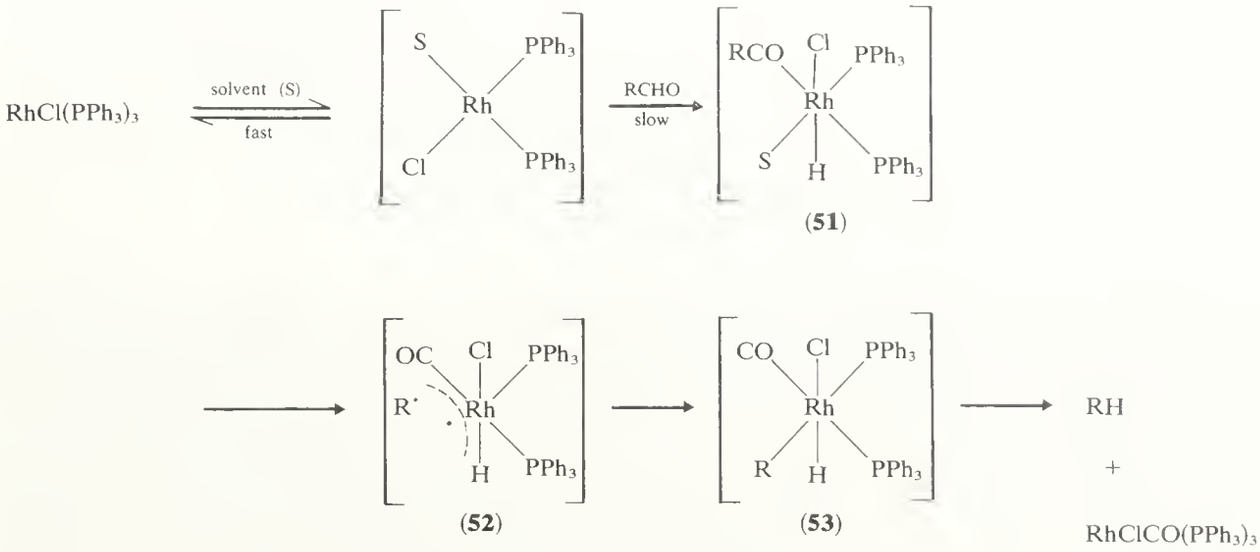
A useful application of aldehyde decarbonylation is the removal of the 4-carboxybenzaldehyde impurity during the purification of terephthalic acid (TA), the starting material in polyester synthesis.[220] TA is manufactured by oxidation of *p*-xylene, which gives 4-carboxybenzaldehyde as an unwanted by-product, difficult to remove from TA. After decarbonylation over palladium, however, the impurity is converted to benzoic acid, which is much more easily separated from TA.[220]

The stoichiometric decarbonylation using tris(triphenylphosphine)rhodium chloride is intramolecular and stereoselective. Thus decarbonylation of deuterioaldehydes leads to 95% retention of deuterium and (*R*)-(−)-2-methyl-2-phenylbutyraldehyde gave (*S*)-(+)-2-phenylbutane of 81% optical purity with retention of configuration (equation 61).[221]



(61)

These results are consistent with the mechanism shown in Scheme 36, in which the first stage is attack of solvent with elimination of triphenylphosphine. This is followed by nucleophilic attack on the aldehyde by the d^8 complex with concomitant hydrogen transfer giving the acyl complex (**51**). In this stage, oxidation of rhodium(I) to rhodium(III) takes place in what is probably the rate-determining step. In the rearrangement of the acyl–rhodium complex with decarbonylation, the high specificity has been attributed to formation of a radical pair (**52**) which may disproportionate to the product or give the alkyl–rhodium species (**53**). The latter on reductive elimination leads to product (Scheme 36). In agreement with this, the more electrophilic the aldehyde or the more nucleophilic the rhodium complex, the faster the decarbonylation proceeds.



SCHEME 36

5.3.10 PHOTOCHEMISTRY OF AROMATIC ALDEHYDES

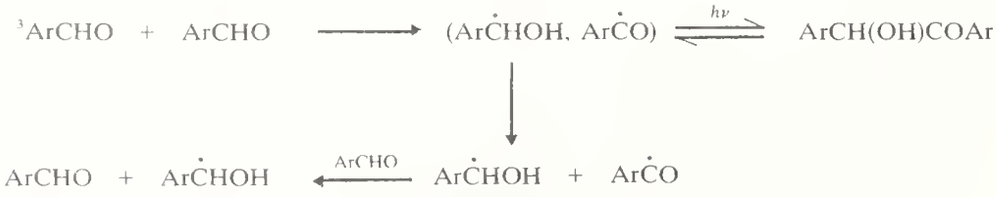
Aldehydes and ketones contain a weak band at 280–300 nm in the ultraviolet spectrum, corresponding to the 'forbidden' $n \rightarrow \pi^*$ transition, *i.e.* the promotion of a non-bonded electron, localized on oxygen, to an empty π^* orbital. The resultant electronic distribution means that the n,π^* excited states resemble alkoxy radicals, having rather electrophilic oxygen and nucleophilic carbonyl carbon atoms. For aromatics or α,β-unsaturated aldehydes, the $\pi \rightarrow \pi^*$ transition is much stronger and of a similar energy so that in these compounds reaction may take place from either n,π^* or π,π^* states; the latter have fewer electrophilic oxygen atoms and this reduces their ability to abstract a hydrogen atom from a substrate.

In aliphatic aldehydes, reaction normally takes place from the n,π^* singlet state. For many aromatic aldehydes, however, conversion from the n,π^* singlet to the longer-lived triplet state (intersystem crossing) takes place before reaction with substrates; polycyclic aromatic aldehydes may still react from a singlet state. The significance of these factors on reactivity will be discussed later in relation to cycloaddition reactions.

When irradiated in propan-2-ol solution, aromatic aldehydes having n,π^* lowest excited states are photoreduced, in a similar manner to other carbonyl groups, to the pinacols. For example, benzaldehyde yields a mixture of (±)- and *meso*-1,2-diphenylethane-1,2-diols in the ratio 1 : 1 (equation 62).[222] Aromatic aldehydes with π,π^* lowest excited states (*e.g.* α-naphthaldehyde) are photostable in propan-2-ol solution.

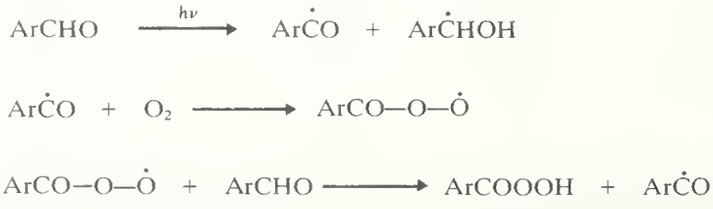
$$\text{PhCHO} \xrightarrow[\text{Pr}^i\text{OH}]{h\nu} \text{PhCHOH—CHOHPh} \qquad (62)$$

Irradiation of benzaldehydes in the absence of oxygen and good hydrogen donors leads to benzoins as the major product. The mechanism shown in Scheme 37 has been elucidated[223] after examination of the polarized n.m.r. spectrum (chemically induced dynamic nuclear polarisation, CIDNP effect)[224] during the photolysis of substituted benzaldehydes.[223] This technique allows the multiplicity of the radical intermediates to be determined and related mechanistically to the final products. The excited triplet state of the aldehyde abstracts the hydrogen from a second aldehyde molecule producing a geminate radical pair, which react within the solvent 'cage' to give the benzoin. Escape of the radicals from the 'cage' yields radicals which may also abstract hydrogen from the aldehyde but do not lead to the benzoin product. The polarization observed in the starting aldehyde arises from the degenerate reaction with hydroxybenzyl radicals (Scheme 37).

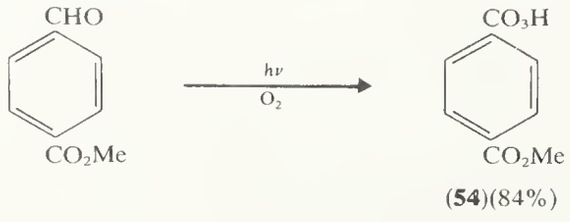


SCHEME 37

Aroyl radical intermediates are also involved in the photo-oxidation of aromatic aldehydes,[225] which occurs *via* the mechanism shown in Scheme 38.[226] The product is the peroxy acid, which can be isolated in many cases. For example, photo-oxidation of *p*-methoxycarbonylbenzaldehyde gives the stable peroxy acid (**54**) (equation 63).[227]



SCHEME 38



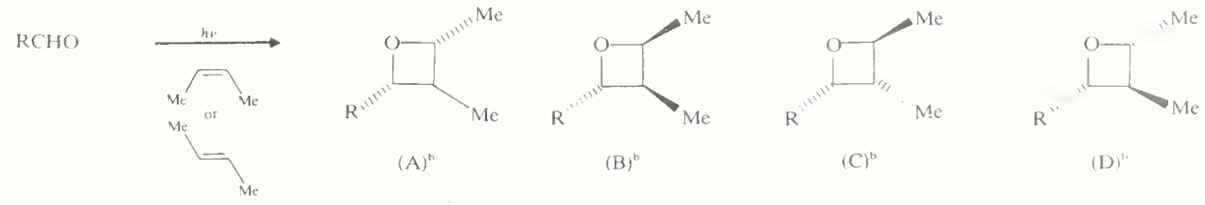
(63)

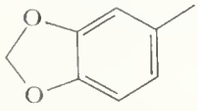
(**54**)(84%)

The photocycloaddition reactions of aromatic aldehydes are in many ways very similar to those of aromatic ketones. In general, most aldehydes and ketones undergo photocycloaddition with olefins to give good yields of oxetans.[228] This reaction, known as the Paterno–Buchi reaction, is discussed in more detail in Section 4.4.4.3. Aliphatic aldehydes react with *cis*- or *trans*-but-2-ene in a highly specific manner (Table 15), the major oxetan isomers retaining the geometry of the starting olefin.[229] This suggests that the reaction proceeds *via* the short-lived singlet n,π^* state of the aldehyde. In contrast, irradiation of benzaldehyde in the presence of *cis*- or *trans*-but-2-ene leads to the same isomeric mixture of all four oxetans in each case. The ratio of the isomers is determined solely by the stabilities of the different conformations of the intermediate biradical (Ar-ĊHOCHMeĊHMe) prior to cyclization. Reaction in this case arises from the longer-lived triplet n,π^* state.[229]

TABLE 15

Photoaddition of Aldehydes to *cis*- and *trans*-But-2-ene[a]

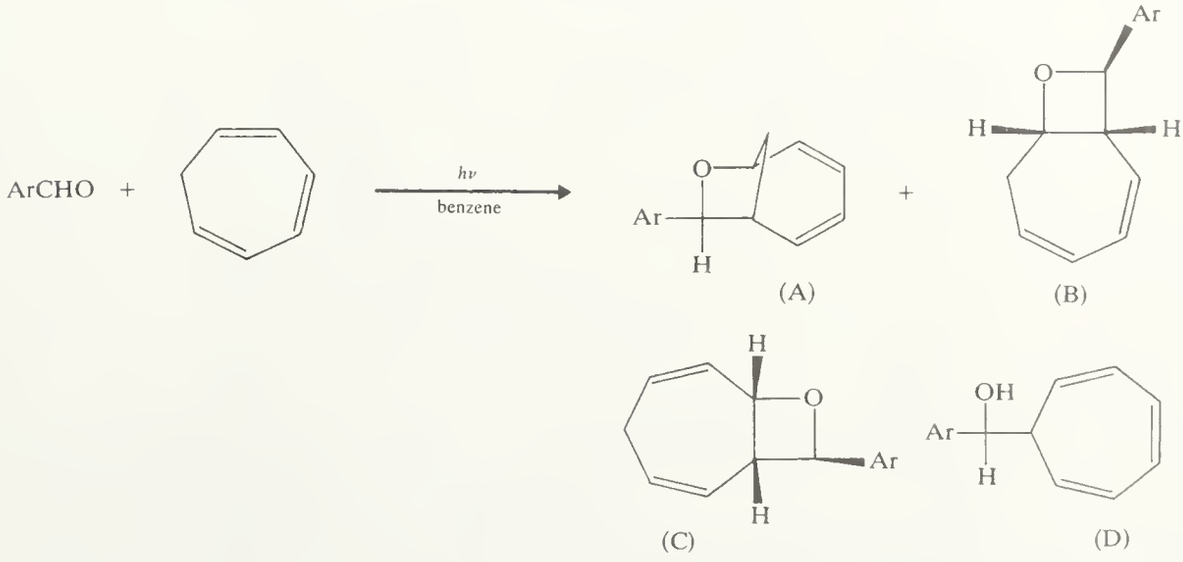


R		A(%)	B(%)	C(%)	D(%)
Me	*cis*	48	40	[c]	11
	trans	4.6	42	[c]	53
Ph	*cis* or *trans*	32	5	19	44
4-$MeOC_6H_4$	*cis* or *trans*	28	5	17	50
	*cis*	41	23	11	25
	trans	14	4	30	52
2-Naphthyl	*cis*	42	38	3	17
	trans	3	3	36	58

[a] Ref. 229. [b] Only one enantiomer depicted in each case. [c] When R = Me, oxetans B and C are identical.

The photocyclization of 2-naphthaldehyde, however, is highly selective (Table 15) and it has been shown that the singlet state is again involved; this is most unusual for aromatic carbonyl compounds since intersystem crossing to the triplet state is normally extremely efficient. The high selectivity of the singlet state reactions may be attributed to a concerted $_{\pi}2_s + _{\pi}2_s$ cycloaddition which, according to the Woodward–Hoffmann rules,[230] is photochemically allowed. Alternatively, a short-lived diradical intermediate may be involved. In the triplet state reactions, the longer lifetime of the triplet diradical allows bond rotation to take place before ring closure leading to loss in selectivity.

An interesting cycloaddition of polycyclic aromatic aldehydes which also proceeds from the excited n,π^* singlet state is the photoaddition to cycloheptatriene.[231] The major products (Scheme 39) are all formed stereospecifically; no trace of stereoisomers could be



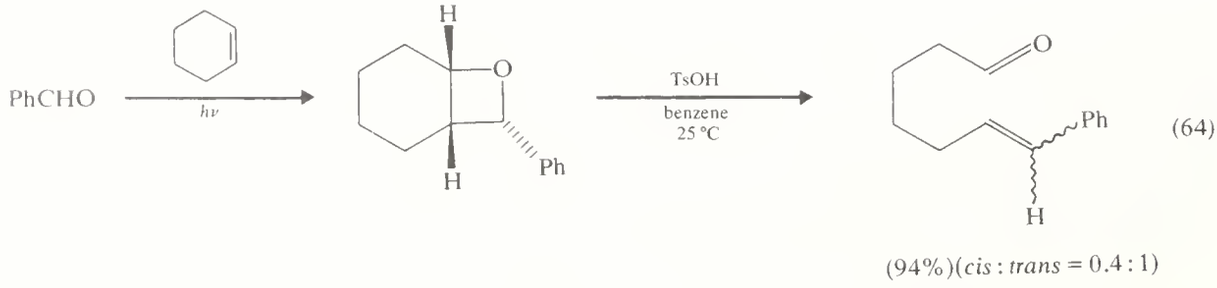
Ar = 1-pyrenyl A (44%) + B (16%) + C (16%) + D (18%)

Ar = 2-naphthyl A (25%) + B (25%) + C (21%) + D (21%)

SCHEME 39

detected. The formation of the major adduct is possibly the first example of a concerted $_{\pi}6_{s}+{}_{\pi}2_{s}$ photocycloaddition to a non-benzenoid 6π-electron system.

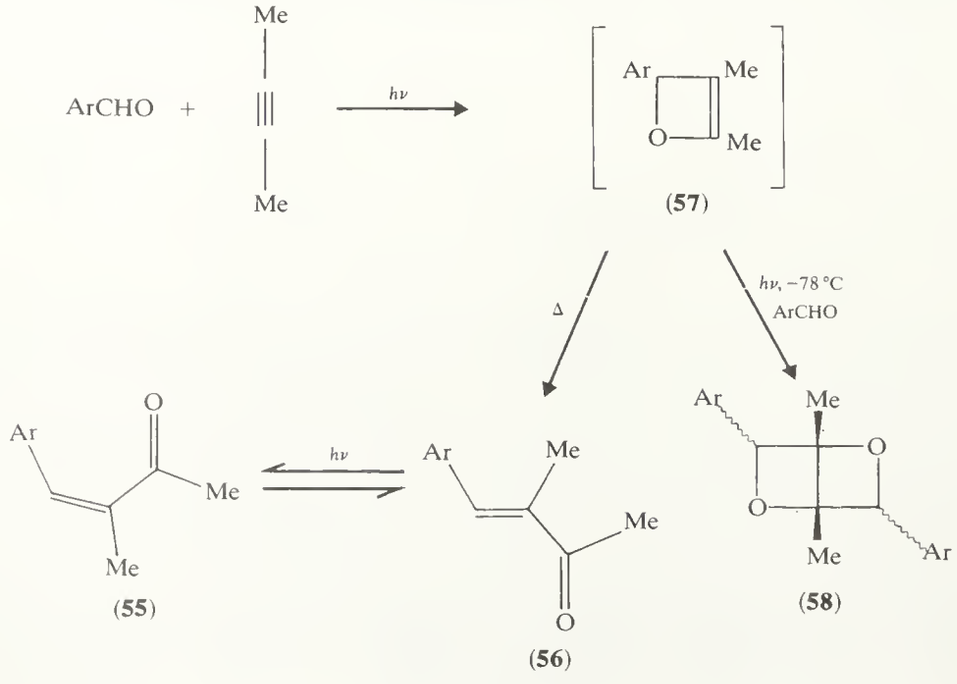
The photocycloadditions of aromatic aldehydes to olefins are synthetically useful since the products can often be cleaved to give a different carbonyl group and olefin; the reaction sequence is thus analogous to olefin metathesis. A particularly useful sequence is the photocycloaddition of benzaldehyde to cyclohexene, which, after cleavage, yields 7-phenylhept-6-enal (equation 64).[232]



(64)

(94%)(*cis* : *trans* = 0.4 : 1)

The photoaddition of aromatic aldehydes to acetylenes is a general reaction, giving moderate yields of α,β-unsaturated ketones (Scheme 40). When benzaldehyde was irradiated in the presence of but-2-yne at room temperature, the product (43%) was a mixture of (*Z*)- and (*E*)-isomers (**55**) and (**56**) in the ratio 2 : 1.[233] After irradiation at −78 °C, however, followed by warming to room temperature, only the (*E*)-isomer was obtained, but subsequent irradiation at room temperature gave the (*Z*)-isomer. The most likely explanation is that an intermediate oxeten (**57**) was initially formed (Scheme 40); this was stable at −78 °C and could be detected spectroscopically, but rearranged to the (*E*)-isomer (**56**) on warming. Photoisomerization of the double bond at room temperature produced the (*Z*)-isomer (**55**). The oxeten (**57**) could also be trapped by irradiation at −78 °C in the presence of aldehyde, giving the novel 2,5-dioxa[2,2,0]hexane ring system (**58**).[233] In the photoaddition of benzaldehyde to hex-1-yne, however, it appears more likely that the products may arise by the addition of benzoyl radicals to the acetylene (equation 65).[234]



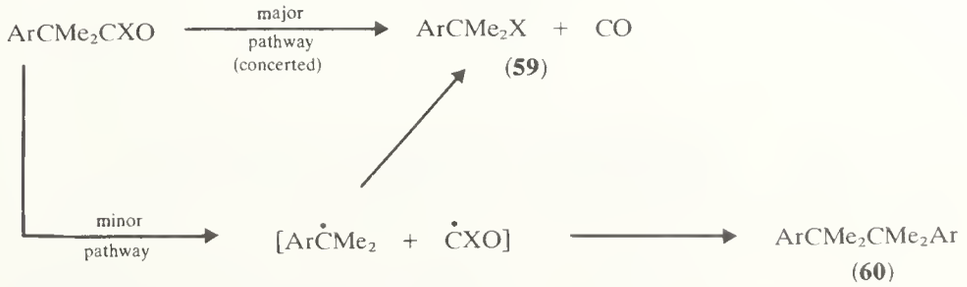
SCHEME 40

$$PhCHO \xrightarrow[C_4H_9C{\equiv}CH]{h\nu} PhCOCH{=}{=}CHC_4H_9 \xrightarrow[PhCHO]{h\nu} PhCOCH_2{-}\underset{\displaystyle COPh}{\underset{|}{C}}HC_4H_9 \quad (57\%) \qquad (65)$$

The photochemistry of α-arylaldehydes, particularly α,α-disubstituted phenylacetaldehydes, is dominated by the decarbonylation process, which yields the hydrocarbons (**59**) and (**60**) (Table 16).[235] The reaction probably proceeds *via* the excited singlet state since triplet sensitizers and quenchers are ineffective. Hydrogen transfer giving the product (**59**) has been shown to occur intramolecularly from deuterium-labelling experiments; the product (**60**), however, arises by coupling of radicals. Although a CIDNP effect was observed in the photolysis of α,α-dimethylphenylacetaldehyde, corresponding to the decarbonylation to cumene, it was demonstrated that a singlet 'caged' radical pair could not give rise to cumene (**59**; Ar = Ph); the CIDNP spectrum could only be rationalized by postulating that some of the cumene arose from the same triplet radical pair as the dimeric product (**60**).[236] The conclusion must be that the cumene arose *via* two pathways: the major, a concerted decarbonylation reaction, and the minor, a radical process which gave a CIDNP effect. This study indicates that the observation of a CIDNP effect is not necessarily proof of a wholly radical mechanism.[236] The CIDNP enhancement or emission intensities can be as high as 1000 times the normal n.m.r. spectral intensity and the CIDNP effect may arise, therefore, from a very minor product or pathway.

TABLE 16

Photochemical Decarbonylation of α-Arylaldehydes[a]



Ar	X	*Yields* (%) (**59**)	(**60**)
C_6H_5	H	75	24
C_6H_5	D	91	9
4-MeC_6H_4	H	72	1
3-MeC_6H_4	H	81	10
3-$MeOC_6H_4$	H	61	19
4-BrC_6H_4	H	71	2
1-Naphthyl	H	100	—

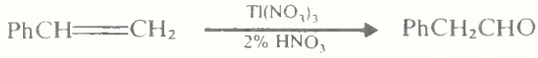
[a] Refs. 235 and 236.

5.3.11 SPECIFIC ALDEHYDES

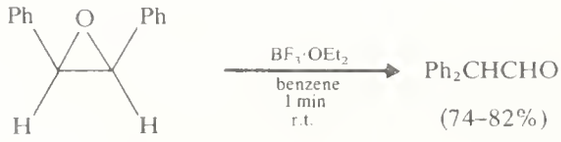
5.3.11.1 Aralkyl aldehydes ($ArCR^1R^2CHO$)

The chemistry of aralkyl aldehydes, such as phenylacetaldehyde, differs little from that expected for aldehydes with rather acidic methylene or methine groups except in methods of synthesis and photochemistry (see Section 5.3.10). The method of choice for the synthesis of phenylacetaldehyde is *via* oxidation of styrene with thallium(III) nitrate

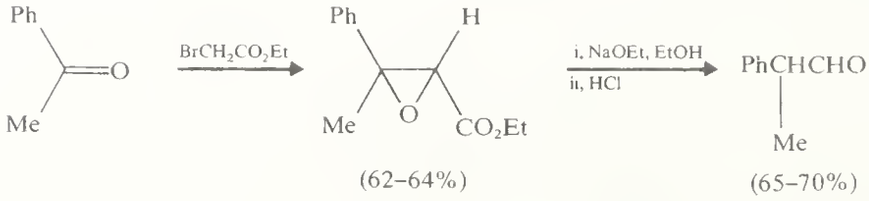
(equation 66),[237] but this method is unfortunately not applicable to other aralkylaldehydes of the type ArCH(R)CHO; oxidation of 1,1-disubstituted olefins with chromyl chloride, however, gives good yields of these aldehydes.[238] The most general synthetic method, particularly for disubstituted aralkyl aldehydes, is *via* acid-catalysed rearrangement of epoxides (equation 67)[239] or acid-catalysed decarboxylation of epoxy acids (equation 68).[240] For the synthesis of optically active aralkyl aldehydes, hydroformylation of olefins using an optically active catalyst gave up to 23% asymmetric induction in some cases (equation 69), particularly if low temperatures and pressures were used.[241]



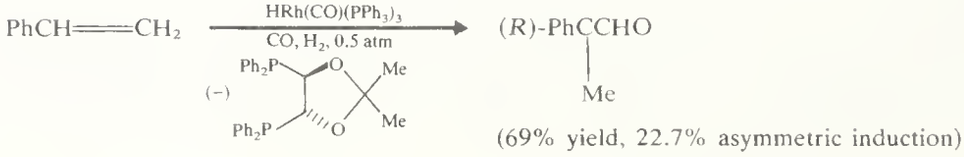
(66)



(67)



(68)

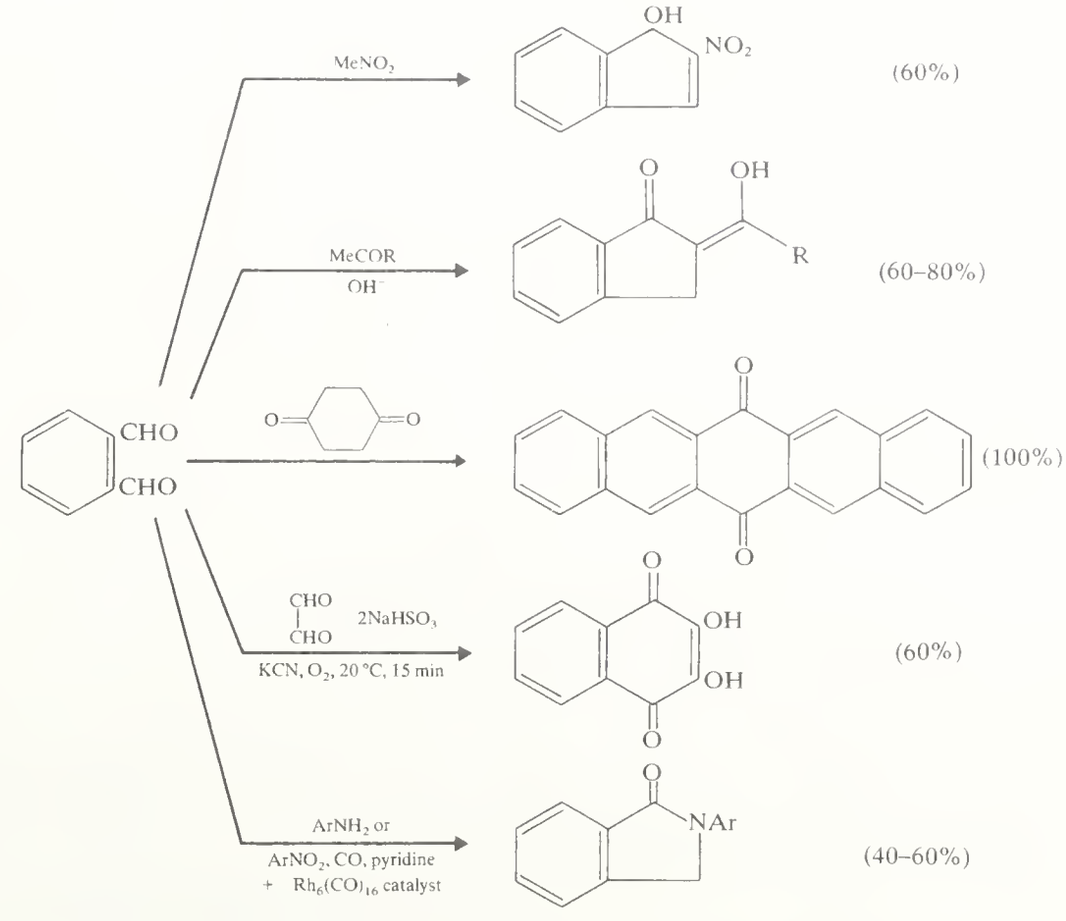


(69)

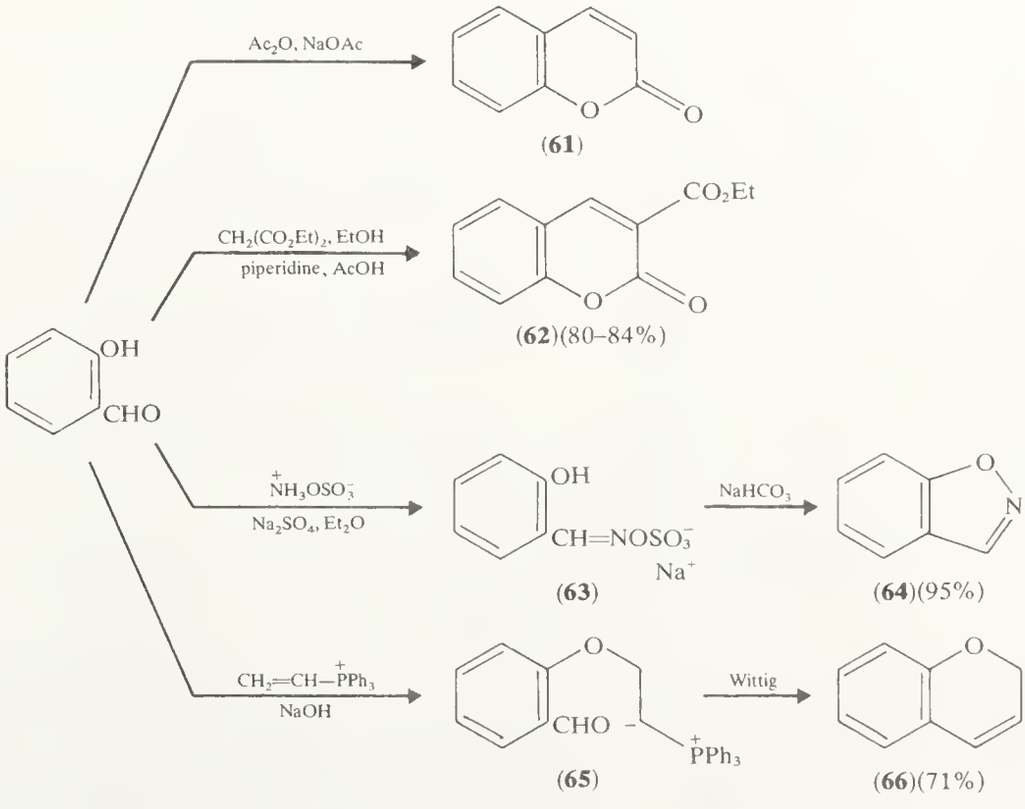
The simplest aralkyl aldehyde, phenylacetaldehyde, m.p. 33–34 °C, b.p. 195 °C, is generally obtained as a difficult to crystallize, colourless oil which polymerizes on standing at room temperature. Its main industrial use is in the perfumery industry, since it has an odour reminiscent of lilac or hyacinth. The chemical properties are similar to those of aliphatic aldehydes (Chapter 5.1).

5.3.11.2 Aromatic dialdehydes

Aromatic dialdehydes can be synthesized by many of the routes described in Section 5.3.2 for monoaldehydes; the most important specific route is *via* oxidation of polycyclic aromatic compounds (Section 5.3.2.14). The chemistry of the simplest aromatic dialdehydes (1,2-, 1,3- and 1,4-diformylbenzene; trivial names *ortho*-, iso-, and *para*-phthalaldehyde) is unremarkable, except for the ease with which the *ortho*-isomer undergoes cyclizations. This characteristic has been widely used in the synthesis of carbocyclic and heterocyclic compounds *via* base-catalyzed condensations[242,243] and benzoin condensation[244] with *o*-phthalaldehyde, or by reactions with amino derivatives[245] (Scheme 41).



SCHEME 41



SCHEME 42

5.3.11.3 *o*-Hydroxybenzaldehydes

The simplest member of the series, salicylaldehyde, is a colourless oily liquid with a bitter almond-like odour, m.p. 197 °C, soluble in hot water. *o*-Hydroxybenzaldehydes undergo most of the common reactions of aldehydes, but the main differences arise from secondary reactions leading to cyclization. These processes, which are important for the synthesis of oxygen-containing heterocycles, are exemplified in Scheme 42. The Perkin and Knoevenagel condensations lead to coumarin derivatives (**61**)[131] and (**62**),[246] whereas the cyclization of the oximesulphonate (**63**) provides an excellent entry into the benzisoxazole system (**64**).[247] The reaction of the phenolate anion of salicylaldehyde with a vinylphosphonium salt generates an ylide (**65**) which, after intramolecular Wittig condensation with the aldehyde group, yields the chromene (**66**).[248]

References

1. J. H. S. Green and D. J. Harrison, *Spectrochim. Acta*, 1976, **32A**, 1265.
2. R. E. Klinck and J. B. Stothers, *Canad. J. Chem.*, 1962, **40**, 1071.
3. G. J. Karabatsos and F. M. Vane, *J. Amer. Chem. Soc.*, 1963, **85**, 3886.
4. T. Nishimura, *Org. Synth. Coll. Vol. 4*, 1963, 713.
5. S. V. Lieberman and R. Connor, *Org. Synth. Coll. Vol. 2*, 1943, 441.
6. W. H. Hartford and M. Darrin, *Chem. Rev.*, 1958, **58**, 1.
7. H. C. Duffin and R. B. Tucker, *Tetrahedron*, 1967, **23**, 2803; 1968, **24**, 389, 6999.
8. W. R. Boon, *J. Chem. Soc.*, 1949, S230.
9. I. Necsoiu, A. T. Balaban, I. Pascaru, E. Sliam, M. Elian, and C. D. Nenitzescu, *Tetrahedron*, 1963, **19**, 1133.
10. K. B. Wiberg and R. Eisenthal, *Tetrahedron*, 1964, **20**, 1151.
11. O. H. Wheeler, *Canad. J. Chem.*, 1964, **42**, 706.
12. I. Necsoiu, V. Przemetchi, A. Ghenciulescu, C. N. Rentea, and C. D. Nenitzescu, *Tetrahedron*, 1966, **22**, 3037.
13. C. N. Rentea, M. Rentea, I. Necsoiu, and C. D. Nenitzescu, *Tetrahedron*, 1968, **24**, 4667.
14. L. Syper, *Tetrahedron Letters*, 1966, 4493.
15. W. S. Trahanovsky and L. B. Young, *J. Org. Chem.*, 1966, **31**, 2035.
16. W. S. Trahanovsky, L. B. Young, and G. L. Brown, *J. Org. Chem.*, 1967, **32**, 3865.
17. L. A. Dust and E. W. Gill, *J. Chem. Soc.* (*C*), 1970, 1630.
18. C. S. Marvel, J. H. Saunders, and C. G. Overberger, *J. Amer. Chem. Soc.*, 1946, **68**, 1085.
19. J. S. Gillespie, Jr., S. P. Acharya, D. A. Shamblee, and R. E. Davis, *Tetrahedron*, 1975, **31**, 3.
20. N. Rabjohn, *Org. Reactions*, 1976, **24**, 261.
21. E. Campaigne, W. M. Budde, and G. F. Schaefer, *Org. Synth. Coll. Vol. 4*, 1963, 31.
22. G. A. Olah and W. S. Tolgyesi, in 'Friedel–Crafts and Related Reactions', ed. G. A. Olah, Interscience, New York, 1964, vol. 2, part 2, chapter 21.
23. S. J. Angyal, *Org. Reactions*, 1954, **8**, 197.
24. F. Krohnke, *Angew. Chem. Internat. Edn.*, 1963, **2**, 380.
25. H. Kamogawa, S. Okabe, and M. Nanasawa, *Bull. Chem. Soc. Japan*, 1976, **49**, 1917.
26. J. C. Roberts and P. Woollven, *J. Chem. Soc.* (*C*), 1970, 278.
27. S. J. Angyal, J. R. Tetaz, and J. G. Wilson, *Org. Synth. Coll. Vol. 4*, 1963, 690.
28. K. Clarke, *J. Chem. Soc.*, 1957, 3807.
29. A. Kalir, *Org. Synth. Coll. Vol. 5*, 1973, 825.
30. N. Kornblum, W. J. Jones, and G. J. Anderson, *J. Amer. Chem. Soc.*, 1959, **81**, 4113; W. W. Epstein and F. W. Sweat, *Chem. Rev.*, 1967, **67**, 247.
31. B. Ganem and R. K. Boeckman, Jr., *Tetrahedron Letters*, 1974, 917.
32. R. E. Manning and F. M. Schaefer, *Tetrahedron Letters*, 1975, 213.
33. V. Franzen, *Org. Synth. Coll. Vol. 5*, 1973, 872.
34. H. B. Hass and M. L. Bender, *Org. Synth. Coll. Vol. 4*, 1963, 932; *J. Amer. Chem. Soc.*, 1949, **71**, 1767, 3482.
35. N. Kornblum, *Angew Chem. Internat. Edn.*, 1974, **14**, 734.
36. A. McKillop and M. E. Ford, *Synth. Comm.*, 1974, **4**, 45; R. L. Letsinger and J. D. Jamison, *J. Amer. Chem. Soc.*, 1961, **83**, 193.
37. G. Cardillo, M. Orena, and S. Sandri, *J.C.S. Chem. Comm.*, 1976, 190; *Tetrahedron Letters*, 1976, 3985.
38. J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Letters*, 1968, 3363.
39. A. Moradpour, H. Kagan, M. Baes, G. Morren, and R. H. Martin, *Tetrahedron*, 1975, **31**, 2139.
40. F. J. Kakis, M. Fetizon, N. Douchkine, M. Golfier, P. Mourgues, and T. Prange, *J. Org. Chem.*, 1974, **39**, 523.
41. G. Cainelli, G. Cardillo, M. Orena, and S. Sandri, *J. Amer. Chem. Soc.*, 1976, **98**, 6737.

42. J. M. Lalancette, G. Rollin, and P. Dumas, *Canad. J. Chem.*, 1972, **50,** 3058.
43. S. L. Regen and C. Koteel, *J. Amer. Chem. Soc.*, 1977, **99,** 3838.
44. W. L. McEwen, *Org. Synth. Coll. Vol. 2*, 1943, 133.
45. H. Gilman, C. G. Brannen, and R. K. Ingham, *J. Amer. Chem. Soc.*, 1956, **78,** 1689.
46. J. C. Bill and D. S. Tarbell, *Org. Synth. Coll. Vol. 4*, 1963, 807.
47. G. A. Olah and S. J. Kuhn, in 'Friedel–Crafts and Related Reactions', ed. G. A. Olah, Interscience, New York, 1964, vol. 3, part 2, chapter 38.
48. D. P. N. Satchell and R. S. Satchell, in 'Chemistry of the Carbonyl Group', ed. S. Patai, Interscience, New York, 1966, chapter 5.
49. N. N. Crounse, *Org. Reactions*, 1949, **5,** 290.
50. G. A. Olah and S. J. Kuhn, *J. Amer. Chem. Soc.*, 1961, **82,** 2380.
51. G. A. Olah, F. Pelizza, S. Kobayashi, and J. A. Olah, *J. Amer. Chem. Soc.*, 1976, **98,** 296.
52. H. Fischer and A. Schwartz, *Annalen*, 1934, **512,** 239.
53. A. Rieche, H. Gross, and E. Hoeft, *Chem. Ber.*, 1960, **93,** 88; *Org. Synth. Coll. Vol. 5*, 1973, 49.
54. W. E. Truce, *Org. Reactions*, 1957, **9,** 37.
55. J. P. Lambooy, *J. Amer. Chem. Soc.*, 1956, **78,** 771.
56. F. M. Aslam, P. H. Gore, and M. Jehangir, *J.C.S. Perkin I*, 1972, 892.
57. A. Kreutzberger, *Arch. Pharm.*, 1971, **304,** 362; *ibid.*, 1969, **302,** 828; *Z. Chem.*, 1970, **10,** 383.
58. C. Jutz, *Adv. Org. Chem.*, 1976, **9,** 225.
59. S. Seshadri, *J. Sci. Ind. Res. India*, 1973, **32,** 128.
60. G. Hazebroucq, *Ann. pharm. franc.*, 1966, **24,** 793.
61. M. R. de Maheas, *Bull. Soc. chim. France*, 1962, 1989.
62. V. I. Minkin and G. N. Dorofeenko, *Russ. Chem. Rev.*, 1960, **29,** 599.
63. A. Vilsmeier and A. Haack, *Ber.*, 1927, **60,** 119.
64. G. J. Martin and S. Poignant, *J.C.S. Perkin II*, 1974, 642.
65. G. Ferre and A. L. Palomo, *Tetrahedrom Letters*, 1969, 2161.
66. Z. Arnold, *Chem. listy*, 1958, **52,** 2013.
67. P. Linda, A. Lucarelli, G. Marino, and G. Savelli, *J.C.S. Perkin II*, 1974, 1610.
68. J. C. Duff and V. I. Furness, *J. Chem. Soc.*, 1952, 1159, and references cited therein.
69. C. F. H. Allen and G. W. Leubner, *Org. Synth. Coll. Vol. 4*, 1963, 866.
70. W. E. Smith, *J. Org. Chem.*, 1972, **37,** 3972.
71. Y. Ogata, A. Kawasaki, and F. Sugiura, *Tetrahedron*, 1968, **24,** 5001.
72. H. Wynberg, *Chem. Rev.*, 1960, **60,** 169.
73. A. Russell and L. B. Lockhart, *Org. Synth. Coll. Vol. 3*, 1955, 463.
74. J. Hine and J. M. van der Veen, *J. Amer. Chem. Soc.*, 1959, **81,** 6447.
75. D. S. Kemp, *J. Org. Chem.*, 1971, **36,** 202; J. M. A. Al-Rawi, J. P. Bloxsidge, C. O'Brien, D. E. Caddy, J. A. Elvidge, J. R. Jones, and E. A. Evans, *J.C.S. Perkin II*, 1974, 1635.
76. K. Hirao, M. Ikegame, and O. Yonemitsu, *Tetrahedron*, 1974, **30,** 2301.
77. P. G. Gassman and D. R. Amick, *Tetrahedron Letters*, 1974, 3463, 889.
78. S. H. Pine, *Org. Reactions*, 1971, **18,** 403.
79. P. G. Gassman and H. R. Drewes, *J. Amer. Chem. Soc.*, 1974, **96,** 3002.
80. D. J. Zwanenberg and W. A. P. Reynen, *Synthesis*, 1976, 624.
81. G. Casnati, M. Crisafulli, and A. Ricca, *Tetrahedron Letters*, 1965, 243.
82. H. Gross, A. Rieche, and G. Matthey, *Chem. Ber.*, 1963, **96,** 308.
83. C. A. Dornfield and G. H. Coleman, *Org. Synth. Coll. Vol. 3*, 1955, 701.
84. A. I. Meyers and E. W. Collington, *J. Amer. Chem. Soc.*, 1970, **92,** 6676.
85. L. I. Smith and J. Nichols, *J. Org. Chem.*, 1941, **6,** 489.
86. A. J. Sisti, *Org. Synth. Coll. Vol. 5*, 1973, 46.
87. A. Schoenberg and R. F. Heck, *J. Amer. Chem. Soc.*, 1974, **96,** 7761.
88. E. Mosettig, *Org. Reactions*, 1954, **8,** 218.
89. E. Mosettig and R. Mozingo, *Org. Reactions*, 1948, **4,** 362.
90. A. I. Rachlin, H. Gurien, and D. P. Wagner, *Org. Synth.*, 1971, **51,** 8.
91. H. Sakurai and Y. Tanabe, *J. Pharm. Soc. Japan*, 1944, **64,** 25.
92. J. A. Peters and H. van Bekkum, *Rec. Trav. chim.*, 1971, **90,** 1323.
93. A. W. Burgstahler, L. O. Weigel, and C. G. Shaefer, *Synthesis*, 1976, 767.
94. L. E. Friedrich and G. B. Schuster, *J. Amer. Chem. Soc.*, 1972, **94,** 1193.
95. S. B. Martin, J. C. Craig, and R. P. K. Chan, *J. Org. Chem.*, 1974, **39,** 2285.
96. H. C. Brown and B. C. Subba Rao, *J. Amer. Chem. Soc.*, 1958, **80,** 5377.
97. D. G. Smith and D. J. H. Smith, *J.C.S. Chem. Comm.*, 1975, 459.
98. T. E. Cole and R. Pettit, *Tetrahedron Letters*, 1977, 781.
99. I. Degani and R. Fochi, *Synthesis*, 1976, 757; J. L. Fry, *J.C.S. Chem. Comm.*, 1974, 45.
100. H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, 1964, **86,** 1085; H. C. Brown and A. Tsukamoto, *ibid.*, 1964, **86,** 1089.
101. A. E. G. Miller, J. W. Biss, and L. H. Schwartzman, *J. Org. Chem.*, 1959, **24,** 627; S. Trofimenko, *ibid.*, 1964, **29,** 3046.
102. T. van Es and B. Staskun, *Org. Synth.*, 1971, **51,** 20.
103. R. W. Murray, *Accounts Chem. Res.*, 1968, **1,** 313.

104. P. S. Bailey and R. E. Erickson, *Org. Synth. Coll. Vol. 5*, 1973, 489, 494.
105. Kirk–Othmer, 'Encyclopaedia of Chemical Technology', Wiley, New York, 1970, vol. 21, pp. 180–196.
106. J. W. Baker and W. G. Moffitt, *J. Chem. Soc.*, 1931, 314.
107. J. W. Baker and C. K. Ingold, *J. Chem. Soc.*, 1930, 431.
108. C. A. Fetscher, *Org. Synth. Coll. Vol. 4*, 1963, 735.
109. H. T. Clarke and E. R. Taylor, *Org. Synth. Coll. Vol. 1*, 1941, 153.
110. D. E. Pearson, H. W. Pope, and W. W. Hargrove, *Org. Synth. Coll. Vol. 5*, 1973, 117.
111. Y. Ogata and A. Kawasaki, in 'Chemistry of the Carbonyl Group', ed. J. Zabicky, Interscience, New York, 1970, vol. 2, p. 1.
112. R. P. Bell and P. E. Sorenson, *J.C.S. Perkin II*, 1976, 1594; R. P. Bell, *Adv. Phys. Org. Chem.*, 1966, **4**, 1.
113. M. Byrn and M. Calvin, *J. Amer. Chem. Soc.*, 1966, **88**, 1916.
114. T. S. Davis, P. D. Feil, D. G. Kubler, and D. J. Wells, *J. Org. Chem.*, 1975, **40**, 1478.
115. V. Okano, L. do Amaral, and E. H. Cordes, *J. Amer. Chem. Soc.*, 1976, **98**, 4201.
116. F. C. Kokesh and R. E. Hall, *J. Org. Chem.*, 1975, **40**, 1632.
117. W. P. Jencks, 'Catalysis in Chemistry and Enzymology', McGraw Hill, New York, 1969, chapter 10; W. P. Jencks, *Progr. Phys. Org. Chem.*, 1964, **2**, 63; J. M. Sayer and W. P. Jencks, *J. Amer. Chem. Soc.*, 1973, **95**, 5637.
118. A. T. Nielsen and W. J. Houlihan, *Org. Reactions*, 1968, **16**, 1; H. O. House, 'Modern Synthetic Reactions', 2nd edn., Benjamin, Reading, Mass., 1972, pp. 629–682; R. L. Reeves, in 'Chemistry of the Carbonyl Group', ed. S. Patai, Interscience, New York, 1966, chapter 12.
119. H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, *J. Amer. Chem. Soc.*, 1973, **95**, 3310.
120. T. Mukaiyama, K. Banno, and K. Narasaka, *J. Amer. Chem. Soc.*, 1974, **96**, 7503.
121. R. Noyori, K. Yokoyama, J. Sakata, I. Kuwajima, E. Nakamura, and M. Shimizu, *J. Amer. Chem. Soc.*, 1977, **99**, 1267.
122. W. A. Kleschick, C. T. Buse, and C. H. Heathcock, *J. Amer. Chem. Soc.*, 1977, **99**, 247.
123. T. Mukaiyama and T. Inoue, *Chem. Letters*, 1976, 559.
124. E. P. Kohler and H. M. Chadwell, *Org. Synth. Coll. Vol. 1*, 1941, 78; G. A. Hill and G. M. Bramann, *ibid.*, p. 81.
125. C. R. Conard and M. A. Dolliver, *Org. Synth. Coll. Vol. 2*, 1943, 167.
126. M. Stiles, D. Wolf, and G. V. Hudson, *J. Amer. Chem. Soc.*, 1959, **81**, 628; S. A. Fine and P. D. Pulaski, *J. Org. Chem.*, 1973, **38**, 1747.
127. E. P. Kohler and E. M. Nygaard, *J. Amer. Chem. Soc.*, 1930, **52**, 4128.
128. G. Jones, *Org. Reactions*, 1967, **15**, 204.
129. I. A. Pearl and D. L. Beyer, *J. Org. Chem.*, 1951, **16**, 221.
130. J. M. Patterson, *Org. Synth. Coll. Vol. 5*, 1973, 585.
131. J. R. Johnson, *Org. Reactions*, 1942, **1**, 210.
132. M. S. Newman and B. J. Magerlein, *Org. Reactions*, 1949, **5**, 413; M. Ballester, *Chem. Rev.*, 1955, **55**, 283.
133. H. E. Zimmerman and L. Ahramjian, *J. Amer. Chem. Soc.*, 1960, **82**, 5459.
134. M. Ballester and P. D. Bartlett, *J. Amer. Chem. Soc.*, 1953, **75**, 2042.
135. J. Seyden-Penne, M. C. Roux-Schmitt, and A. Roux, *Tetrahedron*, 1970, **26**, 2649, 2657.
136. G. Kyriakakou and J. Seyden-Penne, *Tetrahedron Letters*, 1974, 1737.
137. W. L. Dilling, R. A. Hickner, and H. A. Farber, *J. Org. Chem.*, 1967, **32**, 3489.
138. D. J. Dagli, P. S. Yu, and J. Wemple, *J. Org. Chem.*, 1975, **40**, 3173.
139. J. D. White, J. B. Bremner, M. J. Dimsdale, and R. L. Garcea, *J. Amer. Chem. Soc.*, 1971, **93**, 281.
140. G. A. Koppel, *Tetrahedron Letters*, 1972, 1507.
141. H. L. J. Backstrom, *J. Amer. Chem. Soc.*, 1927, **49**, 1460.
142. K. B. Wiberg and R. Stewart, *J. Amer. Chem. Soc.*, 1955, **77**, 1786; F. Freeman, J. B. Brant, N. B. Hester, A. A. Kamego, M. L. Kasner, T. G. McLaughlin, and E. W. Paull, *J. Org. Chem.*, 1970, **35**, 982.
143. R. L. Shriner and E. C. Kleiderer, *Org. Synth. Coll. Vol. 2*, 1943, 538.
144. K. B. Wiberg and G. Szeimies, *J. Amer. Chem. Soc.*, 1974, **96**, 1889; J. Rocek and C.-S. Ng, *ibid.*, p. 2840.
145. R. R. Burtner and J. W. Cusic, *J. Amer. Chem. Soc.*, 1943, **65**, 262.
146. E. J. Corey, N. W. Gilman, and B. E. Ganem, *J. Amer. Chem. Soc.*, 1968, **90**, 5616; N. W. Gilman, *Chem. Comm.*, 1971, 733.
147. A. Nishihara and I. Kubota, *J. Org. Chem.*, 1968, **33**, 2525; J. Castells, H. Llitjos, and M. Moreno-Manas, *Tetrahedron Letters*, 1977, 205; J. C. Trisler and S. K. McKinney, *ibid.*, 1977, 3125.
148. K. Nakagawa, H. Onoue, and K. Minami, *Chem. Comm.*, 1966, 17.
149. A. von Wacek and H. O. Eppinger, *Chem. Ber.*, 1940, **73**, 644.
150. Y. Ogata and Y. Sawaki, *J. Amer. Chem. Soc.*, 1972, **94**, 4189; *J. Org. Chem.*, 1969, **34**, 3985.
151. I. M. Godfrey, M. V. Sargent, and J. A. Elix, *J.C.S. Perkin I*, 1974, 1353.
152. P. Djura, M. V. Sargent, and P. Vogel, *J.C.S. Perkin I*, 1976, 147.
153. M. F. Ansell, A. F. Gosden, V. J. Leslie, and R. A. Murray, *J. Chem. Soc. (C)*, 1971, 1401.
154. M. D. Rausch, W. E. McEwen, and J. Kleinberg, *Chem. Rev.*, 1957, **57**, 417.
155. D. D. Davis and W. B. Bigelow, *J. Amer. Chem. Soc.*, 1970, **92**, 5127.
156. J. H. Stocker and R. M. Jenevein, *J. Org. Chem.*, 1968, **33**, 294, 2145.
157. A. A. P. Schreibmann, *Tetrahedron Letters*, 1970, 4271; M. R. Rifi, in 'Techniques of Chemistry', ed. N. L. Weinberg, Wiley-Interscience, New York, 1975, vol. 5, chapter VIII, p. 87.

158. J. Grimshaw and J. S. Ramsey, *J. Chem. Soc.* (*C*), 1966, 653.
159. E. J. Corey, R. L. Danheiser, and S. Chandrasekaran, *J. Org. Chem.*, 1976, **41,** 260.
160. D. G. Botteron and G. Wood, *J. Org. Chem.*, 1965, **30,** 3871.
161. H. O. House, 'Modern Synthetic Reactions', 2nd edn., Benjamin, Reading, Mass., 1972, p. 45.
162. E. R. H. Walker, *Chem. Soc. Rev.*, 1976, **5,** 23.
163. C. S. Sell, *Austral. J. Chem.*, 1975, **28,** 1383.
164. G. H. Posner, A. W. Runquist, and M. J. Chapelaine, *J. Org. Chem.*, 1977, **42,** 1202.
165. Y. Maki, K. Kikuchi, H. Sugiyama, and S. Seto, *Tetrahedron Letters*, 1977, 263.
166. G. W. Gribble and D. C. Ferguson, *J.C.S. Chem. Comm.*, 1975, 535.
167. Y. Yamamoto, H. Toi, A. Sonoda and S.-I. Murahashi, *J. Amer. Chem. Soc.*, 1976, **98,** 1965.
168. P. N. Rylander, 'Catalytic Hydrogenation over Platinum', Academic. New York, 1967.
169. D. Todd, *Org. Reactions*, 1948, **4,** 378; C. A. Buehler and D. E. Pearson, *Chem. Rev.*, 1974, **74,** 83; Ref. 161, p. 228.
170. E. L. Martin, *Org. Reactions*, 1942, **1,** 155; E. Vedejs, *ibid.*, 1975, **22,** 401.
171. G. Brieger and T.-H. Fu, *J.C.S. Chem. Comm.*, 1976, 757; G. Brieger and T. J. Nestrick, *Chem. Rev.*, 1974, **74,** 567.
172. J. E. McMurry, *Accounts Chem. Res.*, 1974, **7,** 281.
173. J. E. McMurry and M. P. Fleming, *J. Amer. Chem. Soc.*, 1974, **96,** 4708.
174. S. Tyrlik and I. Wolochowicz, *Bull. Soc. chim. France*, 1973, 2147.
175. T. Mukaiyama, T. Sato, and J. Hanna, *Chem. Letters*, 1973, 1041.
176. K. B. Sharpless, M. A. Umbreit, M. T. Nieh, and T. C. Flood, *J. Amer. Chem. Soc.*, 1972, **94,** 6538; E. J. Corey, R. L. Danheiser, and S. Chandrasekaran, *J. Org. Chem.*, 1976, **41,** 260.
177. T. Minami, M. Matsumoto, and T. Agawa, *J.C.S. Chem. Comm.*, 1976, 1053.
178. L. Horner, P. Beck, and V. G. Toscano, *Chem. Ber.*, 1961, **94,** 1323.
179. V. Mark, *J. Amer. Chem. Soc.*, 1963, 85, 1884; *Org. Synth. Coll. Vol. 5*, 1973, 358.
180. S. C. Agarwal and B. L. Van Duuren, *J. Org. Chem.*, 1975, **40,** 2307; *ibid.*, 1977, **42,** 2730; R. G. Harvey, S. H. Goh, and C. Cortez, *J. Amer. Chem. Soc.*, 1975, **97,** 3468.
181. S. Cannizzaro, *Annalen*, 1853, **88,** 129.
182. T. A. Geissman, *Org. Reactions*, 1944, **2,** 94.
183. G. W. Gokel, H. M. Gerdes, and N. W. Rebert, *Tetrahedron Letters*, 1976, 653.
184. E. J. Forbes and M. J. Gregory, *J. Chem. Soc.* (*B*), 1968, 205.
185. D. R. Lachowicz and R. H. Gritter, *J. Org. Chem.*, 1963, **28,** 106.
186. E. J. Forbes and M. J. Gregory, *J. Chem. Soc.* (*B*), 1968, 207.
187. E. P. B. van der Maeden, H. Steinberg, and Th. J. de Boer, *Rec. Trav. chim.*, 1972, **91,** 221.
188. C. R. Hauser, P. J. Hamrick, Jr., and A. T. Stewart, *J. Org. Chem.*, 1956, **21,** 260.
189. K. B. Wiberg, *J. Amer. Chem. Soc.*, 1954, **76,** 5371.
190. A. Lachman, *J. Amer. Chem. Soc.*, 1923, **45,** 2356.
191. Y. Ogata and A. Kawasaki, *Tetrahedron*, 1969, **25,** 929, 2845.
192. D. Luther and H. Koch, *Chem. Ber.*, 1966, **99,** 2227.
193. E. Pfeil, *Chem. Ber.*, 1951, **84,** 229.
194. W. S. Ide and J. S. Buck, *Org. Reactions*, 1948, **4,** 269.
195. J. P. Kuebrich, R. L. Schowen, M. S. Wang, and M. E. Lupes, *J. Amer. Chem. Soc.*, 1971, **93,** 1214.
196. A. Lapworth, *J. Chem. Soc.*, 1903, 995; *ibid.*, 1904, 1206.
197. R. Breslow, *J. Amer. Chem. Soc.*, 1958, **80,** 3719.
198. K. B. Wiberg, *J. Amer. Chem. Soc.*, 1954, **76,** 5371.
199. J. J. Mieyal, G. Bantle, R. G. Votaw, I. A. Rosner, and H. Z. Sable, *J. Biol. Chem.*, 1971, **246,** 5213.
200. H. Stetter, R. Y. Rämsch, and H. Kuhlmann, *Synthesis*, 1976, 733.
201. J. Solodar, *Tetrahedron Letters*, 1971, 287.
202. D. A. White and M. M. Baizer, *J.C.S. Perkin I*, 1973, 2230.
203. W. Tagaki and H. Hara, *J.C.S. Chem. Comm.*, 1973, 891.
204. S. Akabori, M. Ohtomi, and K. Arai, *Bull. Chem. Soc. Japan*, 1976, **49,** 746.
205. G. H. Hakimelahi, C. B. Boyce and H. S. Kasmai, *Helv. Chim. Acta*, 1977, **60,** 342.
206. J. S. Buck and W. S. Ide, *J. Amer. Chem. Soc.*, 1932, **54,** 3302.
207. R. H. Kratzer, K. L. Paciorek, and D. W. Karle, *J. Org. Chem.*, 1976, **41,** 2230.
208. E. M. Levi and C. R. Hauser, *J. Org. Chem.*, 1969, **34,** 2482.
209. H. Wynberg and H. J. M. Sinnige, *Rec. Trav. chim.*, 1969, **88,** 1244.
210. H. Stetter, *Angew. Chem. Internat. Edn.*, 1976, **15,** 639.
211. H. Stetter and G. Dambkes, *Synthesis*, 1977, 403.
212. O. W. Lever, Jr., *Tetrahedron*, 1976, **32,** 1943.
213. E. Aufderhaar, J. E. Baldwin, D. H. R. Barton, D. J. Faulkner, and M. Slaytor, *J. Chem. Soc.* (*C*), 1971, 2175.
214. G. Stork and L. Maldonado, *J. Amer. Chem. Soc.*, 1971, **93,** 5286.
215. G. Stork and T. Takahashi, *J. Amer. Chem. Soc.*, 1977, **99,** 1275.
216. T. Tsuji, in 'Organic Syntheses via Metal Carbonyls', ed. I. Wender and P. Pino, Wiley-Interscience, New York, 1977, vol. 2, p. 595.
217. J. O. Hawthorne and M. H. Wilt, *J. Org. Chem.*, 1960, **25,** 2215.
218. J. Blum, R. Oppenheimer, and E. D. Bergmann, *J. Amer. Chem. Soc.*, 1967, **89,** 2338.

219. K. Ohno and J. Tsuji, *J. Amer. Chem. Soc.*, 1968, **90,** 94, 99.
220. K. Matsuzawa, T. Kimura, Y. Murao, and H. Hashizume, *Ger. Offen.*, 2232253 (*Chem. Abs.*, 1973, **78,** 98244, 84043).
221. H. M. Walborsky and L. E. Allen, *J. Amer. Chem. Soc.*, 1971, **93,** 5465.
222. J. H. Stocker and D. H. Kern, *J. Org. Chem.*, 1968, **33,** 291.
223. G. L. Closs and A. D. Trifunac, *J. Amer. Chem. Soc.*, 1970, **92,** 7227; P. G. Frith and K. A. McLaughlin, *J.C.S. Faraday II*, 1975, 1984.
224. H. D. Roth, *Mol. Photochem.*, 1973, **5,** 91; R. Kaptein, in 'Advances in Free Radical Chemistry', ed. G. H. Williams, Elek, London, 1975, vol. 5, chapter 5; 'Chemically Induced Magnetic Polarisation', ed. A. R. Lepley and G. L. Closs, Wiley, New York, 1973.
225. M. Niclause, J. Lemaire, and M. Letort, *Adv. Photochem.*, 1966, **4,** 25; J. C. Andre, M. Bouchy, and M. Niclause, *J. Photochem.*, 1976, **5,** 1; H. D. Hartzler, *Pure Appl. Chem.*, 1977, **49,** 353.
226. H. J. L. Backstrom and U. Riiner, *Acta Chem. Scand.*, 1966, **20,** 630.
227. N. Kawabe, K. Okada, and M. Ohno, *J. Org. Chem.*, 1972, **37,** 4210.
228. D. R. Arnold, *Adv. Photochem.*, 1968, **6,** 301.
229. N. C. Yang, M. Kimura, and W. Eisenhardt, *J. Amer. Chem. Soc.*, 1973, **95,** 5058.
230. R. B. Woodward and R. Hoffmann, 'The Conservation of Orbital Symmetry', Academic, New York, 1971.
231. N. C. Yang and W. Chiang, *J. Amer. Chem. Soc.*, 1977, **99,** 3163.
232. G. Jones, II, M. A. Aquadro and M. A. Carmody, *J.C.S. Chem. Comm.*, 1975, 206.
233. L. E. Friedrich and J. D. Bower, *J. Amer. Chem. Soc.*, 1973, **95,** 6869.
234. J. S. Bradshaw, R. D. Knudsen, and W. W. Parish, *J. Org. Chem.*, 1975, **40,** 529.
235. H. Kuntzel, H. Wolf, and K. Schaffner, *Helv. Chim. Acta*, 1971, **54,** 868.
236. K. Schaffner, H. Wolf, S. M. Rosenfeld, R. G. Lawler, and H. R. Ward, *J. Amer. Chem. Soc.*, 1972, **94,** 6553.
237. A. McKillop, J. D. Hunt, F. Kienzle, E. Bigham, and E. C. Taylor, *J. Amer. Chem. Soc.*, 1973, **95,** 3635.
238. F. Freeman, R. H. DuBois, and T. G. McLaughlin, *Org. Synth.*, 1971, **51,** 4; F. Freeman, P. D. McCart, and N. J. Yamachika, *J. Amer. Chem. Soc.*, 1970, **92,** 4621.
239. D. J. Reif and H. O. House, *Org. Synth. Coll. Vol. 4*, 1963, 375; R. E. Parker and N. S. Isaacs, *Chem. Rev.*, 1959, **59,** 737.
240. C. F. H. Allen and J. Van Allen, *Org. Synth. Coll. Vol. 3*, 1955, 733.
241. P. Pino, F. Piacenti, and M. Bianchi, in 'Organic Synthesis via Metal Carbonyls', ed. I. Wender and P. Pino, Wiley, New York, 1977, vol. 2, p. 43.
242. F. W. Lichtenthaler, *Angew Chem. Internat. Edn.*, 1964, **3,** 211; 'New Methods of Preparative Organic Chemistry', ed. W. Foerst, Verlag, Weinheim, 1969, vol. IV, p. 155.
243. V. Bruckner, A. Karczag, K. Kormendy, M. Meszaros, and J. Tomasz, *Tetrahedron Letters*, 1960, 5.
244. F. Weygand, *Chem. Ber.*, 1942, **75,** 625.
245. A. F. M. Iqbal, *Helv. Chim. Acta*, 1972, **55,** 798.
246. E. C. Horning, M. G. Horning, and D. A. Dimmig, *Org. Synth. Coll. Vol. 3*, 1955, 165.
247. D. S. Kemp and R. B. Woodward, *Tetrahedron*, 1965, **21,** 3019.
248. E. E. Schweizer, *J. Amer. Chem. Soc.*, 1964, **86,** 2744.

5.4
Aromatic Ketones

T. LAIRD
Imperial Chemical Industries Ltd., Blackley, Manchester

5.4.1 INTRODUCTION
5.4.2 SYNTHESIS OF AROMATIC KETONES
5.4.2.1 Friedel–Crafts acylation 1165
5.4.2.2 The Houben–Hoesch reaction 1169
5.4.2.3 Fries rearrangement
5.4.2.4 Synthesis of aromatic ketones using arene–metal complexes 1173
5.4.3 ELECTROPHILIC AROMATIC SUBSTITUTION 1174
5.4.4 NUCLEOPHILIC ADDITIONS TO THE CARBONYL GROUP
5.4.4.1 Addition of Grignard reagents to aromatic ketones 1176
5.4.5 REDUCTION OF AROMATIC KETONES 1179
5.4.5.1 Asymmetric reduction of aromatic ketones 1181
5.4.5.2 Reductive coupling of aromatic ketones 1183
5.4.6 WILLGERODT REACTION 1185
5.4.7 OXYTHALLATION OF AROMATIC KETONES 1186
5.4.8 PHOTOCHEMISTRY OF AROMATIC KETONES 1189
5.4.8.1 α-Cleavage 1190
5.4.8.2 Photoreduction 1190
5.4.8.3 Intramolecular hydrogen abstraction (Norrish Type II processes) 1192
5.4.8.4 Biomimetic chemistry 1193
5.4.8.5 Photoenolization 1195
5.4.8.6 Photocycloadditions 1197
5.4.9 AROMATIC α-HYDROXYKETONES: BENZOIN AND ITS DERIVATIVES 1198
5.4.10 AROMATIC DIKETONES 1201
5.4.11 AROMATIC TRIKETONES 1203
5.4.12 AROMATIC α-HALOKETONES 1205
5.4.13 ARYLKETENS 1206

5.4.1 INTRODUCTION

The general reactions of aromatic ketones are similar to those of aliphatic ketones except that the aromatic nucleus, as in aromatic aldehydes, reduces the electron deficiency at the carbonyl carbon atom so that the carbonyl group is much less susceptible to nucleophilic attack. The carbonyl group of aromatic ketones, particularly diaryl ketones, is

more sterically hindered than the carbonyl group of aliphatic ketones, further reducing its reactivity towards nucleophiles. Indeed, 2,6-disubstituted aryl ketones, which are very highly hindered, are occasionally attacked preferentially in the aromatic ring (see Section 5.4.4.1). π-Orbital overlap between the carbonyl group and aromatic ring is important and nucleophilic addition to the carbonyl group is thermodynamically less favourable for aromatic than for aliphatic carbonyl compounds, owing to the greater loss in resonance energy in converting a trigonal carbon atom to a tetrahedral centre. However, in many condensations where a double bond is eventually formed in a two-stage addition–dehydration sequence, the overall process may be exothermic, and, under suitable conditions, the reactions can be driven to completion.

In discussing the chemistry of aromatic ketones, it is inevitable that there will be some overlap between Chapters 5.1 and 5.2 (aliphatic aldehydes and ketones) and Chapter 5.3 (aromatic aldehydes). Reactions which are applicable to all carbonyl compounds have therefore been discussed very briefly in this section or not at all, and the emphasis has been placed on the differences between aliphatic and aromatic ketones. If a typical ketonic group reaction has not therefore been mentioned in this section, it should be assumed that aromatic ketones behave in a similar fashion to aliphatic ketones.

Aryl alkyl ketones (ArCOR) are generally colourless or pale yellow water-immiscible liquids or solids having low melting points (Table 1). The simplest member of the series, acetophenone (**1**), occurs naturally in certain essential oils and is used in perfumery. It is obtained industrially as a by-product (0.8% yield) in the oxidation of cumene ($PhCHMe_2$) to phenol and acetone. This is now the major industrial synthetic route. Since (**1**) is easily separated from the other products, this route can provide sufficient acetophenone for use as an intermediate in the fine chemicals industry, *e.g.* for the synthesis of pharmaceuticals, resins, and dyes. Acetophenone is occasionally used as a solvent, since it has a high boiling point, is stable and relatively non-toxic, and has a pleasant odour. Substituted acetophenones (Table 1), which are used to a much lesser extent in industry — mostly in the perfumery business — are manufactured by Friedel–Crafts acylation (see Section 5.4.2).

Diaryl ketones (Ar_2CO) are white or pale yellow water-immiscible solids having low melting points (Table 1). The simplest diaryl ketone, benzophenone (**5**), is a white crystalline solid, m.p. 48–49 °C, but can exist in three other crystalline modifications having even lower melting points. It is used (i) in perfumery, (ii) as a photosensitizer, (iii) as an inhibitor of polymerization for styrene, and (iv) as a mild oxidant. Benzophenone is normally manufactured *via* Friedel–Crafts acylation of benzene (see Section 5.4.2.1); other benzophenones can also be manufactured by scale-up of standard laboratory methods. The exception is fluorenone (**16**) which is manufactured by dehydration and decarboxylation of the dicarboxylic acid (**17**), itself readily available by oxidation of phenanthrene. An important industrial benzophenone derivative is bis-(4-dimethylaminophenyl) ketone (**18**), often called Michler's ketone, which is used as an intermediate in the synthesis of triarylmethane dyes such as Crystal Violet (**19**).

The spectroscopic differences between aliphatic and aromatic ketones are relatively minor. The effect of the aromatic ring on the carbonyl stretching absorption in the infrared spectrum is to cause a shift from ~5.8 μm (alkyl ketones, CCl_4 solution) to 5.92 μm (acetophenone) and 6.0 μm (benzophenone). Electron-donating substituents in the *meta* and *para* positions cause absorption at longer wavelengths and electron-withdrawing substituents have the opposite effect; good correlations of wavelengths for carbonyl absorption with Hammett σ constants are observed.[1] In many cases an *ortho* substituent causes a shift similar to the corresponding *para* isomer, but if chelation to the carbonyl group is possible, absorption at longer wavelength occurs (*e.g.* 4-$NH_2C_6H_4COMe$, 5.96 μm; 2-$NH_2C_6H_4COMe$, 6.06 μm). In some cases, particularly with *ortho*-halogenated ketones, two carbonyl bands are observed;[2] this is caused by different conformations being observable at room temperature, in a manner similar to that described for aromatic aldehydes (see Chapter 5.3). Acetophenones substituted α to the carbonyl group also show a doublet carbonyl in the i.r. spectrum owing to *cis–gauche*

TABLE 1

Physical Properties of Aromatic Ketones[a]

	B.p. (°C/760 *mmHg*)[b]	*M.p.* (°C)	*Semicarbazone m.p.* (°C)	2,4-*Dinitrophenylhydrazone m.p.* (°C)
Acetophenones				
Acetophenone (**1**)	202	20	198–199	238–240
4-Methoxyacetophenone	258	37–38	197–198	232
4-Hydroxyacetophenone	—	109	199	210
4-Methylacetophenone	226	28	204–205	260
3-Methylacetophenone	220	—	203	207
2-Methylacetophenone	214–216	—	210	151–161
4-Chloroacetophenone	232–236	12	204 (160)	231
4-Bromoacetophenone	225	51	208	237
4-Aminoacetophenone	294	106	250	266–267
α-Chloroacetophenone (**2**)[c]	244	59	156	213–215
α-Bromoacetophenone (**3**)[d]	—	50–51	146	212–213
α-Hydroxyacetophenone (**4**)[e]	118[f]	117–118	146	—
Benzophenones				
Benzophenone (**5**)	306	48–49	167	238–239
4-Methoxybenzophenone	354	62–64	—	180
4-Hydroxybenzophenone	—	134–135	194	242
4-Methylbenzophenone	326	55–60	121–122	202
4,4′-Dimethylbenzophenone	335	95	143–144	218–219
4-Chlorobenzophenone	—	78	—	185
4-Bromobenzophenone	—	82	350	230
Miscellaneous				
Propiophenone (**6**)	218–220	20	173–174	190
Isobutyrophenone (**7**)	222	—	181	163
n-Butyrophenone (**8**)	230	11–13	191	190
n-Valerophenone (**9**)	248	—	160	166
1-Acetylnaphthalene (**10**)	302	34	289 (232)	—
2-Acetylnaphthalene (**11**)	301	54–56	237	262
Phenyl benzyl ketone (**12**)[g]	321	60	148	204
Benzil (**13**)	347	95	243–244[i]	185–189[i]
(±)-Benzoin (**14**)	344	133	205–206	245
Indane-1,2,3-trione (**15**)[h]	—	243	—	—

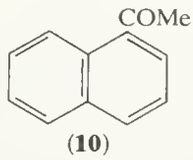
[a] 'Handbook of Tables for Organic Compound Identification', ed. Z. Rappoport, Chemical Rubber Company, Cleveland, 3rd edn., 1967. [b] At 760 mmHg except where stated. [c] Phenacyl chloride. [d] Phenacyl bromide. [e] Phenacyl alcohol. [f] B.p. at 11 mmHg. [g] Deoxybenzoin. [h] The hydrated form is known as 'ninhydrin'. [i] Bis-derivative.

PhCOR

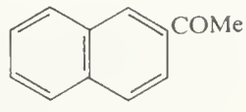
(**1**) R = Me
(**5**) R = Ph
(**6**) R = Et
(**7**) R = Pr^i
(**8**) R = Pr^n
(**9**) R = Bu^n
(**12**) R = CH_2Ph
(**13**) R = COPh
(**14**) R = CH(OH)Ph

$PhCOCH_2X$

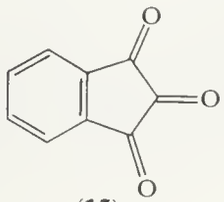
(**2**) X = Cl
(**3**) X = Br
(**4**) X = OH



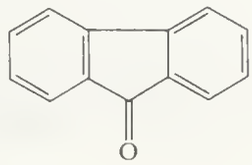
(**10**)



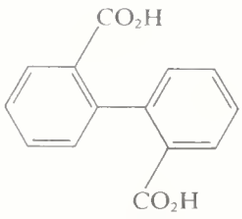
(**11**)



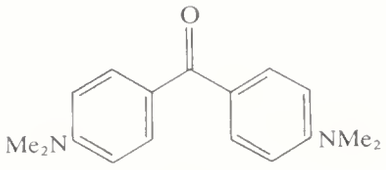
(**15**)



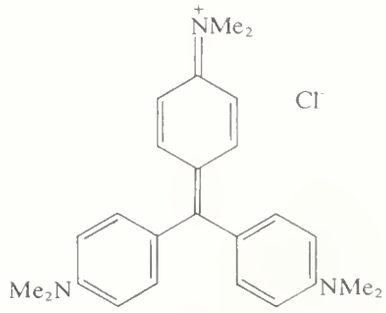
(**16**)



(17)

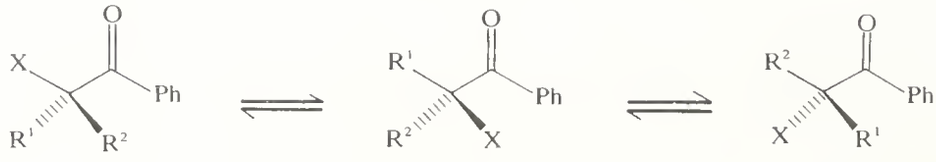


(18)



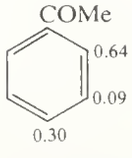
(19)

isomerism (equation 1), the *cis* conformation giving rise to a carbonyl absorption of lower wavelength (*e.g.* $PhCOCH_2Ph$ (**12**), 5.89 μm, *cis*; 5.94 μm *gauche*).

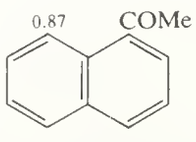


(1)

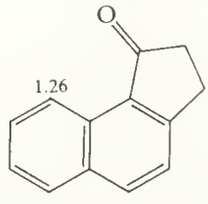
Attachment of an acyl group (RCO) to an aromatic ring causes a marked downfield shift of the *ortho* protons and, to a limited extent, the *para* protons in the ^1H nuclear magnetic resonance spectrum. In polycyclic aromatic ketones, in which a hydrogen atom on an aromatic ring is in a *peri* position, the adjacent carbonyl group causes pronounced deshielding, particularly if the carbonyl group is fixed in a ring.[3] This is illustrated by the progressive downfield shifts (quoted in p.p.m. difference from the parent hydrocarbon) shown in formulae (**20**)–(**23**) as the carbonyl group is forced nearer to the *peri* hydrogen.[4]



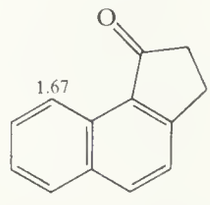
(20)



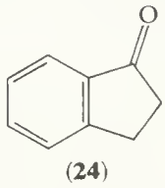
(21)



(22)



(23)



(24)

The protons attached to the carbon atom α to the carbonyl group in aryl alkyl ketones are also shifted downfield by as much as 0.5 p.p.m. (CH_2 in $PhCOCH_2R$) or 1 p.p.m. (*CH* in $PhCOCHR^1R^2$) when compared with aliphatic ketones. This downfield shift does not occur to the same extent, however, if the carbonyl group is in a ring, *e.g.* indan-1-one (**24**); this indicates that steric interaction between *ortho* protons and α methylene or methine protons in aryl alkyl ketones must be at least partly responsible for the downfield shift.[3]

The ultraviolet spectra of aromatic ketones are discussed in Section 5.4.8 in relation to photochemistry. The mass spectra of aromatic ketones are usually relatively simple, the molecular ion fragmenting *via* α-cleavage, leading to an aroyl cation ($ArCO^+$) and an alkyl or aryl radical. For ketones having γ-hydrogen atoms, cleavage with γ-H transfer competes with α-scission in a manner analogous to that observed in aliphatic ketones.

5.4.2 SYNTHESIS OF AROMATIC KETONES

Aromatic ketones can be synthesized by most of the routes which have been described in Chapter 5.2 for aliphatic ketones, and no further discussion of these routes is necessary here. In addition, there are several methods which are particularly suitable for aromatic ketones, the first three methods being examples of electrophilic substitution in an aromatic ring, the fourth an unusual example involving nucleophilic substitution which has recently been examined.

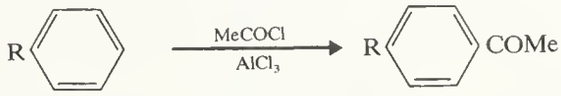
5.4.2.1 Friedel–Crafts acylation

The most important method for the synthesis of aryl ketones is the direct acylation of the aromatic ring using an acid, acid halide, anhydride, or keten, usually in the presence of an acid catalyst such as aluminium chloride.[5] The Friedel–Crafts reaction is applicable to a variety of substrates; mono- and poly-cyclic aromatics bearing many different substituents normally give excellent yields of monoacyl derivatives (Tables 2 and 3). Since the reaction is essentially the nucleophilic attack by the aromatic ring on a carbonyl group, the main function of the catalyst is to increase the carbenium ion character of the carbonyl carbon atom so that attack by the weakly nucleophilic aromatic can take place. Proton acid catalysts (*e.g.* H_2SO_4, HF, CF_3SO_3H) react with the acyl component, generating an acylium ion or its equivalent. Lewis acids ($AlCl_3$, $ZnCl_2$, BF_3, *etc.*) also give rise to the same acylium ions or their equivalents (Scheme 1) and are the most commonly used catalysts. Although the term catalyst is often used, it must be stressed that in most cases one equivalent of Lewis acid must be used, since the products complex with the Lewis acid. Recently, however, examples of genuine catalysis have been reported.[6]

Catalysts which favour acylium ion formation are the most effective; normally the strongest acids are the best (CF_3SO_3H, $AlCl_3$). The acylating species is formed quickly and in the rate-determining step attacks the aromatic ring, presumably *via* a σ-complex as

TABLE 2

Acylation of Substituted Benzenes



R	*Solvent*	*Yield (%)*	*Ref.*
H	Benzene	97	a
Me	Toluene	97	a
Et	Carbon tetrachloride	98	b
Cl	Chlorobenzene	97	a
Br	Bromobenzene	80	a
OH	Nitrobenzene	74[c]	c
OMe	Anisole	100	a
OPh	Carbon tetrachloride	90	b
SMe	Chloroform	98	d
NHCOMe	Sulphuric acid	85	e
Ph	Carbon disulphide	90	f

[a] F. Smeets and J. Verhulst, *Bull. Soc. chim. belges*, 1952, **61**, 694. [b] D. T. Mowry, M. Renoll, and W. F. Huber, *J. Amer. Chem. Soc.*, 1946, **68**, 1105. [c] +16% *o*-Hydroxyacetophenone. N. M. Cullinane and B. F. R Edwards, *J. Appl. Chem.*, 1959, **9**, 133. [d] R. A. Cutler, R. J. Stenger, and C. M. Suter, *J. Amer. Chem. Soc.*, 1952, **74**, 5475. [e] F. Kunckell, *Ber.*, 1900, **33**, 2641. [f] C. V. Ferriss and E. E. Turner, *J. Chem. Soc.*, 1920, **117**, 1140.

in other electrophilic aromatic substitutions. The resultant cyclohexadienyl cation then loses a proton to give the aromatic ketone, which may complex with any Lewis acid present (Scheme 1).

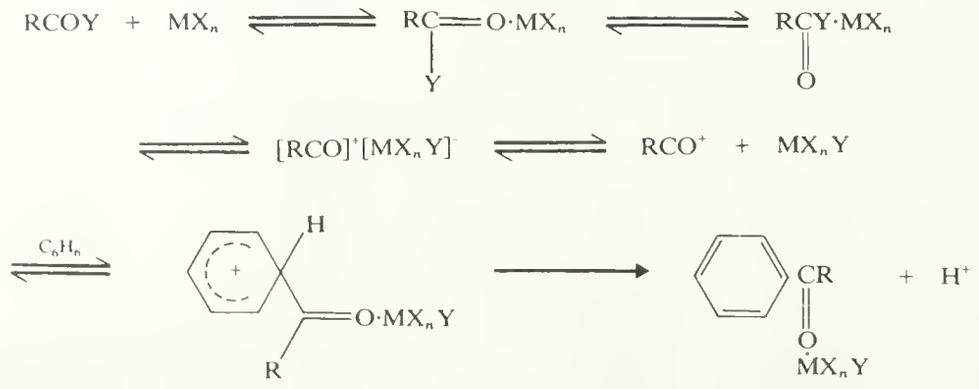
TABLE 3

Acylation of Polycyclic Aromatic Hydrocarbons using Acetyl Chloride–Aluminium Chloride

Hydrocarbon	*Solvent*	*Product*	*Yield (%)*	*Ref.*
Naphthalene	$(CH_2Cl)_2$	1-acetyl	92	a
		2-acetyl	2	a
	$(CH_2Cl)_2$	1-acetyl	33	a
	+ $PhNO_2$(1-equiv)	2-acetyl	49	a
Anthracene	C_6H_6	9-acetyl	58	b
		1-acetyl	16	b
		2-acetyl	4	b
	$PhNO_2$	1-acetyl	4	c
		2-acetyl	10	c
Pyrene	$PhNO_2$	1-acetyl	88	d
Chrysene	CH_2Cl_2	6-acetyl	75	e

[a] G. Baddeley, *J. Chem. Soc.*, 1949, S99. [b] P. H. Gore and C. K. Thadani, *J. Chem. Soc.* (*C*), 1966, 1729. [c] P. H. Gore and C. K. Thadani, *J. Chem. Soc.* (*C*), 1967, 1498. [d] W. E. Bachmann and M. Carmack, *J. Amer. Chem. Soc.*, 1941, **63,** 2494. [e] W. Carruthers, *J. Chem. Soc.*, 1953, 3486.

The exact details of the mechanism have been the subject of much discussion, particularly on the nature of the acylating species. Stable acylium (oxocarbenium) hexafluoroantimonate salts have been isolated and the crystal structure contains a linear $R\overset{+}{C}{=}O$ grouping;[7] these salts are very powerful acylating agents.[8] Complexes of aluminium chloride and benzoyl chloride, however, have also been examined by crystallographic methods and coordination was shown to be between the aluminium and oxygen, rather than involving chlorine.[9] It is likely that the acylating species varies from case to case and may be any of the species formulated in Scheme 1.



SCHEME 1

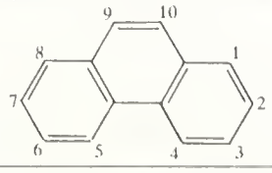
The nature of the solvent is an extremely important factor in Friedel–Crafts reactions. Water and hydroxylic solvents must be rigorously excluded since they react with the acylating agent and Lewis acid catalysts. The usual solvents are nitrobenzene, nitroalkenes, carbon disulphide, ethers, or chlorinated hydrocarbons. The reaction proceeds more efficiently if the catalyst is soluble, but many Lewis acids such as aluminium chloride are insoluble and the reaction is conducted in a heterogeneous manner. Nitrobenzene and ethers, however, coordinate with aluminium chloride and confer some solubility. Ethylene dichloride is a good solvent for acyl halide–aluminium chloride complexes so that any

excess of Lewis acid can be removed by filtration; this procedure, known as the Perrier method, allows the acylation to be carried out using stoichiometric quantities of acylating agent and 'catalyst', with the substrate being added last. This is an important method for the acylation of polyalkyl aromatics, where excess of aluminium chloride can cause isomerization of alkyl groups in the reactant, *e.g. o*- to *m*-xylene.[10]

The profound effect of a change in solvent is best illustrated by the results on the acylation of polycyclic aromatics, which lead to different isomeric product ratios in different solvents. For example, the acetylation of phenanthrene gives a mixture of five monoacetylphenanthrenes, the yields being dependent on solvent (see Table 4).[11] The solvent competes with acetyl chloride to form a complex with aluminium chloride and this may determine the nature and size of the acylating species. The latter effect is particularly important in determining the amounts of the more hindered isomers (1-, 4-, and 9-isomers). Thus in nitrobenzene, which becomes associated with the acetyl chloride–aluminium chloride complex, the bulky reagent preferentially attacks at the less hindered 2- and 3-positions (Table 4).[11]

TABLE 4

Acetylation of Phenanthrene[a]



Solvent	*Acetylphenanthrene isomer* (%) 1–	2–	3–	4–	9–
$PhNO_2$	3	23	66	3	5
$MeNO_2$	3	27	63	1	6
C_6H_6	14	9	47	1	29
$C_2H_4Cl_2$	1	4	36	5	54
$CHCl_3$	17	7	38	1	37
CS_2	5	11	47	6	31

[a] See ref. 11.

Even the presence of one equivalent of nitrobenzene can alter dramatically the product ratio, *e.g.* in the acetylation of naphthalene (Table 3).[12] In this case the increased size of the acylating agent causes the 2-acetyl derivative to be formed, but, in cases where the acylation is reversible, it seems likely that the product ratio reflects the thermodynamic stabilities of the products. Equilibration of the initially formed product can occur when the electrophilicity of the reagent is diminished by complexing with nitrobenzene.[13]

Acylation of monosubstituted benzene derivatives normally leads to almost exclusive *para* substitution (the *o*:*p* ratio is 30:1 for the acetylation of toluene), but can be affected by the electrophilicity of the acylating agent.[14] The more electrophilic the acylating agent, then the more the transition state resembles the starting materials, and selectivity is lowered as steric factors become less important (see Table 5).[14]

TABLE 5

Acylation of Toluene ($RCOCl/AlCl_3$)[a]

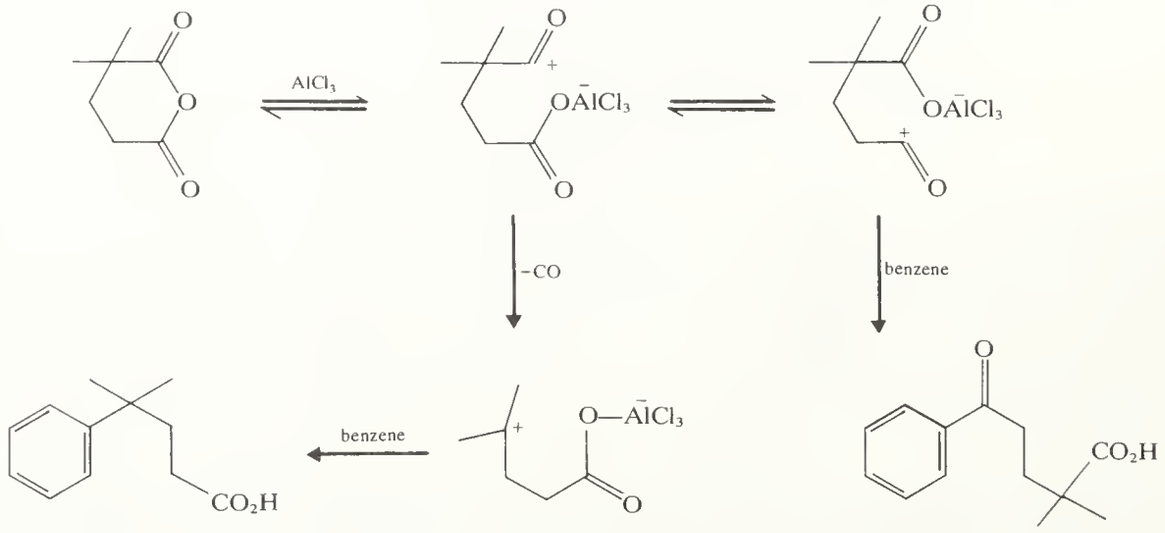
R	*Solvent*	*Products* ($RCOC_6H_4Me$) *ortho* (%)	*meta* (%)	*para* (%)
Me	CS_2	2.5	2.0	95.5
Pr^i	CS_2	3.2	2.4	94.4
CH_2Cl	CS_2	11.1	2.3	86.6
$CHCl_2$	CS_2	17.3	3.2	79.5
Ph	$MeNO_2$	8.1	1.2	90.7
C_6F_5	$MeNO_2$	35.4	7.8	56.8
$2,4\text{-}(NO_2)_2$	$MeNO_2$	42.4	3.0	54.6

[a] See Ref. 14.

Anhydrides are used much less often than acyl halides for the acylation of aromatics. Recently, however, it has been shown that mixed trifluoromethanesulphonic–carboxylic anhydrides, *e.g.* (**25**), prepared by the reaction of an acyl halide with silver trifluoromethanesulphonate, are extremely powerful acylating agents.[15] Benzene is converted to benzophenone in 92% yield at room temperature in the absence of any catalyst (equation 2). The trifluoromethanesulphonic acid can be recovered as the barium salt.

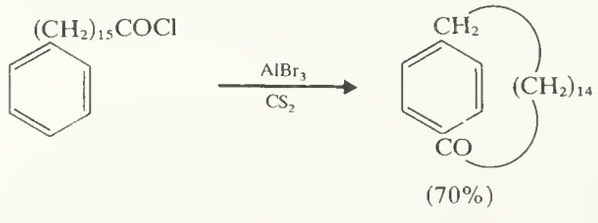
$$\mathrm{PhCOCl} \xrightarrow[-\mathrm{AgCl}]{\mathrm{CF_3SO_3Ag}} \underset{(\mathbf{25})}{\mathrm{PhCOOSO_2CF_3}} \xrightarrow[20\,^\circ\mathrm{C},\,5\,\mathrm{h}]{\text{benzene}} \underset{(92\%)}{\mathrm{PhCOPh}} + \mathrm{CF_3SO_3H} \qquad (2)$$

Cyclic anhydrides are very useful for the synthesis of ketoacids under Friedel–Crafts conditions (Scheme 2). When the cyclic anhydride is constitutionally unsymmetrical, and particularly when the anhydride possesses substituents in the α position, steric factors dictate which ketoacid is formed.[16] A side reaction is decarbonylation of the intermediate complex (Scheme 2). This process is favoured when a stable carbenium ion can be formed but, since the reaction is reversible in some cases, decarbonylation can be prevented by conducting the reaction in the presence of excess of carbon monoxide.[17]

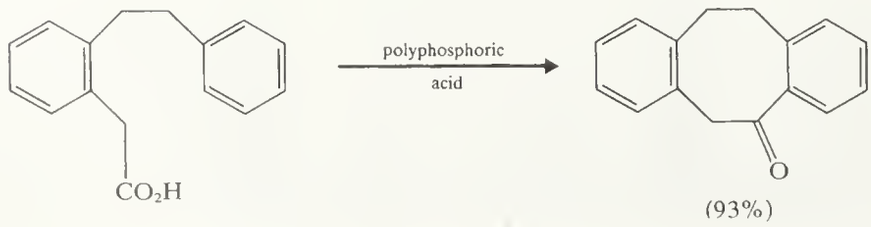


SCHEME 2

Intramolecular Friedel–Crafts acylation is the most important general method for the synthesis of cyclic ketones and has been used for the synthesis of medium- and large-membered ring aromatic ketones, *e.g.* paracyclophanes (equation 3).[18] Cyclic aromatic ketones can also be synthesized by intramolecular dehydration of carboxylic acids, polyphosphoric acid being the most widely used catalyst (equation 4).[19]



(70%) (3)



(93%) (4)

5.4.2.2 The Houben–Hoesch reaction

The Houben–Hoesch reaction[20,21] is similar to the Gattermann aldehyde synthesis; both involve acylation of electron-rich aromatics by a nitrile. The ketone synthesis (Table 6) is carried out by passing HCl through a mixture of the substrate and the nitrile, often in ether solution; for less reactive substrates, a Lewis acid catalyst ($ZnCl_2$ or $AlCl_3$) is added. The initial product is a ketimine hydrochloride (**26**), which can be isolated, but normally is hydrolysed immediately to the ketone by boiling water (equation 5).

$$\mathrm{ArH} \xrightarrow[ZnCl_2]{RCN,\ HCl} \mathrm{ArC(R)=NH\cdot HCl}\ (\mathbf{26}) \xrightarrow{H_2O} \mathrm{ArCOR} + \mathrm{NH_4Cl} \qquad (5)$$

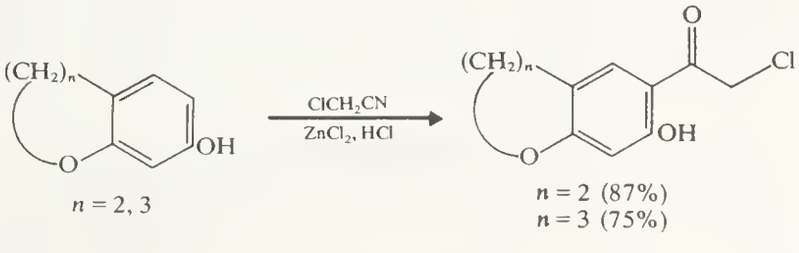
TABLE 6
Ketones Synthesized by the Houben–Hoesch Method

Reactant	*Nitrile*	*Catalyst*	*Product*	*Yield* (%)	*Ref.*
Benzene	Cl_2CHCN	$AlCl_3$	α,α-Dichloroaceto-phenone	83	a
Phenol	Cl_3CCN	$AlCl_3$	4-Hydroxy-α,α,α-tri-chloroacetophenone	90	b
Anisole	Cl_3CCN	$ZnCl_2$	4-Methoxy-α,α,α-tri-chloroacetophenone	70	c
Phenetole	$ClCH_2CN$	$ZnCl_2$	4-Ethoxy-α-chloro-acetophenone	8	c
Aniline	CH_3CN	$AlCl_3$	4-Aminoacetophenone	—	d
Phloroglucinol	CH_3CN	$ZnCl_2$	2,4,6-Trihydroxy-acetophenone	87	e
1-Ethoxynaphthalene	$ClCH_2CN$	$ZnCl_2$	1-(α-chloroacetyl)-4-ethoxynaphthalene	86	c

[a] J. Houben and W. Fischer, *Ber.*, 1931, **64**, 2645. [b] J. Houben and W. Fischer, *J. prakt. Chem.*, 1929, **123**, 262. [c] J. Houben and W. Fischer, *Ber.*, 1927, **60**, 1759. [d] H.-T. Wu, *J. Amer. Chem. Soc.*, 1944, **66**, 1421. [e] K. C. Gulati, S. R. Seth, and K. Venkataraman, *Org. Synth. Coll. Vol. 2*, 1943, 522.

The active 'acylating' species is a matter of conjecture and may depend on reaction conditions. In the absence of catalyst, the cation ($R\overset{+}{C}{=}NH$) is the most likely 'acylating' agent, whereas, in the presence of zinc chloride, the complex ($R\overset{+}{C}NH\ ZnCl_3^-$) is probably involved.[21,22] The reaction of these species with aromatic compounds is then a straightforward electrophilic substitution, the reactions being first order in aromatic and nitrile. As in other electrophilic substitutions, *ortho*- and *para*-substituted products are obtained.[21,22]

The reaction is limited to reactive aromatics, particularly polyhydric phenols (equation 6),[23] phenol ethers, and heterocyclic systems such as pyrroles, thiophens, and indoles (Table 6). Alkyl and halo aromatics will only react with very electrophilic nitriles (*e.g.* CCl_3CN) whereas simple phenols give iminoesters, $ArOC(=NH)Me$.[24]



(6)

5.4.2.3 Fries rearrangement[25,26]

The rearrangement of esters of phenols in the presence of Lewis acids to give *ortho*- and *para*-acylphenols was first recognized by Fries to be a very general reaction and has since then been used in the synthesis of a variety of aromatic and heteroaromatic hydroxyketones. The reaction is normally carried out by heating the ester with the 'catalyst' at temperatures up to 200 °C either neat or in the presence of an inert solvent. In general, the lower the temperature, the higher the yield of *p*-acylphenol.[27] At higher temperatures, *ortho* substitution is favoured (see Table 7), *i.e.* the opposite temperature effect to the Friedel–Crafts acylation.

TABLE 7

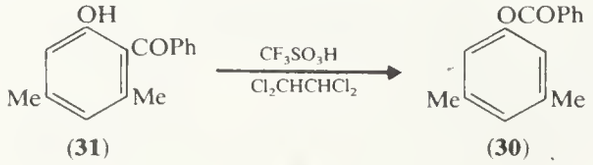
Fries Rearrangement of Phenolic Esters using Aluminium Chloride Catalyst

Ester	*Solvent*	*Conditions*	*Yield (%)* *ortho*[a]	*para*[b]	*Ref.*
Phenyl acetate	$PhNO_2$	24 h, r.t.	—	75	c
Phenyl acetate	—	24 h, 165 °C	70	—	c
Phenyl benzoate	—	15 min, 140 °C	—	100	c
m-Cresyl acetate	$PhNO_2$	24 h, r.t.	—	82	c
m-Cresyl acetate	—	24 h, 165 °C	95[d]	—	c
p-Cresyl acetate	—	10 min, 120 °C	90	—	c
Catechol diacetate	$PhNO_2$	2 h, 75 °C	—	80[e]	f
2-Naphthyl acetate	CS_2	4 h, 120 °C	40[g]	—	h
Acetylsalicylic acid	$PhNO_2$	4 h, 60 °C	—	60	c

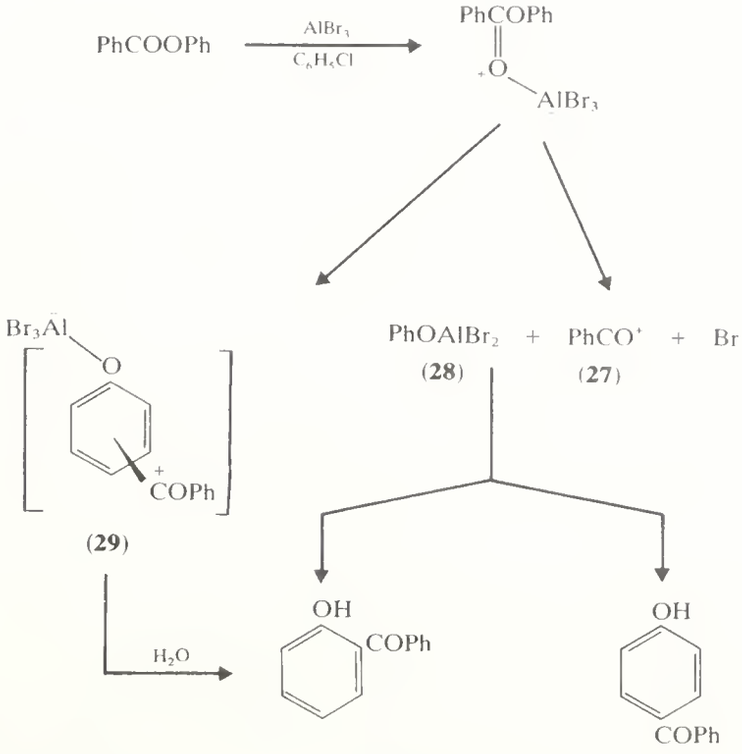
[a] *ortho* to the phenolic group. [b] *para* to the phenolic group. [c] Ref. 27. [d] 2-Acetyl-5-methylphenol. [e] 4-Acetylcatechol. [f] K. W. Rosenmund and H. Lohfert, *Ber.*, 1928, **61**, 2601. [g] 1-Acetyl-2-naphthol. [h] K. Fries, *Ber.*, 1921, **54**, 709.

The reaction is applicable to the synthesis of a wide range of aromatic hydroxyketones (Table 7). The usual 'catalysts' are aluminium chloride, titanium tetrachloride, stannic chloride, or boron trifluoride; normally at least 1 mole of 'catalyst' is used per mole of reactant. Recently, however, trifluoromethanesulphonic acid has been shown to be an effective catalyst for certain phenolic esters when present in trace amounts.[28]

The mechanism of the reaction is now envisaged to take place *via* both inter- and intra-molecular pathways (Scheme 3).[29] The intermolecular route leads to an acylium ion (**27**) and a phenoxyaluminium derivative (**28**), which combine giving a mixture of *ortho* and *para* products. The intramolecular process proceeds *via* a π-complex (**29**) which yields mainly *ortho* product (Scheme 3). The intermolecular process is favoured by the presence of excess of Lewis acid so that, under these conditions, the proportion of the *ortho* isomer diminishes. In the presence of 1 mole of acid, the intermolecular process is again favoured, although an exception is when trifluoromethanesulphonic acid is the catalyst. In this case, only 2 mole percent of catalyst is required and under these conditions almost exclusive *ortho* substitution takes place. The use of CF_3SO_3H catalyst has provided further insight into the mechanism of the rearrangement. Whereas phenyl benzoate underwent Fries rearrangement using CF_3SO_3H as catalyst, surprisingly, 3,5-dimethylphenylbenzoate (**30**) did not.[28] The expected product (**31**) is more hindered than the ester (**30**), but this would account for the stability of (**30**) only if the rearrangement were reversible. It was found subsequently that the ketone (**31**), independently synthe-



(31) (30) (7)



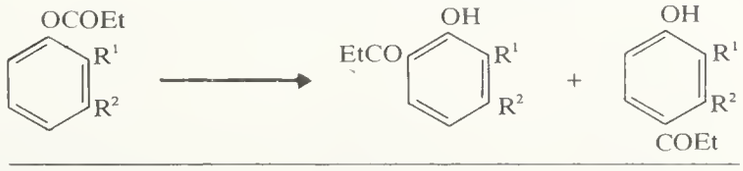
SCHEME 3

sized, rearranged in 90% yield to the ester (**30**) on heating with CF_3SO_3H (equation 7), indicating that in certain cases the Fries rearrangement may be a reversible process.[28]

The synthetic potential of the reaction depends on achieving selectivity in the formation of *ortho* or *para* product. A recent study[30] has emphasized the importance of the catalyst on the *ortho–para* ratio (Table 8). In general, it was found that titanium tetrachloride in the absence of solvent gave the best yields of *ortho* product, whereas boron trifluoride or antimony pentachloride in nitromethane solution offered some selectivity for *para* substitution.[30]

TABLE 8

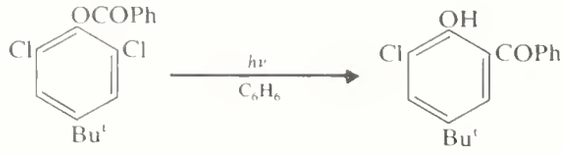
Effect of Catalysts on the Fries Rearrangement[a]



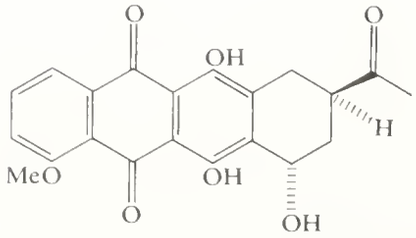
R^1	R^2	*Solvent*	*Conditions*	*Catalyst*	*Yield (%) ortho*	*para*
Me	H	—	3 h 50 °C	$AlCl_3$	16	55
Me	H	—	3 h 50 °C	$TiCl_4$	37	—
Me	Me	—	3 h 50 °C	$AlCl_3$	37	10
Me	Me	—	3 h 50 °C	$TiCl_4$	84	3
Me	Me	$MeNO_2$	24 h 20 °C	$AlCl_3$	94	2
Me	Me	$MeNO_2$	24 h 20 °C	$TiCl_4$	44	4
H	H	$MeNO_2$	7 d 20 °C	$AlCl_3$	20	80
H	H	$MeNO_2$	7 d 20 °C	$TiCl_4$	12	56
H	Me	—	3 h 50 °C	$AlCl_3$	25	21
H	Me	—	3 h 50 °C	$TiCl_4$	42	3
Bu^t	H	$MeNO_2$	24 h 20 °C	$AlCl_3$	46	20
Bu^t	H	$MeNO_2$	24 h 20 °C	$SbCl_5$	6	52
Bu^t	H	$MeNO_2$	24 h 20 °C	BF_3	1	24
Bu^t	H	$MeNO_2$	24 h 20 °C	$TiCl_4$	15	54

[a] See Ref. 30.

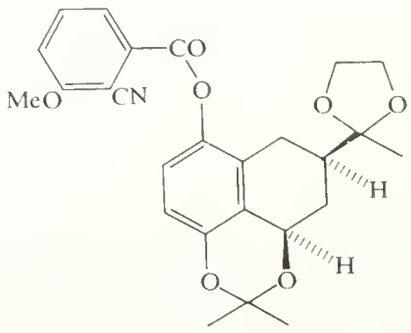
The Fries rearrangement also proceeds photochemically, giving the same products *via* an entirely different mechanism.[31] The photochemical route is a useful alternative since groups which are eliminated in the acid-catalysed rearrangement (*e.g.* Bu^t) are retained in the photoreaction.[32] In contrast, other groups (*e.g.* Cl, OMe) may be eliminated in the photo-Fries rearrangement (equation 8). The mild, acid-free, conditions of the photo-Fries rearrangement offer an attractive synthetic route to complex natural products containing aromatic hydroxyketone groupings. For example, the key step in the synthesis of the antibiotic 9-deoxydaunomycinone (**32**) was the photo-rearrangement of the ester (**33**) to ketone (**34**) in 48% yield.[33]



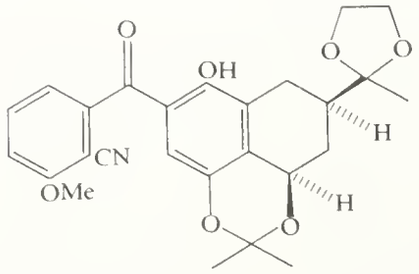
(8)



(**32**)



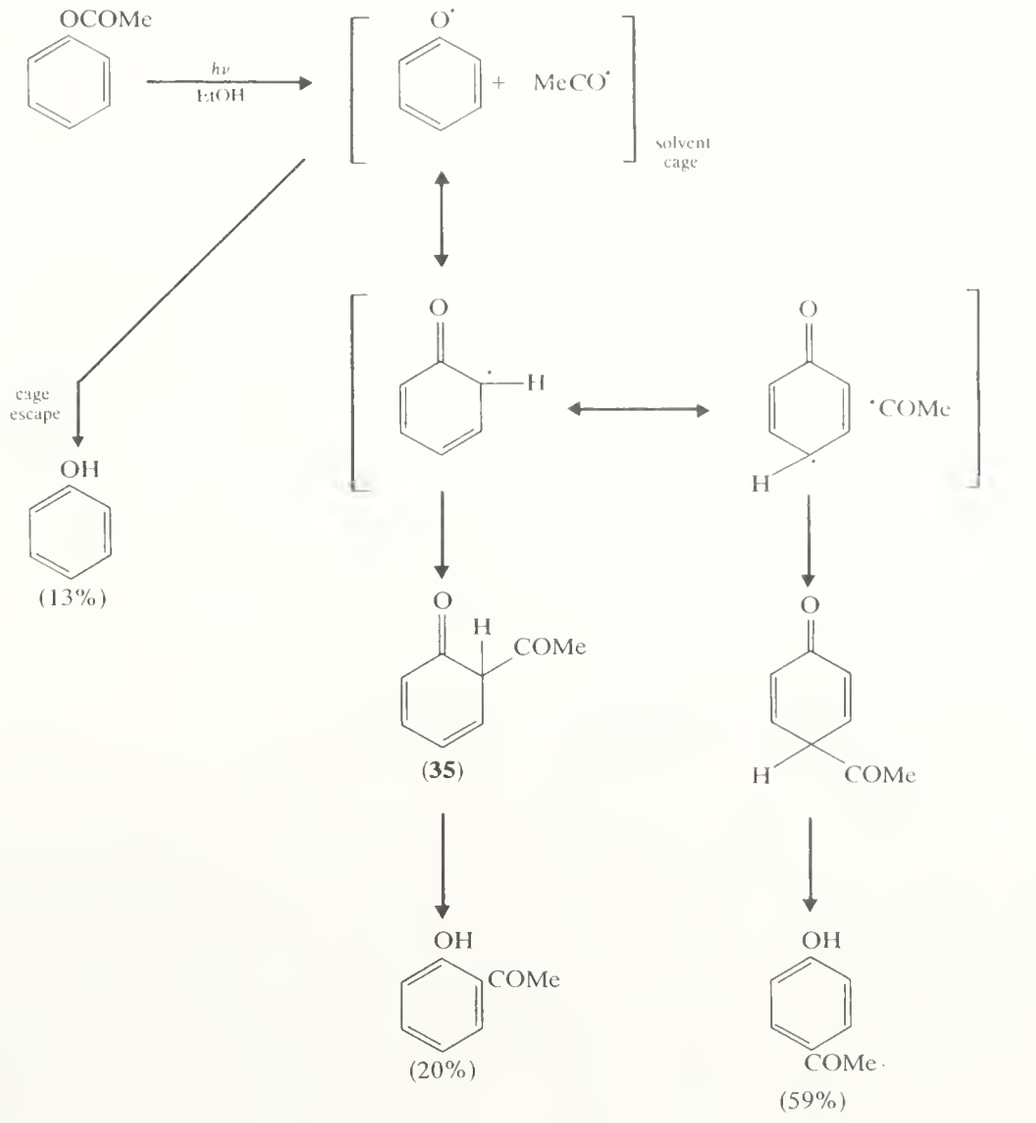
(**33**)



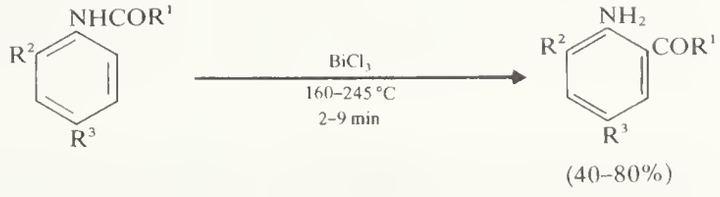
(**34**)

In general, *ortho* substitution is favoured, especially in polar solvents, but cleavage to the phenol is also enhanced in these solvents. Electron-donating substituents on the phenol or electron-withdrawing substitutents on the acyl group again favour *ortho* substitution.[34] In a recent review of the photo-Fries rearrangement,[31] it was suggested that the rearrangement to the *ortho* product took place *via* an allowed suprafacial [1,3]-sigmatropic rearrangement. Flash photolysis studies, however, rule out this route and an intramolecular radical mechanism proceeding within the solvent cage has been shown[35] to lead to *ortho* and *para* products (Scheme 4); the phenoxy radical, escaping from the solvent cage, reacts with solvent to give the cleavage product. The intermediate cyclohexadienone (**35**) was also detected spectroscopically[35] (Scheme 4).

A similar rearrangement also occurs with *N*-arylamides, giving *o*- and *p*-amino-ketones.[36] This reaction, sometimes called the photoanilide rearrangement,[31] generally gives more by-products than the photo-Fries rearrangement.[36] The thermal analogue has never given yields which were preparatively useful, but recently it has been shown that, by using bismuth trichloride as catalyst, moderate yields of ring-acylated anilines could be obtained (equation 9).[37]



SCHEME 4

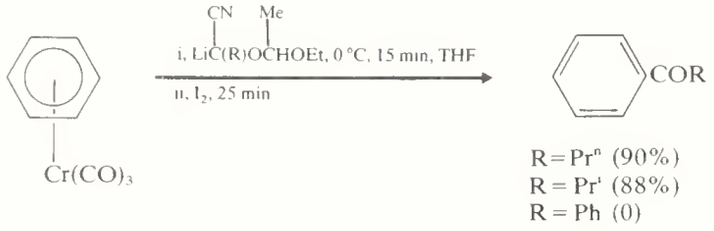


(9)

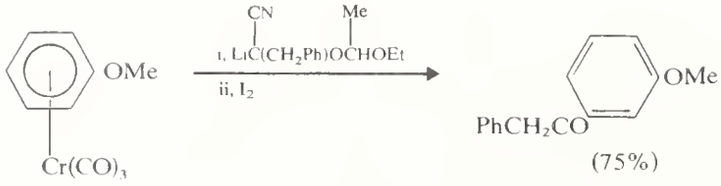
5.4.2.4 Synthesis of aromatic ketones using arene–metal complexes

This reaction has been included since, although it has not yet been widely used, it has great potential, uses a novel approach, and is mechanistically interesting. The formation of arenetricarbonylchromium complexes is an example of polarity inversion ('umpolung').[38] Whereas arene rings are normally susceptible to electrophilic attack, after formation of the tricarbonylchromium complex the unsubstituted aromatic ring can be readily attacked by nucleophiles. If the protected acyl carbanions introduced recently by Stork and Maldonado[39] are used as nucleophiles, aryl alkyl ketones can be synthesized in excellent yields (equation 10).[40] The method fails for diaryl ketones which can, however, be prepared in 80–90% yields by displacement of chlorine from the corresponding chlorobenzene–tricarbonylchromium complexes.[41] The most useful synthetic aspect is that substitution in

the toluene or anisole complexes yielded exclusively the *meta* substitution product (equation 11).[42] The scope and applications of this novel method have yet to be fully explored, but it seems likely that many more nucleophilic substitution reactions of these complexes will be used in the future for the introduction of *meta* substituents.



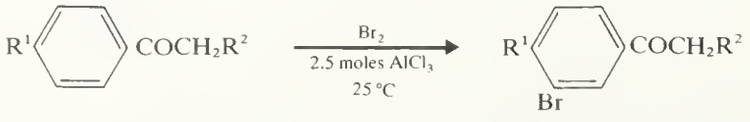
(10)



(11)

5.4.3 ELECTROPHILIC AROMATIC SUBSTITUTION

The deactivating effect of the carbonyl group on the aromatic ring makes electrophilic substitution difficult and, in the absence of additional activating substituents, reactions only occur under vigorous conditions. Thus nitration of acetophenone using nitric acid in fuming sulphuric acid gives *m*-nitroacetophenone (90%), the selectivity decreasing as the acid strength is lowered, in the same way as with aromatic aldehydes.[43] Nuclear halogenation of aromatic ketones is readily achieved using the 'swamping catalyst' conditions successful for aromatic aldehydes[44] (see Section 5.3.4), and under these conditions (excess of aluminium halide), no side-chain halogenation of acetophenones or halogenation of aromatic alkyl groups takes place. Using one mole of halogenating agent, acetophenones are substituted in the *meta* position in good yield (equation 12), whereas benzophenone gives only 3,3′-dihalobenzophenones.[44] Dichlorination and tetrachlorination of acetophenone using 2 or 4 moles of reagent yield 2,5-dichloroacetophenone (43%) and 2,3,5,6-tetrachloroacetophenone (67%) respectively, whereas bromination using excess of reagent produced only a complex mixture. In the bromination of 4-methylacetophenone, however, 3,5-dibromo-4-methylacetophenone could be obtained in 57% yield.[44]



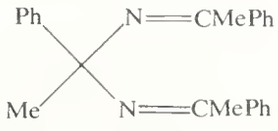
(12)

$R^1 = H, R^2 = H$ (71%)
$R^1 = Me, R^2 = H$ (60%)
$R^1 = Et, R^2 = H$ (59%)
$R^1 = H, R^2 = Me$ (60%)

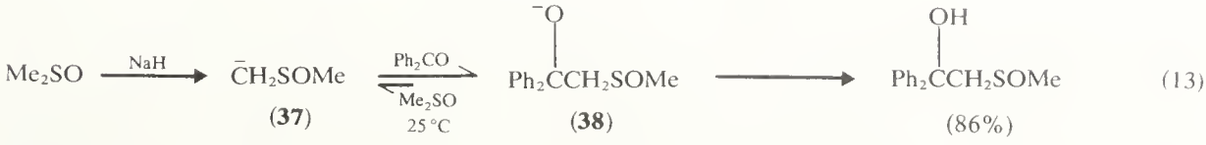
5.4.4 NUCLEOPHILIC ADDITIONS TO THE CARBONYL GROUP

The addition of simple nucleophiles such as OH^-, NH_2OH, NH_2NHPh, and CN^- to aryl alkyl ketones takes place readily provided that both *ortho* positions on the aromatic ring are not substituted. Acetophenone forms an oxime, semicarbazone, phenylhydrazone, and cyanohydrin in the usual manner, but not a bisulphite adduct. The addition of ammonia to

acetophenone yields the product (**36**) in a manner similar to that observed for benzaldehyde (Section 5.3.4), but condensations with amines require much more drastic conditions than for aromatic aldehydes. Benzophenone, in which the carbonyl group is much more hindered, forms an oxime and semicarbazone, *etc.* but not a cyanohydrin or a bisulphite adduct. This reflects the large loss in stabilization energy in proceeding from a trigonal carbonyl group, stabilized by π-orbital overlap with one or both aromatic rings, to a tetrahedral addition product. With nucleophiles such as NH_2OH, the initial adduct is readily dehydrated, forming a C=N bond, and π-orbital overlap is restored; the overall process is therefore much more thermodynamically favourable. These two-stage reactions in which the first stage is reversible can thus be driven to completion. Additions to diaryl ketones also take place readily with strongly nucleophilic carbanions, *e.g.* $\bar{C}H_2SOCH_3$ (**37**)[45] since the initially formed intermediate carbanion (**38**) is more stable than (**37**) and the equilibrium lies to the right (equation 13).

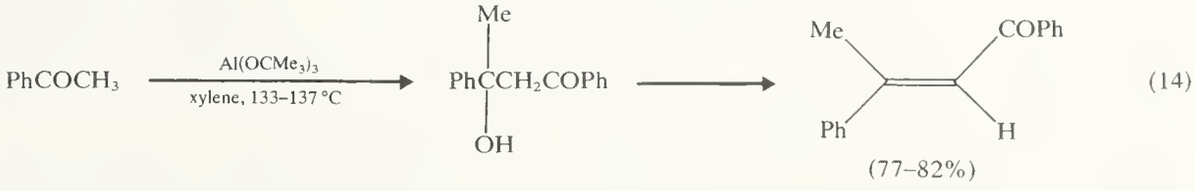


(**36**)



(13)

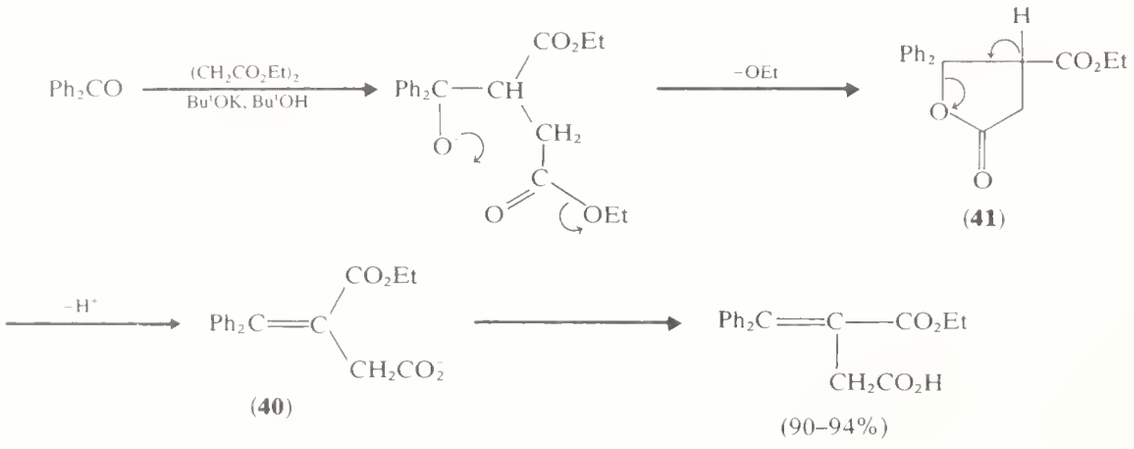
In the aldol condensation and related reactions (see Sections 5.1.5.2 and 5.2.7.1), aryl alkyl ketones are attacked at the carbonyl group much less readily than are aromatic aldehydes and so condensation of the aldehyde with the ketonic methylene group takes place (see Section 5.3.4.1). Self-condensation of ketones such as acetophenone take place only under severe conditions (equation 14), when good yields of α,β-unsaturated ketones can be obtained.[46] Condensations of aryl ketones with aliphatic aldehydes and ketones are normally unsuccessful unless methods such as the directed aldol route (Section 5.1.5.2) developed by Wittig[47] are used.



(14)

Diaryl ketones undergo condensations with active methylene compounds, but yields are often unsatisfactory. For the Knoevenagel condensation, it is often advantageous to convert the diaryl ketone to the imine (**39**) before condensation with the active methylene group.[48] The Stobbe condensation (see Section 5.1.5.2) is often successful with hindered ketones when other types of aldol condensation fail. This can be attributed to the irreversible formation of the carboxylate anion (**40**) from the intermediate lactone (**41**) (Scheme 5).[49] The addition of phosphorus or sulphur ylides to diaryl ketones also leads to excellent yields of olefins (Chapter 10.6) or oxirans (Chapter 11.15) respectively, provided that the ylide is not stabilized by electron-withdrawing groups (*i.e.* is strongly nucleophilic) and is relatively unhindered. In cases where phosphorus ylides do not react, use of the corresponding phosphonate anion (see Chapter 10.5) often leads to successful results.

(**39**)



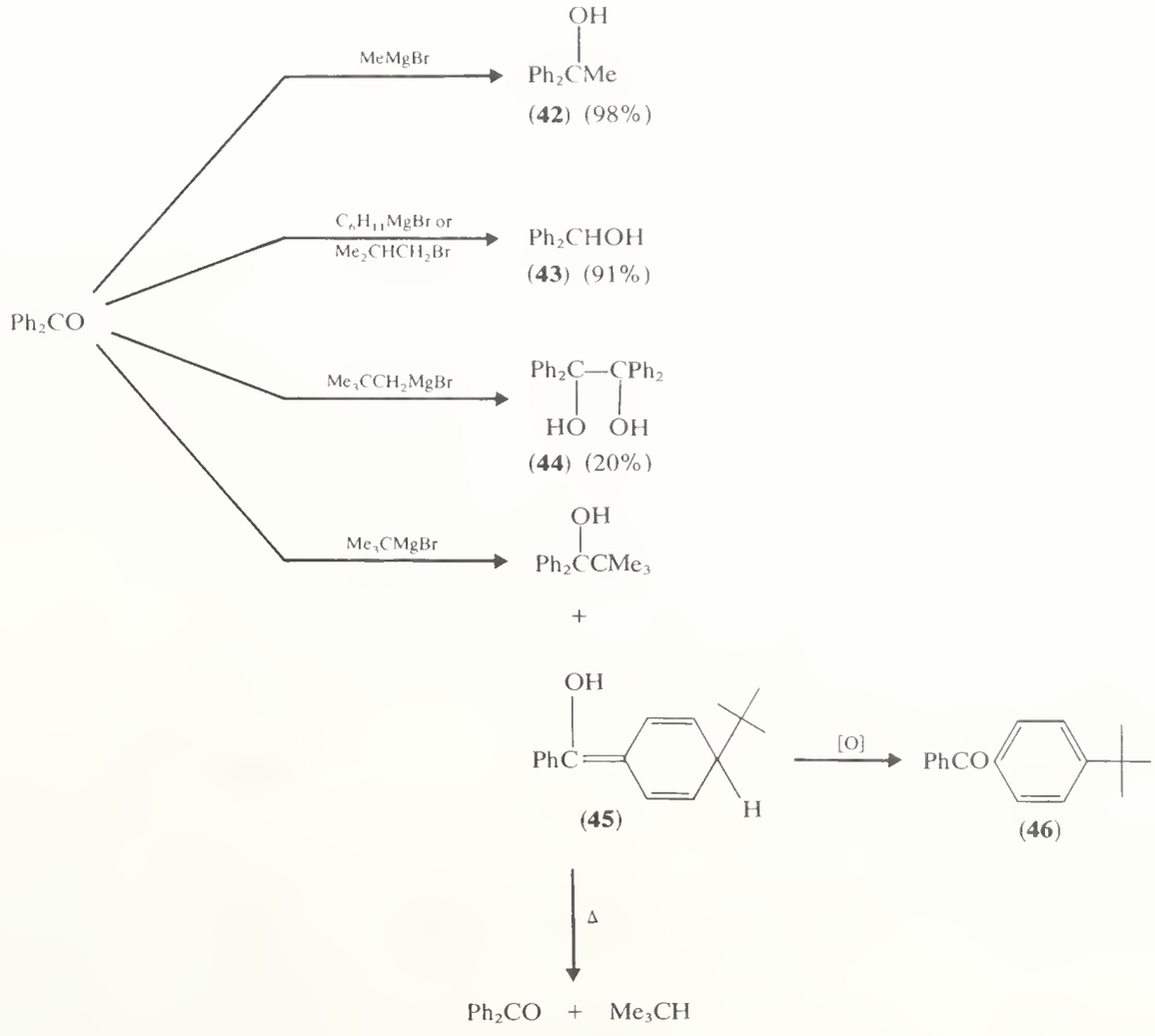
SCHEME 5

5.4.4.1 Addition of Grignard reagents to aromatic ketones

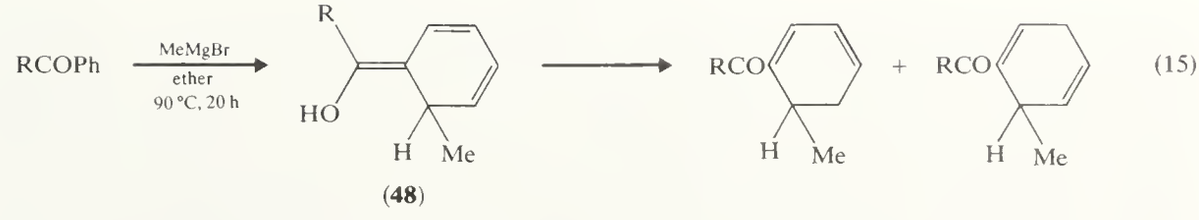
The addition of Grignard reagents to aromatic ketones often proceeds normally to give tertiary alcohols, but, occasionally, conjugate addition to the aromatic ring, pinacol formation, or reduction of the carbonyl group take place. The factors which affect the relative proportions of these four pathways have been the subject of intense research activity and it is only during the past ten years that the mechanisms have been deciphered.[50,51] The research has been limited by the fact that the nature of the Grignard reagent, which is an equilibrium mixture of RMgX and R_2Mg with associated species, is affected by subtle changes in reaction conditions and reproducibility is a problem. Much of the recent understanding has been achieved by the examination of additions to benzophenones since, under a variety of conditions, all four modes of reaction have been observed. Thus reaction of benzophenone with methylmagnesium bromide yields the normal adduct (**42**), whereas with cyclohexyl or isobutyl Grignard reagents reduction to the alcohol (**43**) takes place (Scheme 6).[51] Neopentylmagnesium halides cause bimolecular reduction to the pinacol (**44**),[52] whereas t-butylmagnesium chloride adds not only to the carbonyl group (1,2-addition) but also to the *para* position of the aromatic ring (Scheme 6).[53,54] It was thought previously that the addition of the t-butyl Grignard gave only 1,2-addition; it has now been shown that the error arose because the intermediate (**45**) in the 1,6-addition reverts to benzophenone on heating. Oxidation of the dihydro derivative (**45**), however, yields the aromatized product (**46**) (Scheme 6).

Recent work by the groups of Holm[51,53,56] in Denmark and Ashby[50,54,55] in the United States has shown that the relative amounts of the four possible pathways depend on the nature of the Grignard reagent and the ketone, the solvent, the order of addition of the reactants, the purity of the magnesium used to prepare the Grignard reagent, and the presence of transition metal catalysts. Under the normal conditions, addition of benzophenone to methylmagnesium bromide in ether gives the alcohol (**42**) in high yield *via* a polar mechanism (Scheme 7), possibly involving an initial complex (**47**) between Grignard reagent and ketone.[50] However, traces of transition metals which are often present in commercial magnesium turnings catalyse the alternative single electron-transfer mechanism (Scheme 7),[55] which leads to radical species detectable by e.s.r. spectroscopy.[51] Formation of the normal product (**47**) still occurs but by-products such as pinacols increase to 70% as the amount of transition metal is increased to 0.5 mole %.[54,55] With very highly hindered ketones, conjugate addition takes place and in one case the intermediate enol (**48**) has been isolated (equation 15).[56] A change in solvent from ether to HMPT has been observed to increase the amount of pinacol formed in some cases.[57]

The addition of Grignard reagents, derived from hindered alkyl halides, to aromatic ketones and the addition of n-alkylmagnesium halides to highly hindered ketones has been known for many years to give rise to addition to the aromatic ring, and this can be a



SCHEME 6

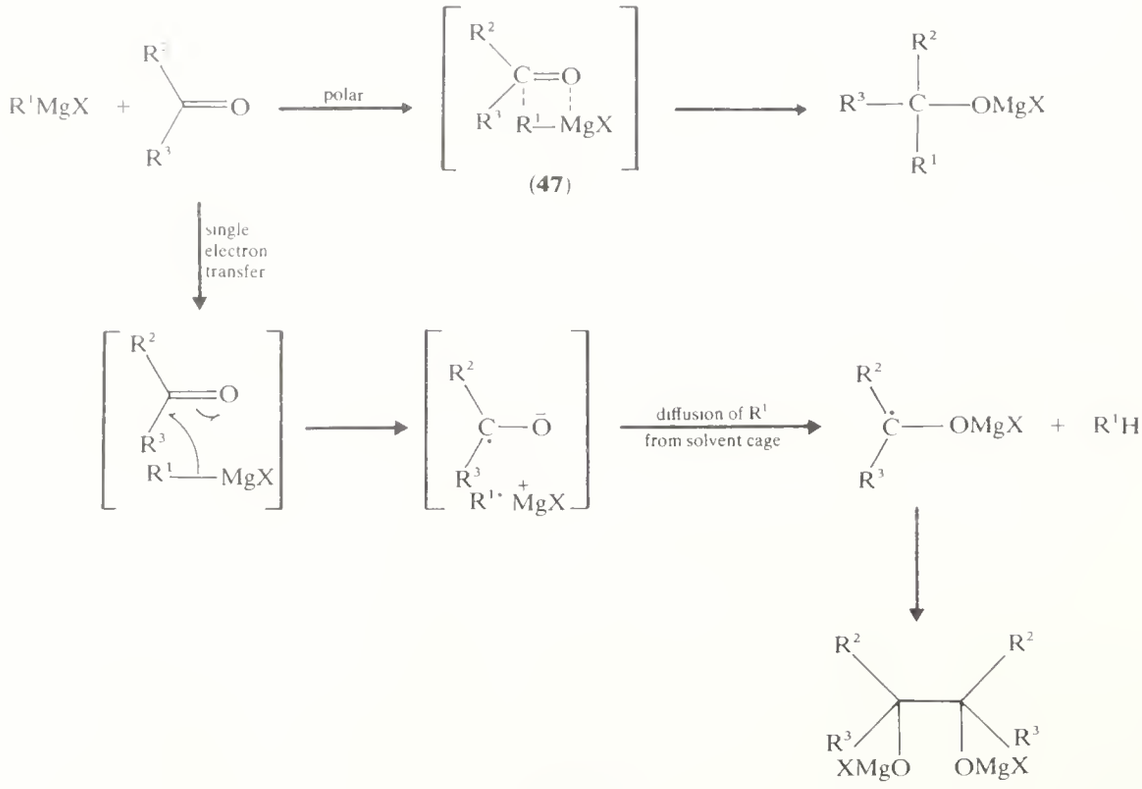


R = 2,4,5,6-tetramethylphenyl

useful method of alkylating polycyclic aromatic ketones.[58] The addition of t-butylmagnesium chloride to benzophenones leads to both normal 1,2-addition to the carbonyl group and conjugate addition to the aromatic ring (Table 9) *via* a single electron-transfer mechanism.[53,54]

The electron transfer is the rate-determining step; thus the rate of reaction is hardly affected by the presence of two *ortho*-methyl groups in the benzophenone, whereas there is a large rate decrease in the corresponding rate of addition of methylmagnesium halides to benzophenone after the introduction of methyl groups in the 2- and 6-positions.[53] Addition of the t-butyl group to the 2-position of the aromatic ring occurs if the 4-position is blocked by a large group (but not by a methyl, see Table 9), whereas the addition to the carbonyl group (1,2-addition) is hindered by two *ortho* substituents (Table 9).[53,54]

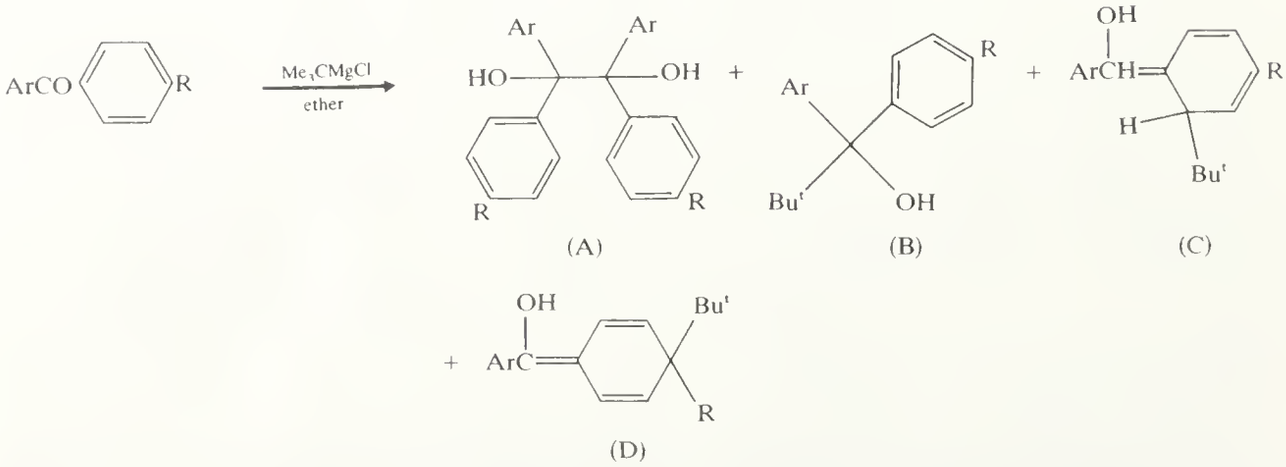
The reduction of aromatic ketones by Grignard reagents usually occurs with alkylmagnesium halides having branched chains and a β-hydrogen, but is also known with



SCHEME 7

TABLE 9

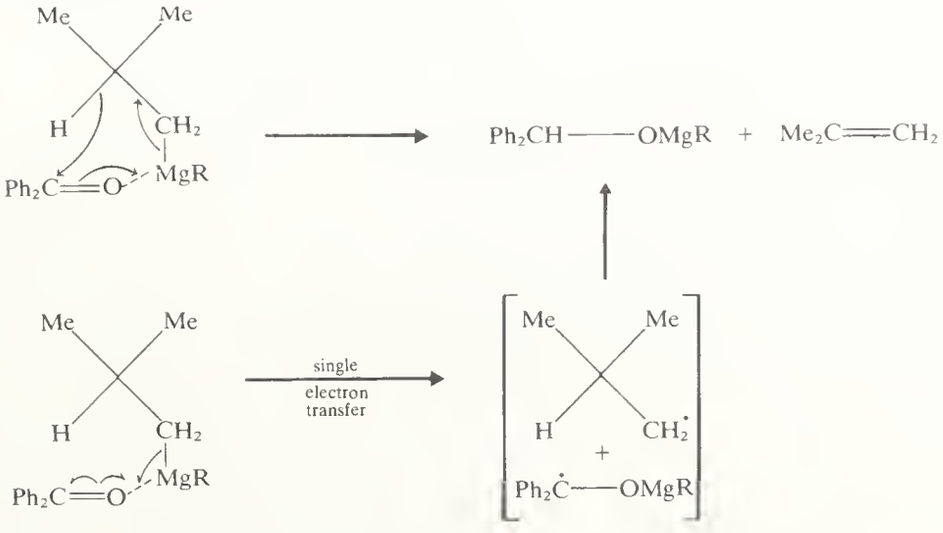
Addition of t-Butylmagnesium Chloride to Benzophenones[a]



Ar	R	*Yield (%) of pinacol* (A)	1,2-*addition* (B)	*Yield (%) of* 1,4-*addition* (C)	1,6-*addition* (D)
H	H	6	44	0	50
4-MeC_6H_4	Me	12	55	0	33
4-$Bu^tC_6H_4$	Bu^t	21	40	39	0
4-ClC_6H_4	Cl	0	50	21[b]	29[b]
2,4,6-$Me_3C_6H_2$	H	0	0	0	100
2,4,6-$Me_3C_6H_2$	Me	0	0	0	100
2,3,5,6-Me_4C_6H	H	0	0	0	100[c]

[a] Ref. 53. Products (C) and (D) were usually oxidized to substituted benzophenones. [b] Subsequent loss of HCl gives a substituted benzophenone which undergoes further addition of Me_3CMgCl. [c] The enol was isolated in 70% yield in this case.

simple Grignards such as n-butylmagnesium bromide. Two possible mechanisms have been postulated (Scheme 8):[51] a cyclic process and single electron transfer. On the basis of kinetic studies using the Grignard reagent from isobutyl bromide (Me_2CHCH_2Br) and its 2-deuteriated analogue (Me_2CDCH_2Br), it has been shown that the single electron-transfer process, which should show only a secondary isotope effect, at least partially operates if the Grignard reagent is present in excess but that in the presence of excess of ketone the reaction proceeds *via* the cyclic mechanism, which shows a primary isotope effect (Scheme 8). The ratio of reduction to addition products is also decreased by a factor of 2.5 by the introduction of a β-deuterium atom into the organomagnesium compound. Thus the order of addition of the reagents can determine the reaction mechanism. Reduction sometimes occurs when a large excess of methylmagnesium halide is used, but this has been shown to be due to the formation of small quantities of magnesium hydrides.[59] Use of highly purified 'single crystal' magnesium, however, eliminates the reduction process and high yields of products by normal 1,2-addition are observed even with a vast excess of Grignard reagent.[59]



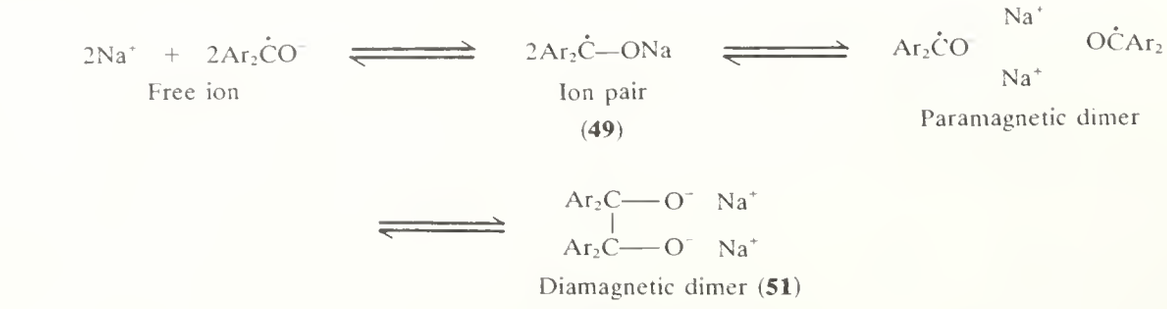
SCHEME 8

In summary, a much greater understanding of the mechanism of addition of Grignard reagents to benzophenones has arisen over the past ten years.[50] Highly purified magnesium and the absence of transition metals are required to ensure that a polar mechanism is favoured. If the oxidation potential of the Grignard and the reduction potential of the ketone are high and the solvent is not very polar, then a polar mechanism is again favoured. Conversely, when the oxidation potential of the Grignard and the reduction potential of the ketone are low, when the solvent is polar, or the magnesium used is impure, a single electron-transfer mechanism operates, and by-products are likely to be observed.

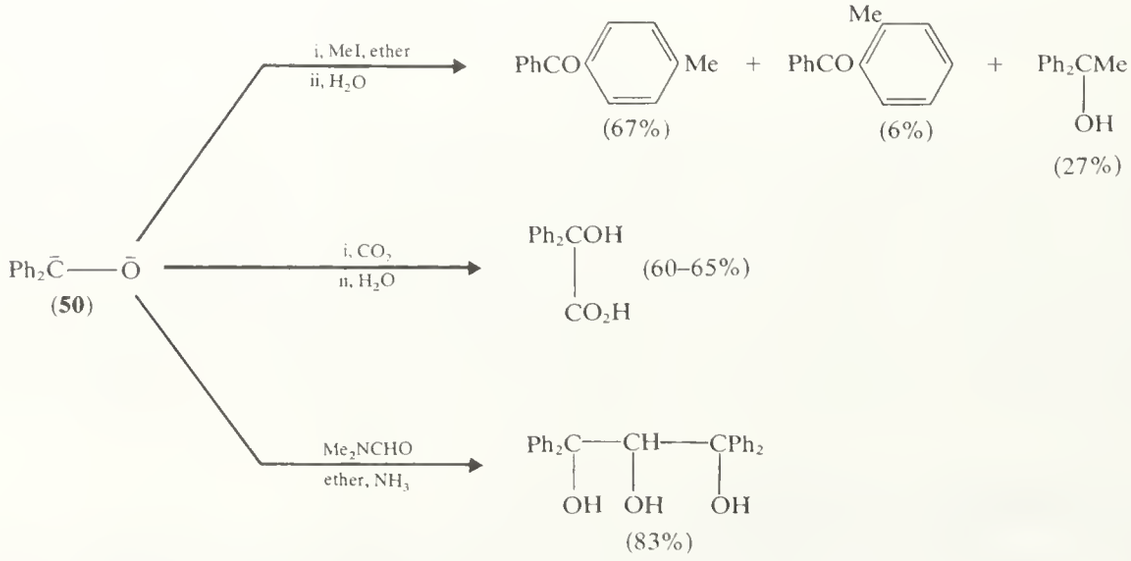
5.4.5 REDUCTION OF AROMATIC KETONES

The reduction of aldehydes and ketones has been discussed at length in Sections 5.1.4.2 and 5.2.14; therefore only the significant differences between aromatic and aliphatic ketones will be discussed in this section. Aromatic ketones, particularly diaryl ketones, are much more readily reduced to the radical anion, $Ar_2\dot{C}—\bar{O}$ (**49**), than aliphatics and under certain conditions the dianion, $Ar_2\bar{C}—\bar{O}$ (**50**), may be formed.[60] The appearance of a blue colour on treating benzophenone with sodium in an inert atmosphere was first observed almost 90 years ago, but it was not until 1913 that it was realised that the coloration was due to the ketyl (radical ion) of structure $Ph_2\dot{C}—ONa$ (or a dimeric form). More recent evidence from e.s.r. spectroscopic data, u.v. and visible spectra, and paramagnetic susceptibility measurements indicates that, at least for diaryl ketones, the equilibrium

shown in Scheme 9 exists, the position of the equilibrium varying with solvent.[60] Non-polar solvents favour the dimer (**51**) whereas polar solvents such as THF and dimethoxyethane reduce the amount of dimer (**51**) in the equilibrium mixture. It is thus readily apparent why dissolving metal reductions of diaryl ketones often lead to pinacol formation. Aryl substituents stabilize the radical ions which therefore have longer lifetimes; appreciable concentrations of radical ions then build up and subsequently dimerize. Under certain conditions, formation of the dianion (**50**) occurs; stabilization by delocalization of the negative charge on the aromatic ring is apparently important, since alkylation can lead to ring-substituted products under certain circumstances (Scheme 10).[61] In most cases, however, reaction of the dianion (**50**) with electrophiles leads to bond formation with the carbonyl carbon atom.[62] Both the radical anion (**49**) and dianion (**50**) are very strong bases and abstract protons from any available source such as alcohols and even aliphatic ketones, producing diarylmethanol derivatives or tetraarylpinacols, *via* the intermediate radical $Ar_2\dot{C}$—OH. In electrochemical reductions[63] which lead to these radicals, pinacols are formed preferentially under acidic conditions, whereas diarylmethanols result in basic media.

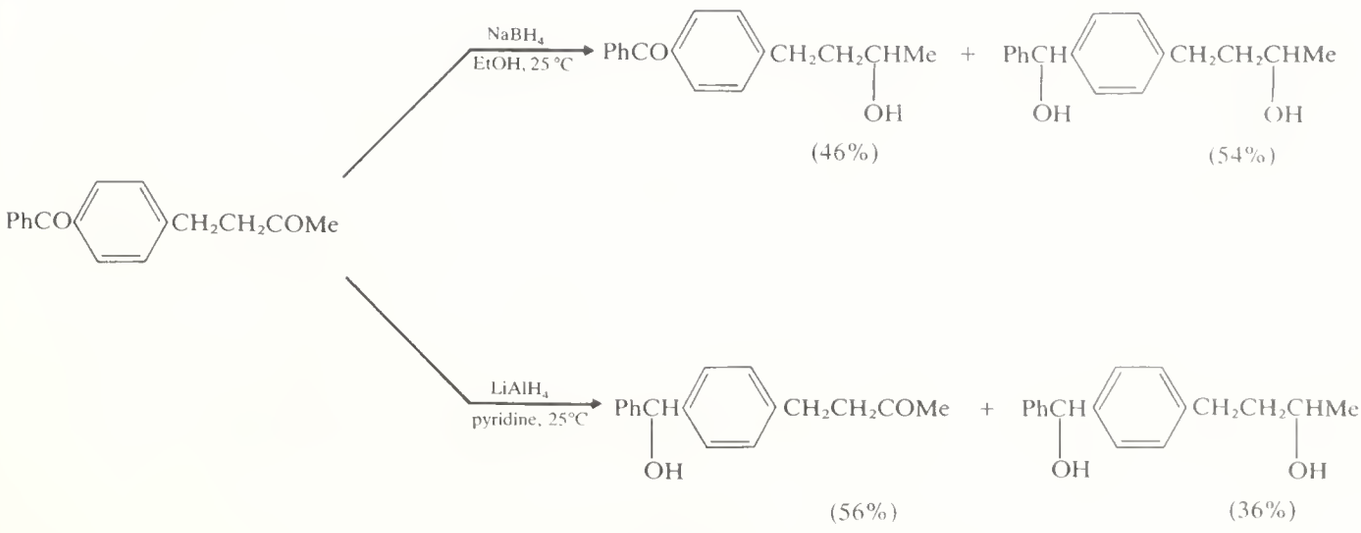


SCHEME 9



SCHEME 10

Metal hydride reductions of aromatic ketones, in which the carbonyl group is more electron deficient than in aliphatic ketones, takes place much less readily under most conditions. Thus in some cases an aliphatic ketonic group can be reduced in the presence of an aromatic ketone (Scheme 11); the reagent derived from lithium tetrahydridoaluminate and pyridine, however, reverses this trend (Scheme 11).[64] Aromatic ketones are more difficult to reduce than aromatic aldehydes and reduction of an aldehyde in the presence of a ketone is often possible (see Section 5.3.6).



SCHEME 11

5.4.5.1 Asymmetric reduction of aromatic ketones

The asymmetric reduction of prochiral ketones to chiral alcohols can be performed using a variety of reagents, the most effective being chiral aluminium or magnesium complexes.[65] The reduction proceeds *via* competing diastereoisomeric transition states, and the extent of asymmetric reduction usually depends on the difference in free energy of activation of the two diastereoisomeric transition states leading to the enantiomeric alcohols. Since this energy difference is usually no more than 500 calories (2100 joules), the effects of changes in substrate, reagent, solvent, and temperature are often remarkable and sometimes unpredictable. The topic has been the subject of intense study over the past decade and much of the work has involved the reduction of aryl alkyl ketones, which in general give higher selectivity than dialkyl or diaryl ketones. This is due to the relatively different steric demands in the two groups attached to the carbonyl group and possibly also to coordination of the aryl group in the transition state.

The asymmetric reduction of aryl alkyl ketones has been examined using a variety of reagents (Table 10). With the complexes formed by addition of naturally occurring, optically active, amino alcohols (*e.g.* quinine, cinchonidine, ephedrine) to lithium tetrahydridoaluminate, moderate optical yields (40–50% asymmetric induction) of the 1-phenylalkanols were obtained in ethereal solution, with lower optical yields of the enantiomer being obtained in THF.[66] This shows the importance of the solvent complexing with the reagent in the transition state. A more remarkable finding is that reduction of acetophenone using the synthetic chiral amino alcohol (**52**) complexed with lithium tetrahydridoaluminate (ratio 2.3:1) gave 1-phenylethanol with a 68–75% excess of the (*R*)-enantiomer when freshly prepared reagent was used.[67] When the amino alcohol–aluminium complex was allowed to stand for several hours at room temperature, reduction of acetophenone gave 1-phenylethanol with up to 75% excess of the (*S*)-enantiomer. The results are difficult to explain but, nevertheless, are synthetically very useful.[67] A similar reversal of selectivity has been observed in the reduction of aromatic ketones with monosaccharide (**53**)–lithium tetrahydridoaluminate complexes, depending on whether one of the two available hydrogen atoms on the metal is initially removed by treatment with one equivalent of ethanol.[68]

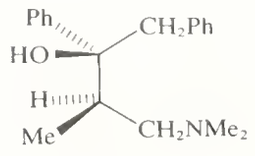
In an attempt to remove the ambiguities caused by coordinating solvents, the reduction of aromatic ketones using tris[(*S*)-2-methylbutyl] aluminium has been examined in pentane solution.[69] It was found that for acetophenone the asymmetric induction was relatively independent of temperature, but for propiophenone the selectivity *decreased* at low temperatures. When the aluminium alkyl was complexed with ether, however, the

TABLE 10

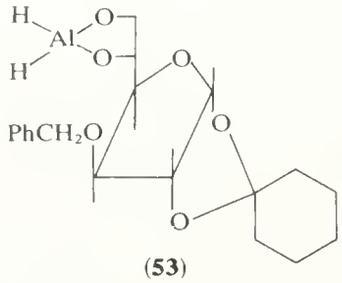
Comparison of Asymmetric Reducing Agents in the Reduction of Aromatic Ketones to Alcohols

Ketone	*Optical purity of alcohol (%) and configuration using* $LiAlH_4$–*alkaloid*[a]	$LiAlH_4$–(**53**)[b]	AlH_3–(**54**)[c]	R_3Al[d]	$LiAlH_4$–(**52**)[e]	$LiAlH_4$–(**55**)[f]
PhCOMe	48 (*R*)	71 (*R*)	84 (*S*)	6 (*S*)	68 (*R*)	68 (*R*)
PhCOEt	—	46 (*R*)	—	13 (*S*)	—	62 (*R*)
$PhCOCHMe_2$	—	—	—	44 (*S*)	38 (*R*)	43 (*R*)
α-Tetralone	—	—	—	—	—	3.7 (*S*)
$PhCH_2COMe$	3 (*R*)	—	16 (*S*)	—	—	0.5 (*S*)
$C_6H_{13}COMe$	6 (*S*)	25 (*R*)	—	—	—	4 (*S*)

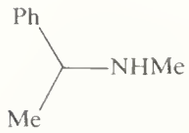
[a] Ref. 66. [b] Ref. 68. [c] G. M. Giongo, F. Di Gregorio, N. Palladino, and W. Marconi, *Tetrahedron Letters*, 1973, 3195. [d] Ref. 69. [e] Ref. 67. [f] Ref. 70.



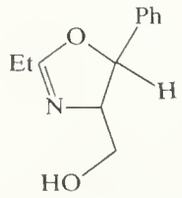
(**52**)



(**53**)

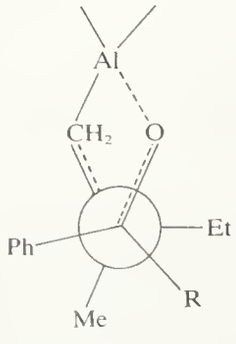


(**54**)

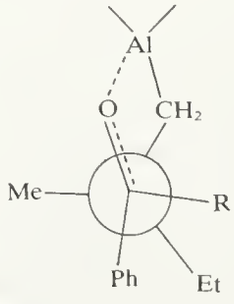


(**55**)

opposite temperature effect was observed, *i.e.* the selectivity increased at lower temperatures.[69] By considering the four possible cyclic transition states involving weak coordination of the aluminium atoms with the carbonyl oxygen, the results can be rationalized. Transition states (**56**) and (**57**) would lead to the (*S*)-alcohol whereas (**58**) and (**59**) would lead to the (*R*)-enantiomer; in practice, (*S*)-alcohol predominates. Of the four possible transition states, a consideration of electronic factors leads to the conclusion[69] that (**57**) and (**59**) would be of higher energy than (**56**) and (**58**), in which the aryl group is *gauche* to the Al—CH_2 bond. Of the transition states (**56**) and (**58**), (**56**) is the least hindered, and the effect of making R more bulky is to render (**58**) more conformationally rigid. A reduction in temperature would reduce the conformational mobility in both (**56**) and (**58**), but more so in (**56**), so that lowering the temperature *reduces* the free energy difference

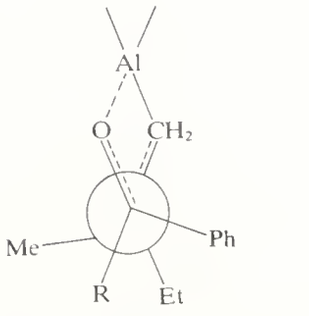


(**56**)

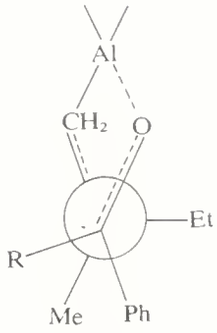


(**57**)

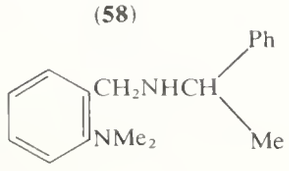
between the two and lower selectivity is observed. When the alkyl aluminium is complexed with ether, the coordination of the aluminium to the carbonyl group is much weaker, the transition states are looser and therefore the opposite temperature effect is observed.[69]



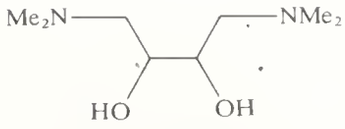
(58)



(59)



(60)

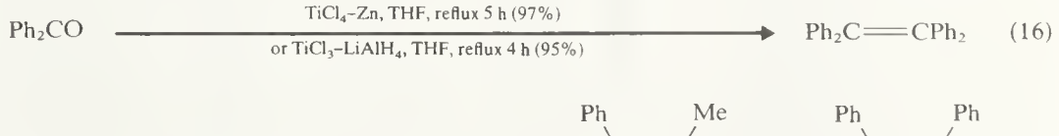


(61)

One of the most successful chiral reducing agents for aryl alkyl ketones is the complex formed between the 2-oxazoline (**55**)[70] and lithium tetrahydridoaluminate. The complex ($oxazoline_2AlH_2$) is soluble in THF even at −78 °C and at this temperature ketones are reduced in 80–90% yield and high optical purity (Table 10) if two moles of reagent are used. The chiral oxazoline can be easily recovered in 70–95% yield after the reaction.[70] The chiral diamine (**60**)[71] and the amino alcohol (**61**)[72] have also been used recently, giving optical yields of 40–50% in the reduction of aryl ketones.

5.4.5.2 Reductive coupling of aromatic ketones

One of the more interesting classes of reagents to be introduced recently is the low-valent titanium species generated by treatment of titanium(III) or titanium(IV) chloride with reducing agents. These reagents, which have found many uses in synthetic organic chemistry,[73] will promote the reductive coupling of aldehydes and ketones to olefins. The 'first-generation' reagents, Ti(II) species, prepared by reduction of titanium(IV) chloride with zinc or magnesium, reduced only aromatic aldehydes and ketones to constitutionally symmetrical olefins (equations 16 and 17).[74] The stronger reagent $TiCl_3$–$LiAlH_4$, introduced by McMurry,[75] is much more versatile and some aliphatic ketones also undergo the reaction. This reagent,[75] however, gave erratic results with some aliphatic carbonyl compounds, but an active Ti(0) species, prepared by reducing Ti(III) chloride with metallic lithium or potassium, gave excellent results with both aromatic and aliphatic aldehydes and ketones; it is now the preferred reagent for the synthesis of constitutionally symmetrical olefins. The mechanism of these transformations has been discussed in Section 5.3.6.1 and is shown in Scheme 29 of this chapter.

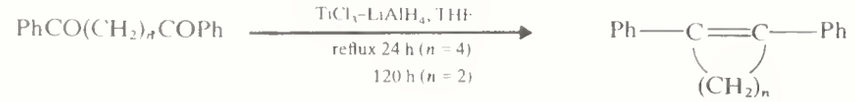


(16)

(17)

(92%) (82:18)

The scope of these reductive coupling reactions has recently been extended. Firstly, intramolecular couplings giving cyclic diaryl olefins proceeded in moderate yield (equation 18),[76] and secondly, constitutionally unsymmetrical olefins could be prepared using this method. When acetone was used in excess, coupling of aromatic ketones using $TiCl_3$–Li proceeded to give mainly unsymmetrical products after removal of the volatile 2,3-dimethylbut-2-ene by-product (Table 11).[77] In contrast, coupling of aliphatic ketones



(18)

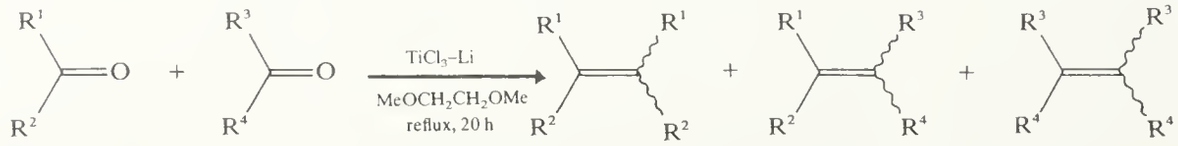
$n = 4$ (25%)
$n = 2$ (40–61%)

(19)

with acetone gave the expected statistical distribution of olefins (Table 11).[77] This result was surprising, considering that the reduction potentials of aromatic ketones (such as benzophenone) are 1.0–1.5 V less negative than that of acetone and therefore reduction to the anion radical ($Ar_2\dot{C}—\bar{O}$) should take place more rapidly than with acetone. Coupling of these anion radicals should give preferentially constitutionally symmetrical olefins. It appears likely, therefore, that the Ti(0) species reduces the anion radical to the dianion ($Ar_2\bar{C}—\bar{O}$) which reacts with acetone to give the products (equation 19). On this basis, good yields of constitutionally unsymmetrical olefins in mixed coupling reactions were expected, provided that reduction of one component to the dianion occurred before reduction of the second component to the radical ion. This has recently been demonstrated (Table 11).[77]

TABLE 11

Ti(0)-induced Mixed Carbonyl Coupling[a]



(A) (B) (C)

R^1R^2CO	R^3	R^4	*Ratio* $R^1R^2CO:R^3R^4CO$	*Yield* (%) A	B	C
Cycloheptanone	Me	Me	1:4	26	50	—[b]
Benzophenone	Me	Me	1:4	trace	94	—[b]
Fluorenone	Me	Me	1:4	0	84	—[b]
Acetophenone	Me	Me	1:4	16	65	—[b]
1-Indanone	Me	Me	1:4	24	71	—[b]
Benzophenone	Me	Me	1:1	14	81	—[b]
Benzophenone	—$(CH_2)_5$—		1:1	19	78	6
Benzophenone	C_5H_{11}	H	1:1	9	84	8
Benzophenone	Bu^t	Bu^t	1:1	90	—	—
Fluorenone	Me	Me	1:1	8	74	—[b]
Fluorenone	—$(CH_2)_6$—		1:1	7	77	17
Fluorenone	Ph	Me	1:1	8	70	15

[a] Ref. 77. [b] Product too volatile to isolate.

5.4.6 WILLGERODT REACTION

The original reaction, discovered by Willgerodt in 1887,[78] involved the conversion of an aryl methyl ketone into an arylacetamide by heating with aqueous ammonium polysulphide. The reaction has subsequently been extended to a variety of substrates; when aryl alkyl ketones were subjected to the same conditions, ω-arylalkanoic acids were obtained.[79] For example, propiophenone yielded 3-phenylpropionamide (82%). This unique reaction has been applied to the synthesis of a wide range of polycyclic aromatic alkanoic acids, which could otherwise be obtained only by multistage syntheses (Table 12).

TABLE 12
Conversion of Aryl Alkyl Ketones to ω-Arylalkanoic Acids[a]

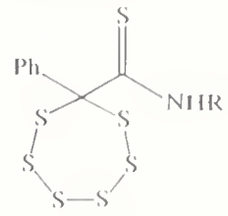
$$ArCO(CH_2)_nCH_3 \xrightarrow[S]{R_2NH} Ar(CH_2)_{n+1}C(=X)NR_2$$

Ar	*n*	*Willgerodt* [$(NH_4)2S_x$] *Yield*, (X = O, %)	*Kindler modification* [*morpholine*, *S*] *Yield* (X = S, %)
C_6H_5	0	50	94
4-ClC_6H_4	0	35	47
2-HOC_6H_4	0	0	59
4-$MeOC_6H_4$	0	25	62
3-$H_2NC_6H_4$	0	—	61
1-naphthyl	0	88	—
4-PhC_6H_4	0	84	94
2-Fluorenyl	0	70	—
2-Phenanthryl	0	82	—
1-Pyrenyl	0	92	—
3-Pyridyl	0	70	74
3-Carbazolyl	0	85	—
C_6H_5	1	82	65
1-Pyrenyl	1	67	—
C_6H_5	2	32	49
1-Pyrenyl	2	55	—
C_6H_5	3	29	14
C_6H_5	5	25	—

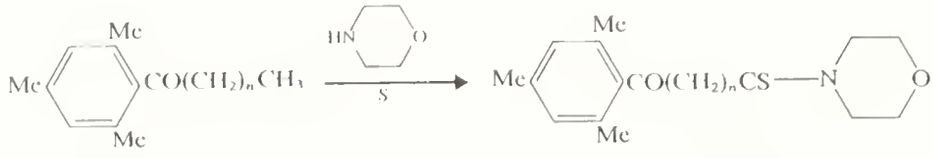
[a] Ref. 79.

One of the practical disadvantages of the Willgerodt reaction, the need for pressure equipment, can be overcome by using the Kindler modification in which an aliphatic amine, *e.g.* morpholine, and sulphur are used in place of ammonium polysulphide. The reaction is conducted at a lower temperature (130–150 °C) and consequently groups such as OH and NH_2, which do not survive the original Willgerodt conditions, remain unchanged in the Kindler modification (Table 12); the product is the thioamide which is easily hydrolysed by acid or base to the alkanoic acid in high yield.

The mechanism of the reaction has been the subject of much discussion and, although many suggestions have been put forward, no single mechanism accounts for all of the following observations. (i) There is no skeletal rearrangement; ^{14}C-labelled acetophenone gave phenylacetamide in which the carbon atoms remain in the same positions.[80] (ii) When the alkyl chain contained a quaternary carbon atom adjacent to the carbonyl group, only reduction of the carbonyl group to a methylene group took place.[81] (iii) Use of $PhCOCH_2CD_2Et$ led to 95% loss of *both* deuterium atoms.[82] A possible mechanism for the Kindler modification is shown in Scheme 12 for the transformation of propiophenone into 3-phenylpropionamide. The carbonyl group is converted to a thiocarbonyl group, which is α-thiolated, then transferred down the chain by desulphurization and further thiolation. In some cases,[83] intermediates (**62**), derived from thioketones, have been isolated. α-Thiolation of the methylene group, however, may take place directly; in support of this theory, the hindered ketones (**63**) give the ketothioamides (**64**)[84] (equation 20).

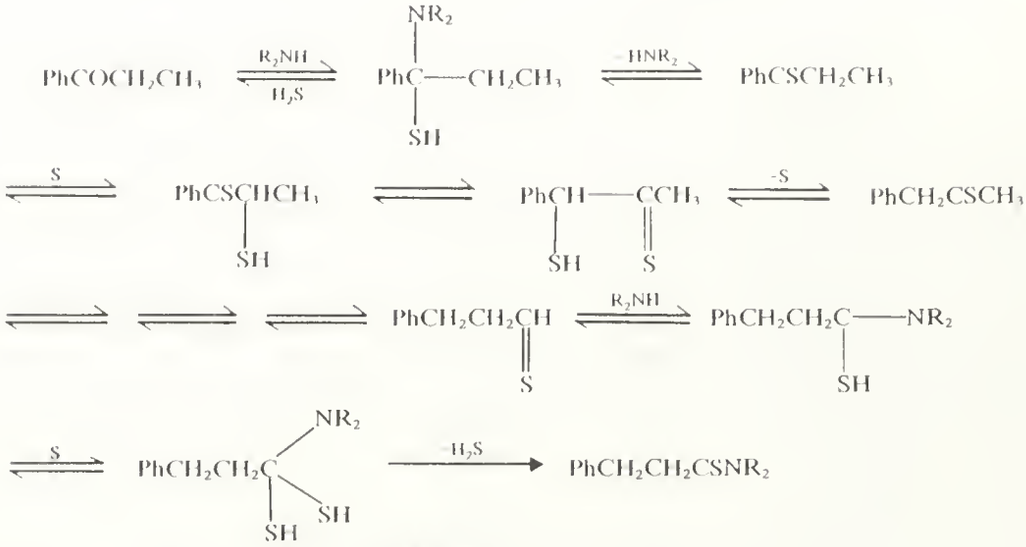


(62)



(63) (64) (20)

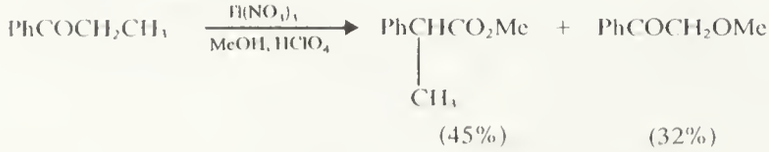
$n = 0$ (35%)
$n = 1$ (30%)
$n = 2$ (35%)



SCHEME 12

5.4.7 OXYTHALLATION OF AROMATIC KETONES

The transformation of aryl methyl ketones to arylacetic acid derivatives can be more efficiently carried out using thallium(III) nitrate in methanol as the oxidizing agent.[85] This is but one of a number of interesting reactions discovered during recent research on uses of thallium in organic synthesis by groups working at Princeton and the University of East Anglia.[86,87] The arylacetic ester synthesis has several advantages over the Willgerodt reaction: room temperature reaction, higher yields, and simple isolation procedure.[85] The scope of the reaction is illustrated in Table 13. Amino ketones cannot be used owing to complexing with the thallium reagent; after protection as the amide, however, the reaction proceeds in good yield. Deactivated aromatics, containing electron-withdrawing groups, give poor yields and ketones containing additional olefinic groups cannot be used since oxythallation of the double bond competes. When propiophenone was the substrate, a mixture of methyl 2-phenylpropionate (45%) and 2-methoxypropiophenone (32%) was obtained (equation 21).[85]



(45%) (32%) (21)

TABLE 13

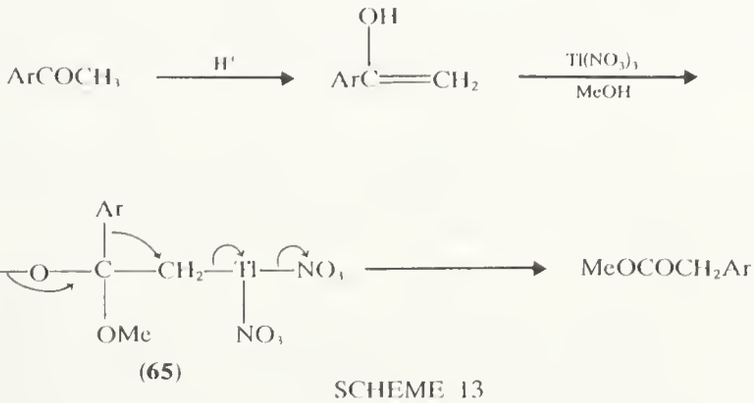
Oxidative Rearrangement of Aryl Ketones to Arylacetic Esters[a]

$$ArCOCH_3 \longrightarrow ArCH_2CO_2Me$$

Ar	*Time* (h)	*Conditions A*[b] *Yield* (%)	*Conditions B*[b] *Yield* (%)
C_6H_5	5	84[c]	36
4-BrC_6H_4	15	35	89
4-MeC_6H_4	4	86	84
4-HOC_6H_4	2	64	—
4-$O_2NC_6H_4$	24	<5	50[e]
2-$MeOC_6H_4$	12	62	—
4-$MeOC_6H_4$	1	89	92
4-$PhCONHC_6H_4$	0.5[d]	66	—
1-Naphthyl	2	91	—
2-Naphthyl	2	89	—

[a] Refs. 85–89. [b] A = $Tl(NO_3)_3$, MeOH, trace $HClO_4$, room temp; B = $Tl(NO_3)_3$, K-10; methylene chloride, room temperature, 4–30 min. [c] By-product $PhCOCH_2OMe$ (6%) isolated. [d] Reaction conducted at 50 °C. [e] $Tl(NO_3)_3$–florisil, carbon tetrachloride, room temperature, 90 min.

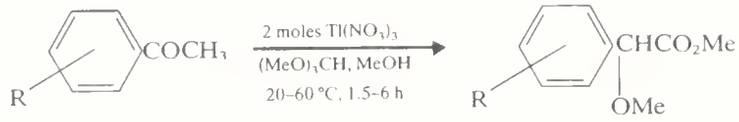
The mechanism shown in Scheme 13, which, in contrast to the Willgerodt reaction, involves aryl migration, has been proved to be correct by using ^{14}C-labelled acetophenone. The mechanism involves acid-catalysed enolization and oxythallation of the enol double bond followed by oxidative rearrangement with 1,2-aryl migration. Methanolysis of the carbon–thallium bond in the intermediate (**65**) leads to the methoxy ketone by-products; this reaction pathway, in which the α carbon atom may have carbenium ion character is stabilized by the presence of α-alkyl substituents. In agreement with this principle, the reaction of thallium nitrate with 2-methoxyacetophenone gave no rearrangement, only methoxylation to the acetal of phenylglyoxal, $PhCOCH(OMe)_2$.[85]



(**65**)

SCHEME 13

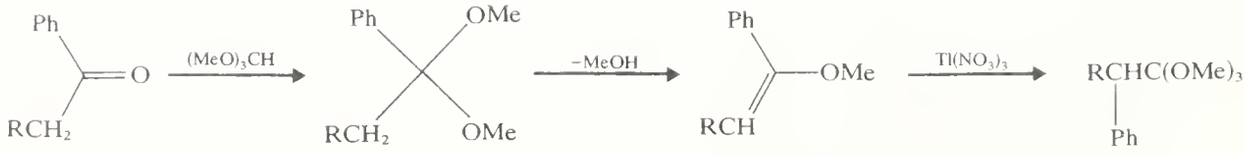
In contrast, when the conditions were changed slightly by the inclusion of trimethyl orthoformate (which removes the water of hydration in the thallium reagent), the products were the rearranged α-methoxy esters (**66**) (equation 22).[88] The esters (**66**) were *not* derived from the phenylacetic esters by a methoxylation reaction; the mechanism was envisaged to proceed *via* two successive methoxythallations (Scheme 14).[88] In the absence of water, the intermediate orthoesters eliminate methanol rather than be hydrolysed to the esters. When propiophenone and butyrophenone were reacted, no α-methoxylation took place and 2-phenyl-propionic (100%) and -butyric esters (93%) were isolated; the second oxythallation is hindered by the presence of an alkyl and aryl group on the same carbon and the reaction stops at the first stage (Scheme 14).[88]

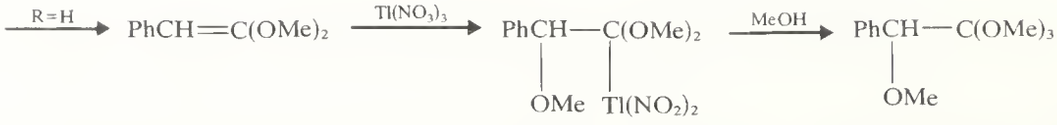


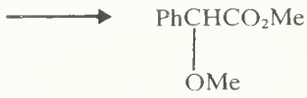
(22)

(**66**)

R = H (70%)
R = 4-OMe (81%)
R = 4-NO_2 (87%)
R = 3-PhO (97%)

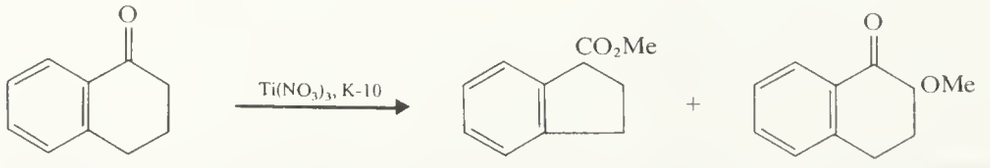






SCHEME 14

By absorbing thallium nitrate and methanol on an inexpensive acidic montmorillonite clay (K-10), an even more effective reagent for the conversion of aryl ketones to arylacetic esters has been produced.[89] The oxidative rearrangements took place in an inert solvent (*e.g.* CH_2Cl_2, heptane) in 5–30 minutes at room temperature to give high yields of esters (Table 13), even in cases where thallium nitrate gave only moderate yields. Propiophenone and butyrophenone also reacted to give high yields of esters, and the cyclic ketone (**67**) gave only the oxidative rearrangement product (**68**; 50%) and the methoxylated ketone (**69**; 50%) when treated with the supported thallium reagent (equation 23); using thallium nitrate in methanol, at least ten products were formed.[89]



(**67**) (**68**) (50%) (**69**) (50%) (23)

The practical advantages in carrying out reactions using supported reagents are numerous. When using inorganic reagents it is often difficult to find a solvent which dissolves both reagent and organic substrate; using a supported reagent, any inert solvent which dissolves the substrate can be used. Isolation of the product is easily carried out by filtration followed by evaporation. When the toxic thallium reagents are used, an important factor is that the thallium remains tightly bound to the support at the end of the reaction. After filtration, no thallium could be detected by atomic absorption spectroscopy

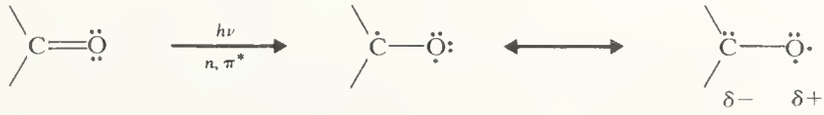
in the filtrate or the product even from a molar scale reaction.[89] Thus the problem of toxic waste disposal is eliminated and the regeneration of the reagent may be possible under certain circumstances. It is for these reasons that the use of supported reagents is now attracting the attention of many pharmaceutical companies for the industrial synthesis of fine chemicals.

The oxidative rearrangements using supported thallium(III) nitrate proceed faster and more selectively than using unsupported reagent. The support (K-10) has a lamellar structure and it appears likely that the substrate is adsorbed between the layers which contain unhydrated thallium and methanol on the surface of the clay. This may pose a limitation on the method since bulky aromatics or polycyclic aromatics which are too large to fit into the layered structure will not react. Supports which do not have the lamellar structure do not function as selectively as K-10.[89]

5.4.8 PHOTOCHEMISTRY OF AROMATIC KETONES

Over the last 20 years, there has been a tremendous surge of interest in organic photochemistry so that it has now become a major branch of organic chemistry.[90] The mechanisms of photochemical reactions, and, in particular, of carbonyl compounds, are now reasonably well understood and this has enabled photochemistry to be exploited for synthetic purposes. When a molecule is converted into its excited state, the excess of energy over the ground state and the change in electron distribution enable reactions to take place which are impossible in ground-state chemistry, and it is this potential for new modes of reaction which has engaged the interest of many chemists over the last few years.

The photochemistry of aromatic carbonyl compounds, particularly ketones, has played a large part in the development of synthetic and mechanistic photochemistry.[91–93] For typical phenyl ketones the long-wavelength absorption at approximately 325 nm in the u.v. spectrum corresponds to the $n \rightarrow \pi^*$ transition in which an electron is promoted from a non-bonding orbital, localized mainly on oxygen, to an antibonding π^* orbital spread over both carbon and oxygen. The n,π^* excited state is therefore not as electron-deficient around the carbon atom as the ground state and nucleophilic attack at the carbon atom in the excited state is relatively unimportant. The main reactions of the n,π^* state resemble those of an alkoxy radical, since the excited carbonyl group has an unpaired electron in the *p*-orbital of the oxygen atom (equation 24).



(24)

In aromatic carbonyl compounds, excitation to the first excited singlet is followed by very rapid intersystem crossing to the triplet state, which possesses more diradical character than the singlet. Typical n,π^* triplet energy values are 72 kcal mol^{-1} (302 kJ mol^{-1}) above the ground state for phenyl alkyl ketones and 68 kcal mol^{-1} (285 kJ mol^{-1}) for benzophenone. However, the π,π^* triplet states of aromatic ketones are of comparable energy (75 kcal mol^{-1}, 315 kJ mol^{-1}) to the n,π^* triplets; substituents on the phenyl ring or even a change of solvent may cause the π,π^* state to have lower energy. Excitation to a π,π^* triplet causes electron density to move from the aromatic ring towards the carbonyl group so that, as in the ground state, the carbonyl group is electron rich. π,π^* States are, in consequence, much less reactive than n,π^* states.

Electron-donating substituents in the aromatic ring stabilize the π,π^* triplet and destabilize the n,π^* triplet. A similar stabilizing effect takes place in polar solvents. With acetophenone, the introduction of one methyl group into the aromatic ring is enough to invert the energies of the triplet states, whereas in benzophenone only strongly electron-donating groups such as NH_2 make the lowest triplet π,π^* in character. Groups which are

inductively electron-withdrawing (*e.g.* CF_3) stabilize the n,π^* state whereas other electron-withdrawing groups (*e.g.* halogen, CN) which conjugate with the carbonyl group stabilize both states.

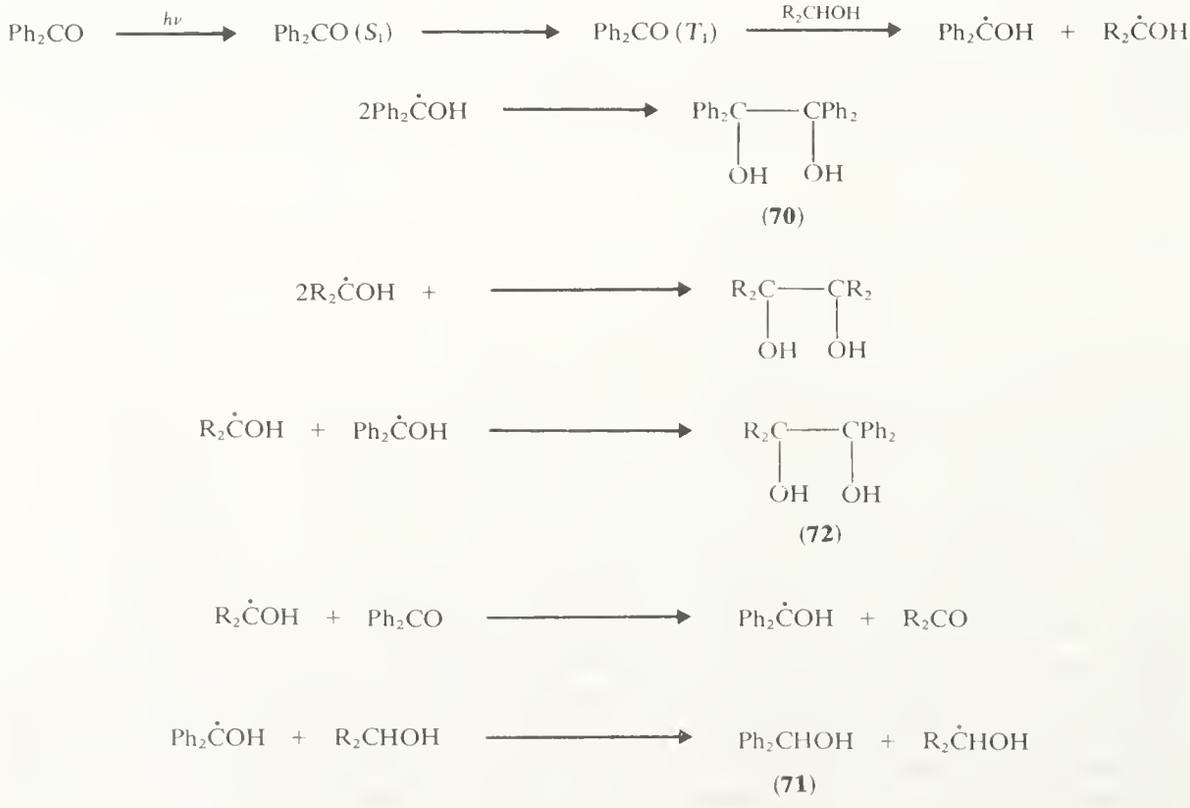
Acylbiphenyls and acylnaphthalenes have π,π^* lowest excited triplets, the nearest n,π^* triplets being more than 6 kcal mol^{-1} (25 kJ mol^{-1}) above. π,π^* Triplets are much less reactive, for example, in hydrogen abstraction reactions; the rate of hydrogen abstraction is normally a function of the energy gap between the n,π^* and π,π^* states and varies appreciably with solvents.

5.4.8.1 α-Cleavage

Whereas aliphatic ketones undergo α-cleavage — the 'Norrish type I' process — giving an acyl radical and an alkyl radical, aromatic ketones do not normally undergo this process since the typical carbon–carbon bond strength (325 kJ mol^{-1}) is greater than the energy available in the triplet states of aromatic ketones. Ketones with weaker bonds, *e.g.* aryl t-alkyl ketones,[94] some benzyl ketones,[95,96] and benzoin ethers[97] are cleaved. The latter reaction is extremely important commercially since benzoin ethers are among the most common initiators for photopolymerization[97] (see Section 5.4.9). Ketones with π,π^* lowest excited states are either very slowly cleaved (*e.g.* *p*-methoxyphenyl t-butyl ketone) or are photostable (*e.g.* *p*-biphenylyl t-butyl ketone).

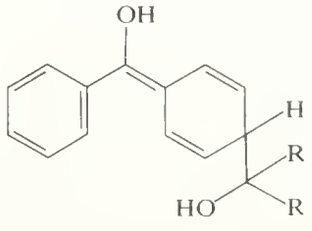
5.4.8.2 Photoreduction

The photoreduction of ketones is one of the best known reactions in photochemistry.[98,99] It was first discovered by Ciamician and Silber,[100] who found that a solution of benzophenone in alcoholic solvents was slowly converted in sunlight to the corresponding pinacol. The reaction has since been studied in great detail and the mechanism is shown in Scheme 15.[101]

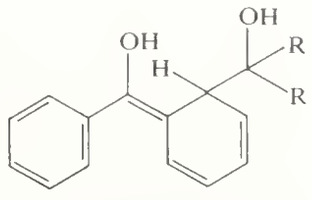


SCHEME 15

In isopropanol solution, reduction occurred with a quantum yield as high as 2, *i.e.* absorption of one photon of energy gave rise to products derived from two molecules of benzophenone. The reason is that the radical generated from isopropanol transfers another hydrogen to a ground state molecule of benzophenone. At room temperature, a quantitative yield of pinacol (**70**) was obtained, but if the temperature was raised to 100 °C the product was the alcohol (**71**). When methanol was the solvent, the products were concentration dependent; irradiation of a 0.2M solution of benzophenone in methanol gave (100%) the pinacol (**70**) whereas irradiation of a 0.0001M solution gave (90%) the product (**72**; R = H) formed by addition of methanol. Cross-coupling products were also observed when toluene was the solvent.[92] Recently, evidence has been presented for the formation of transient *ortho*- and *para*-coupled products in photoreduction reactions.[102] These transients, (**73**) and (**74**), which absorb light and inhibit the photoreduction process, react with oxygen to give benzophenone, but have been shown not to give rise to the pinacol (**72**).

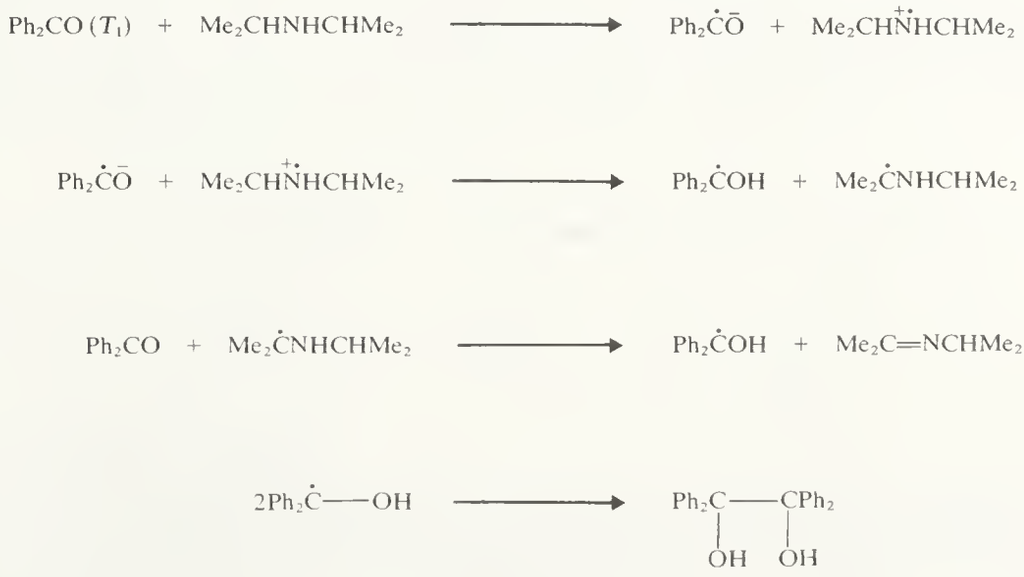


(**73**)



(**74**) R = Me, Ph

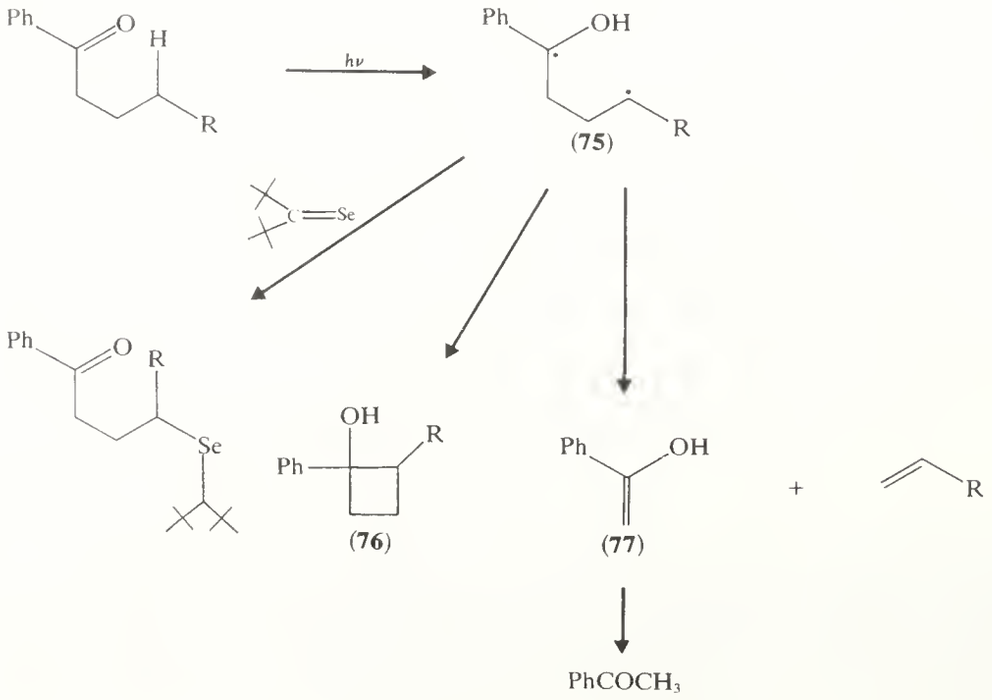
Photoreduction of aryl ketones by alcohols is generally an efficient process for n,π^* but not for π,π^* triplet excited states. If amines are used as donors, however, then n,π^* and π,π^* triplets are photoreduced equally well.[103] In the latter cases, a charge-transfer mechanism has been shown to be involved by the detection of intermediate radical ions by e.s.r. spectroscopy.[104] The mechanism for the reaction of benzophenone with primary and secondary amines is shown in Scheme 16. Further evidence for a specific interaction between carbonyl group and amine is that photoreduction of acetophenone using an optically active amine as solvent gave rise to 6% asymmetric induction in the pinacol product, whereas when an optically active alcohol was used, only racemic pinacols were obtained.[103]



SCHEME 16

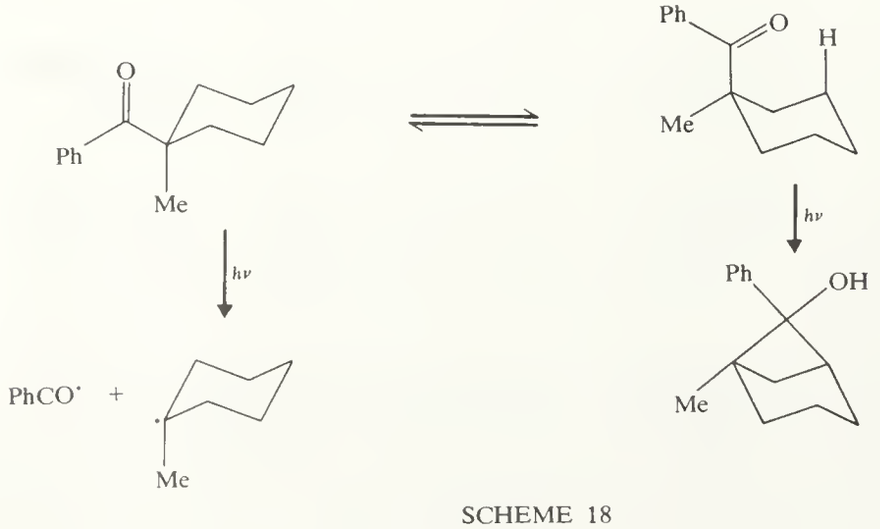
5.4.8.3 Intramolecular hydrogen abstraction (Norrish Type II processes)

Aromatic ketones having a γ-hydrogen atom can, like aliphatic ketones, undergo intramolecular hydrogen abstraction *via* a cyclic six-membered transition state which leads to an intermediate diradical (**75**). This intermediate can either ring close to the cyclobutanol (**76**) or cleave to the enol (**77**) together with an olefin (Scheme 17).[91,105] The diradical (**75**) has been trapped by a variety of reagents, *e.g.* di-t-butyl selenoketone.[105]



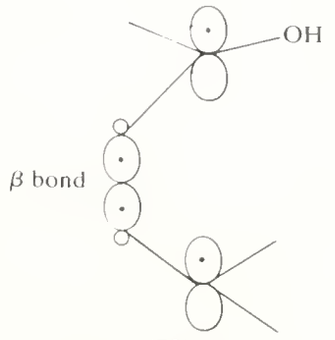
SCHEME 17

The excited-state reactions of aromatic ketones are very fast, even compared with conformational changes, and, in some cases, the ground-state conformation dictates the photochemical pathway taken. Excitation of 1-benzoyl-1-methylcyclohexane yields two triplets; the shorter-lifetime triplet undergoes γ-hydrogen abstraction whereas the longer-lifetime triplet (10^{-7} s) undergoes α-cleavage (Scheme 18).[106] The rate of cyclohexane ring inversion ($10^5\ s^{-1}$) is too slow to allow equilibration of excited-state conformers in which the benzoyl group is either axial or equatorial.[106]

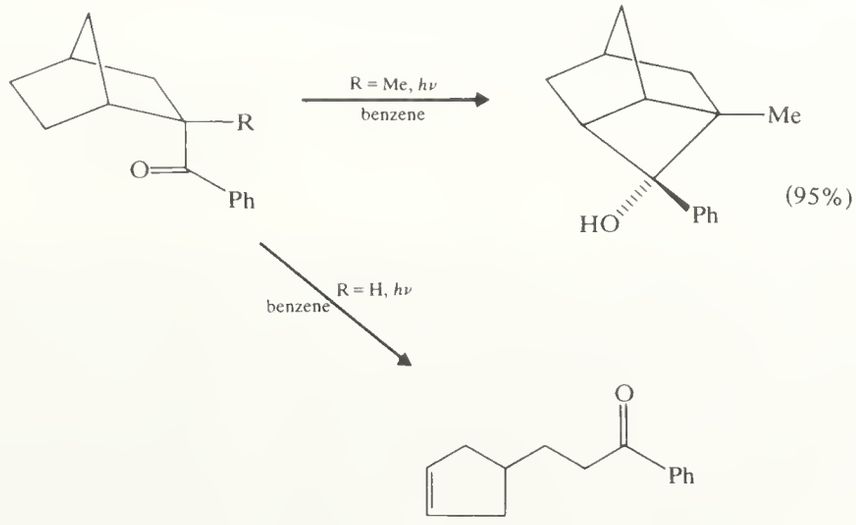


SCHEME 18

The formation of cyclobutanols is a synthetically very useful reaction, especially in rigid systems. This is due to the steric requirement for the competing β-cleavage reaction of the diradical, which only occurs when the β-bond is in the same plane as the radical sites — see (**78**).[107] In molecules in which β-cleavage is prevented by steric factors, high yields of cyclobutanols can be obtained.[107] In the example in Scheme 19, the correct alignment for β-cleavage can only be achieved by eclipsing the methyl and phenyl groups, so that cyclobutanol formation is more favourable; in the absence of the methyl group, β-cleavage occurs.[108]

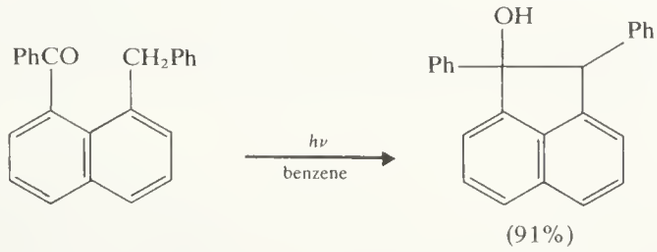


(**78**)



SCHEME 19

Although γ-hydrogen abstraction is a very general process, electronic or geometric factors may influence the reaction so that other hydrogen atoms may be abstracted *via* five-, seven-, or eight-membered transition states[109–111] (equation 25).

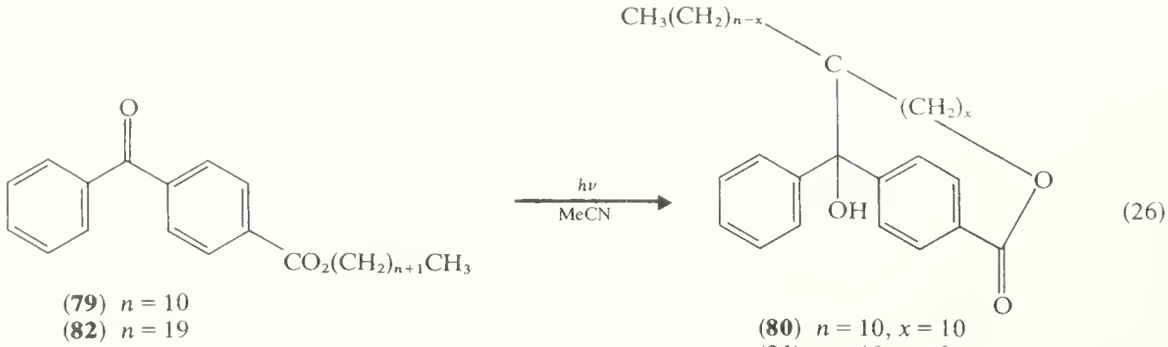


(91%) (25)

5.4.8.4 Biomimetic chemistry[112]

One of the most interesting applications of the photochemistry of aromatic ketones has been the attempt by Breslow and co-workers to mimic the regio- and stereo-selectivity of enzymes by imposing orientation on otherwise unselective reactions.[112] In Nature the dehydrogenation of stearic acid to oleic acid by *Micobacterium phlei* is extremely regioselective. To try to emulate this type of reaction, Breslow has examined the remote

functionalization of long-chain n-alkanols by irradiation of the alkyl esters of benzophenone-4-carboxylic acid, expecting that the geometry of the system would dictate which hydrogen atom in the substrate would be abstracted by the benzophenone triplet (equation 26). When (**79**) was irradiated the major product (**80**; 65%) arose by attack at C-11, the minor (**81**; 28%) by attack at C-10. No attack at the methyl group was observed, probably owing to electronic rather than geometric factors. When the alkyl chain was lengthened, less regioselectivity was observed, since the system was more flexible. Increasing the temperature, however, led to an increase in regioselectivity.[113] Irradiation of the ester (**82**) at room temperature gave a mixture of cyclized products in which functionalization of the chain had taken place at C-11 to C-16, each in 10–20% yield. At 60–65 °C, however, the major product (**83**; 32%) arose by attack at C-18.

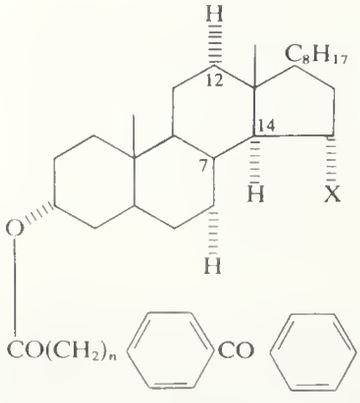


(26)

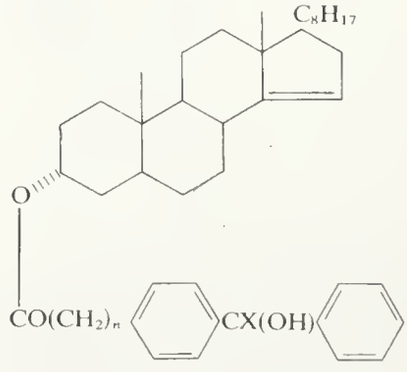
(**79**) $n = 10$
(**82**) $n = 19$

(**80**) $n = 10, x = 10$
(**81**) $n = 10, x = 9$
(**83**) $n = 19, x = 17$

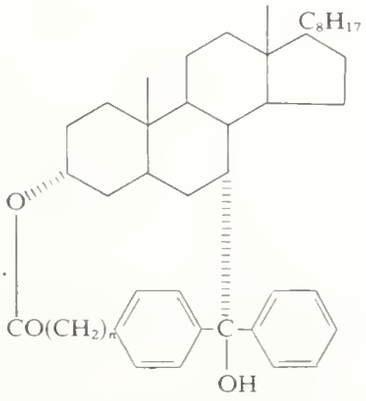
Although these reactions are not synthetically attractive, the remote functionalization of more rigid substrates, particularly steroids, has been used to obtain products which hitherto have been difficult to synthesize.[114] It was predicted, after examination of molecular models, that on irradiation of the benzophenone-4-propionic acid ester of 3α-cholestanol (**84**), functionalization would occur at C-12, C-14, and C-7. Irradiation of (**84**) at a concentration (10^{-3}M) low enough to prevent intermolecular reactions gave rise to an olefin (**85**; 35%) and two lactones (**86**; 45%) and (**87**; 19%). The olefin was formed by abstraction of the hydrogen attached to C-14, followed by further abstraction by the resultant radical to give the olefin. The lactones (**86**) and (**87**) were formed by abstraction of the hydrogen atoms at C-7 and C-12 followed by coupling of the resultant diradicals.



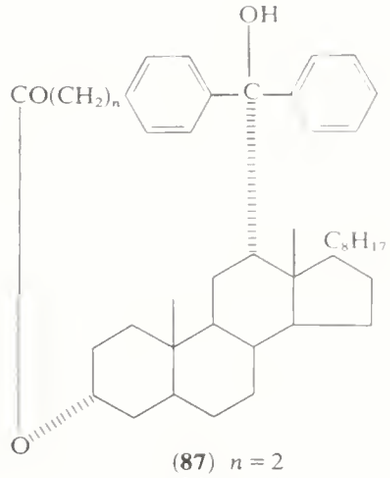
(**84**) $n = 2$, X = H
(**88**) $n = 1$, X = H
(**92**) $n = 1$, X = D



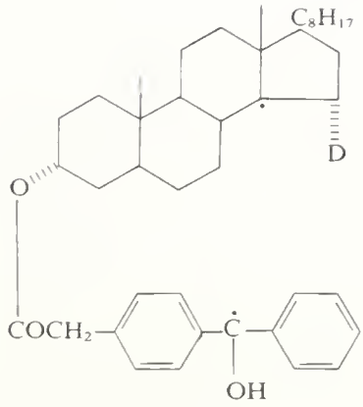
(**85**) $n = 2$, X = H
(**89**) $n = 1$, X = H
(**93**) $n = 1$, X = D



(**86**) $n = 2$
(**90**) $n = 1$



(**87**) $n = 2$
(**91**) $n = 1$



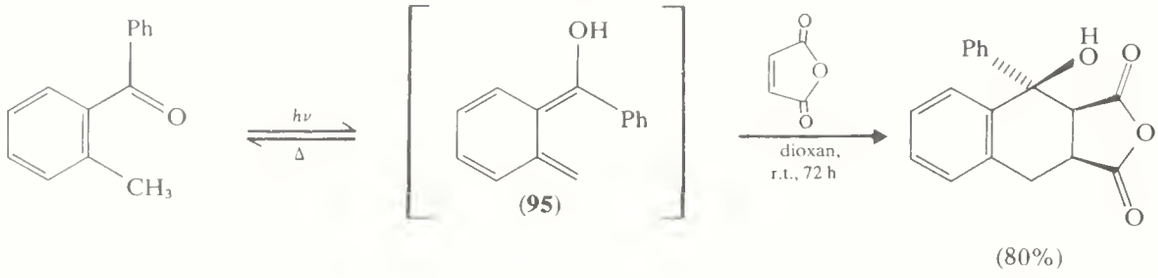
(**94**)

The corresponding benzophenone-4-acetic acid ester (**88**) gave olefin (**89**; 55%) and two lactones (**90**; 17%) and (**91**; 4%) besides intermolecular pinacol (16%). The mechanism of formation of the olefin has been examined in detail using the deuteriated derivative (**92**) containing 83% deuterium at C-15. On irradiation, the product (**93**) contained 78% deuterium attached to the benzhydrol carbon atom. This shows that the mechanism is by abstraction of the hydrogen atom at C-14 (rather than at C-15) by the excited carbonyl group to form an intermediate diradical (**94**), which then abstracts deuterium from C-15 giving the olefinic product. Thus both hydrogen and deuterium transfer have been directed by the geometry of the system.[114]

In these olefin-forming reactions the induced chiral centre on the benzhydrol carbon atom was not, however, formed selectively; the olefins (**85**) and (**89**) were mixtures of diastereoisomers in approximately equal proportions.[115] In contrast, the lactonic products (**90**) and (**91**) were isolated as single diastereoisomeric products, but lengthening the carbon chain by only one carbon atom led to a more flexible system and the lactones (**86**) and (**87**) were again mixtures of diastereoisomers in equal proportions.[115]

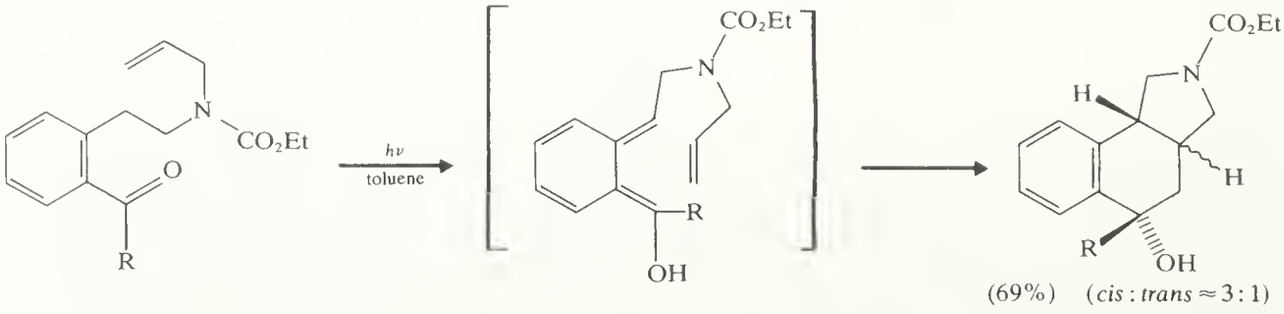
5.4.8.5 Photoenolization[116]

The introduction of substituents bearing α-hydrogen atoms *ortho* to a carbonyl group in an aromatic ring has a dramatic effect on the photochemistry. The quantum yields of normal photoprocesses such as photoreduction are lowered because of competition from photoenolization, a special example of γ-hydrogen abstraction in which an *o*-quinodimethane rather than a diradical is formed. The enol (**95**) is easily converted back into starting material in protic solvents, in the presence of bases, or at high temperatures. The intermediate photoenol has been detected spectroscopically and can be trapped by reaction with oxygen[117] or by dienophiles such as maleic anhydride (equation 27).[118]



(27)

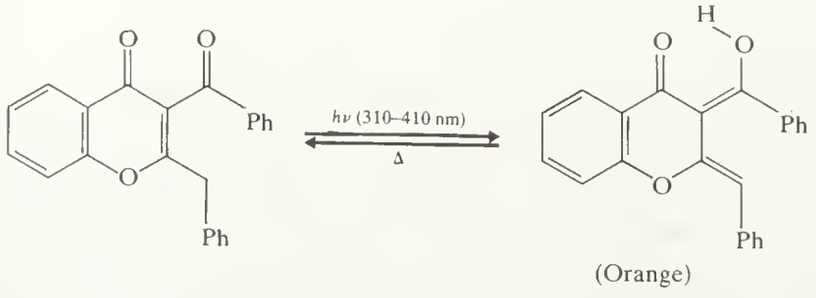
In the latter case only one isomer, the all-*cis* adduct, was formed and it was clearly derived by cycloaddition to the (*E*)-dienol intermediate (**95**). This is in agreement with other evidence which indicates that the (*E*)-isomers are almost always formed on irradiation of *ortho*-substituted aromatic aldehydes and ketones.[116] When the constrained system (**96**) was used so that only a (*Z*)-dienol could be formed, no photoenol could be trapped with dienophiles, and the products arose from the intermediate diradical (**97**).[119]



(28)

Photoenolization has considerable synthetic potential as an annelation method,[120] intramolecular Diels–Alder reactions of the dienol occurring even with unactivated olefins (equation 28).[121]

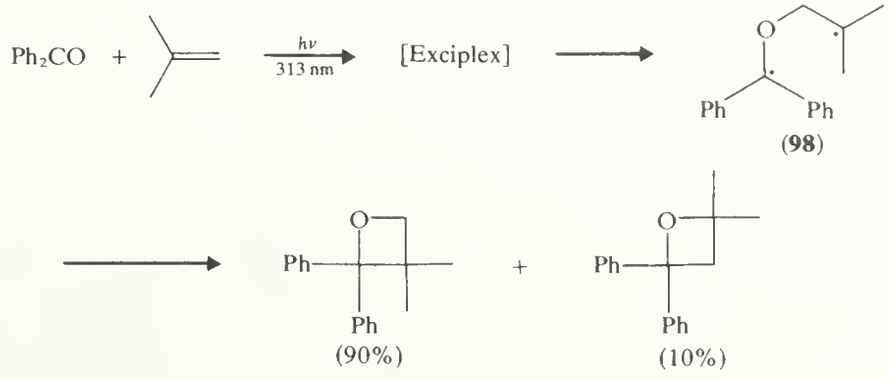
Photoenolization reactions often display photochromism, the phenomenon in which a colour is produced by irradiating at one wavelength and a bleaching occurs either thermally or by irradiation at a different wavelength.[122] For these systems to be important industrially, more stable enols are required so that bleaching does not occur at room temperature. Even stabilization by incorporation in a β-diketone,[123] however, gives an enol with a lifetime of only a few seconds at room temperature (equation 29).



(29)

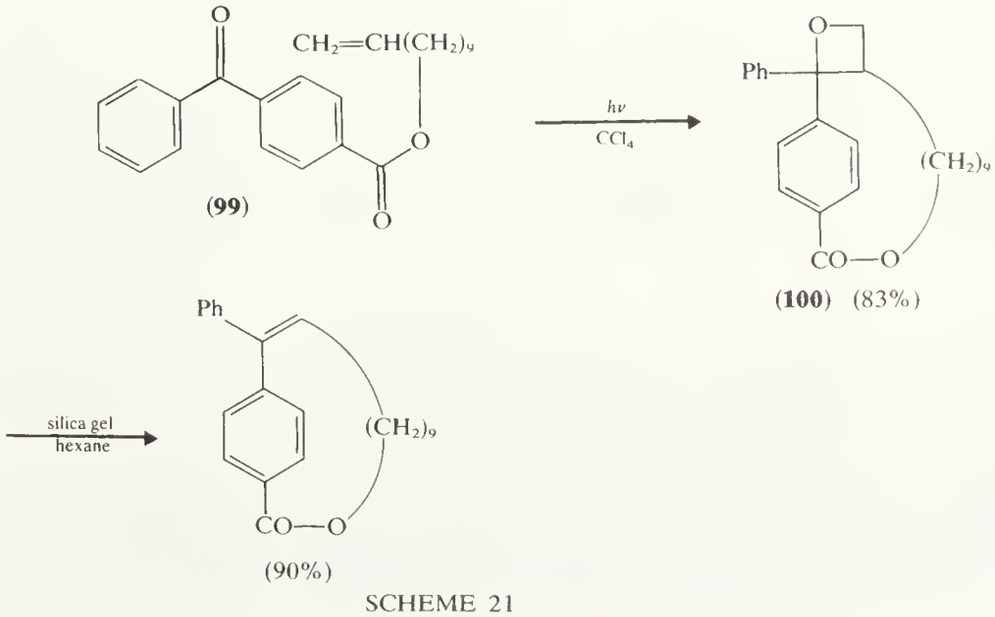
5.4.8.6 Photocycloadditions

On irradiation in the presence of alkenes or alkynes, carbonyl compounds undergo cycloaddition to give four-membered ring oxygen heterocycles (Scheme 20).[124] The reaction is regioselective but not normally stereoselective. Cycloaddition to a *cis*- or *trans*-olefin usually leads to the same mixture of *cis*- and *trans*-oxetans in each case. The detailed mechanism has not been settled, but evidence favours the formation of an excited charge-transfer complex between the carbonyl compound as acceptor and the ground-state alkene as donor.[125] Reaction then leads to a diradical (**98**) which ring closes to the oxetan (Scheme 20). The more stable diradical is formed preferentially and the relative stabilities of the possible diradicals usually determine the selectivity. Aromatic carbonyl compounds react *via* the n,π^* triplet and the resultant diradical is therefore a triplet. Spin inversion must take place before ring closure (Scheme 20) and, within the time taken for this process, the biradical rotates and stereoselectivity is lost.[126] It has been shown that in reactions with olefins the n,π^* singlet state of the carbonyl group (*e.g.* in aliphatic carbonyl compounds) reacts stereoselectively whereas the n,π^* triplet shows no selectivity. In contrast to aliphatic ketones, aromatic ketones do not react with olefins such as acrylonitrile since in the excited triplet carbonyl group the electron-deficient oxygen atom will not attack such an electron-deficient olefin;[91] aromatic aldehydes, however, react normally to give oxetans (Section 5.3.10).[127]



SCHEME 20

An interesting intramolecular ketone–olefin cycloaddition has recently been used in a novel cyclophane synthesis (Scheme 21).[128] A dilute solution of the keto-olefin (**99**) on irradiation in carbon tetrachloride solution gave the oxetan (**100**) which lost formaldehyde



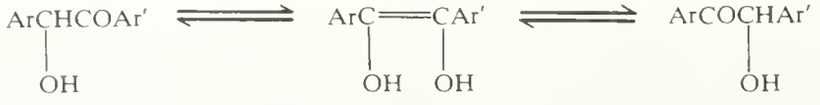
SCHEME 21

on treatment with silica gel. The reaction is restricted to less-strained cyclophanes in this series; highly strained bicyclic oxetans have been synthesized, however, *via* intramolecular [2+2] cycloaddition.[129]

The photoaddition of aromatic ketones to acetylenes takes place readily to give oxeten intermediates, which break down to yield α,β-unsaturated ketones[130] in a manner analogous to that of aromatic aldehydes (see Section 5.3.10).

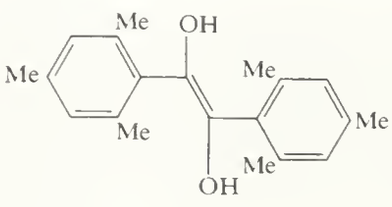
5.4.9 AROMATIC α-HYDROXYKETONES: BENZOIN AND ITS DERIVATIVES

Although the chemistry of benzoins, ArCH(OH)COAr′, has been studied for several decades, it is only recently that benzoin and the ethers have gained industrial importance. They are now used extensively as photoinitiators for radical polymerization. Constitutionally symmetrical and unsymmetrical benzoins are readily synthesized by the benzoin condensation (Section 5.3.8) and constitutionally symmetrical benzoins can be prepared from esters of aromatic acids *via* the acyloin condensation[131] (Chapter 9.8). Constitutionally unsymmetrical benzoins are isomerized in the presence of acids and bases to the more stable isomer (*i.e.* the carbonyl group is adjacent to the aromatic ring with the more electron-releasing substituent), the reaction presumably proceeding *via* the enediol (**101**) (equation 30). Certain enediols can be isolated when generated by reduction of benzils;[132] if a 2,6-disubstituted aromatic ring is present, then ketonization is sterically hindered and the enediol (**102**) is stable.[132] Heterocyclic benzoins often exist only in the enediol form if stabilization by hydrogen bonding in a chelate is possible, *e.g.* (**103**).[132] In the latter case only the (*E*)-isomers are known, whereas with highly hindered enediols both (*E*)- and (*Z*)-isomers are usually present. It has recently been demonstrated that the dianion of the enediol (**101**) can be generated from benzoin and sodium hydroxide under phase-transfer catalysis conditions,[133] and can be trapped with alkylating agents. With simple alkyl sulphates and *p*-toluenesulphonates the (*E*)-isomer (**104**) was obtained, but with bifunctional alkylating agents the heterocyclic product (**105**) arose from the (*Z*)-isomer; a new crown ether synthesis has since been developed using this method (Scheme 22).[133]

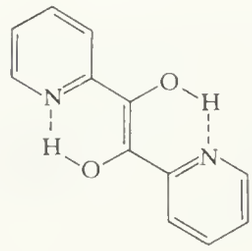


(30)

(**101**)

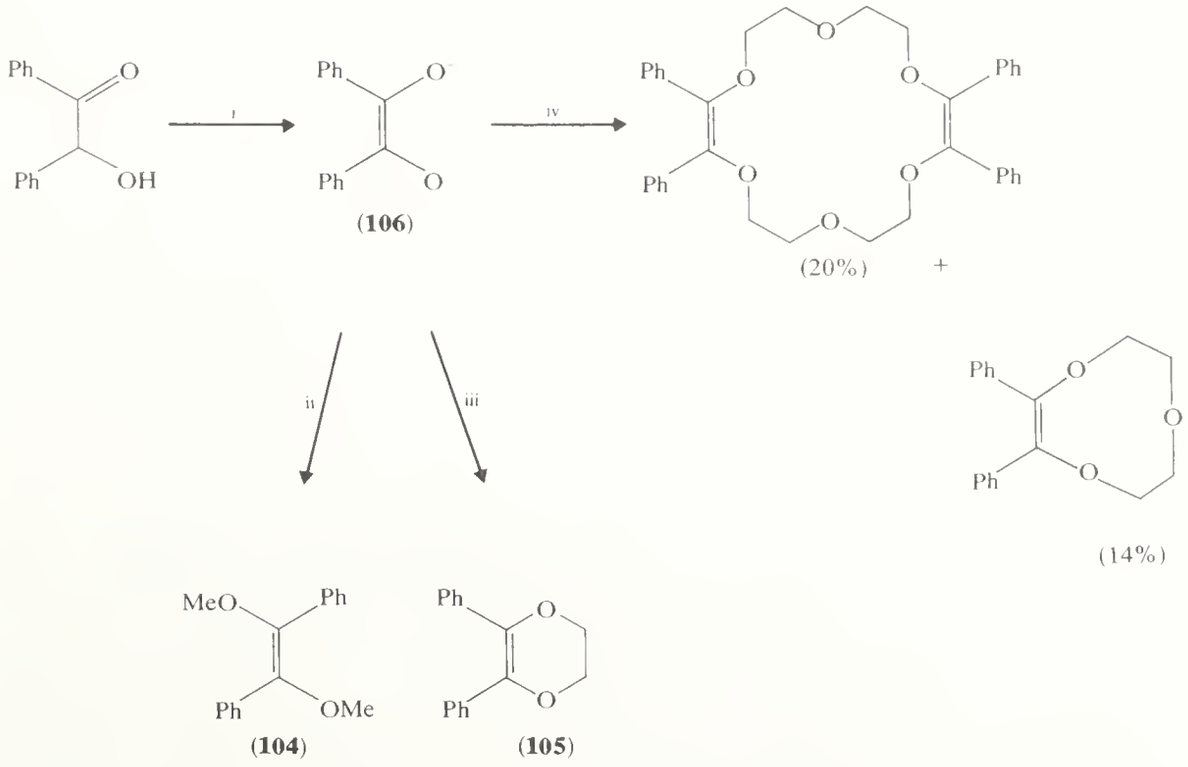


(**102**)



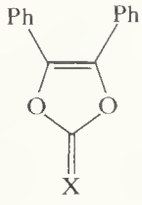
(**103**)

The dianion (**106**) is well known as an intermediate in the acyloin condensation, and under these conditions has been trapped using trimethylsilyl chloride (Me_3SiCl).[131,134] It would be expected that the 'free dianion' would prefer to exist in the *s-trans* geometry for steric and electrostatic reasons, yet trapping with Me_3SiCl gives only the (*Z*)-isomer, indicating that coordination to a counter-ion may allow the *s-cis* geometry to be stabilized. The dianion (**106**) can also be trapped by phosgene[135] or carbon disulphide–iodomethane[136] to give heterocyclics (**107**) and (**108**); the latter on heating with triethyl phosphite yields diphenylacetylene (35%).[136]



i, 50% aq. NaOH, $Bu_4\overset{+}{N}Br^-$ benzene, 80 °C, 4 h; ii, Me_2SO_4; iii, $TsOCH_2CH_2OTs$; iv, $(TsOCH_2CH_2)_2O$.

SCHEME 22

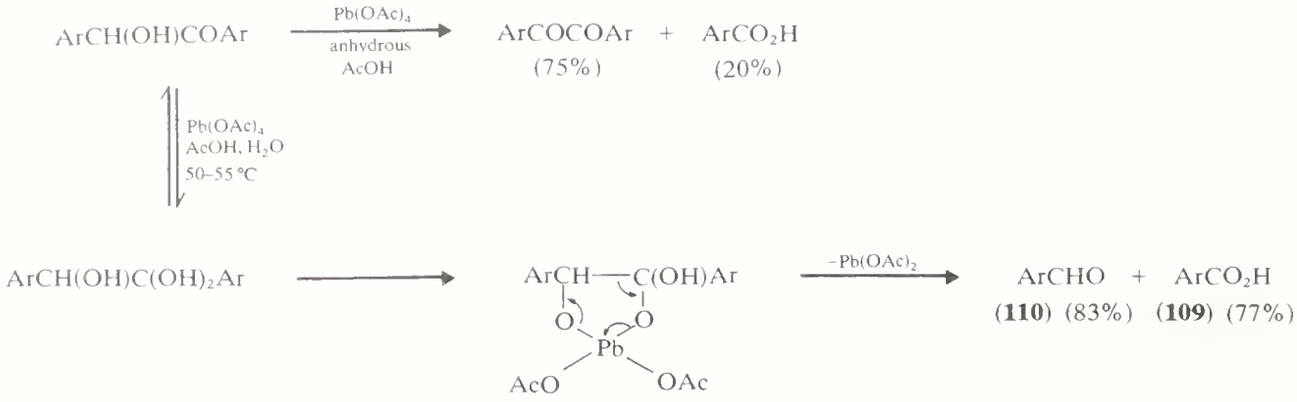


(**107**) X = O
(**108**) X = S

The oxidation of benzoins to benzils takes place readily in air in the presence of catalysts which promote enolization to the extremely air-sensitive enediols, *e.g.* (**101**); the rate-determining step in these oxidations is usually the enolization stage.[137] The usual reagents are nitric acid or copper(II) acetate–pyridine in the presence of air,[138] for industrial processes, although bismuth oxide in acetic acid (equation 31)[139] is the reagent of choice for laboratory scale oxidations. Recently, however, potassium hexacyanoferrate(III)[140] in basic solution has been shown to oxidize benzoins in excellent yields under very mild conditions.[140]

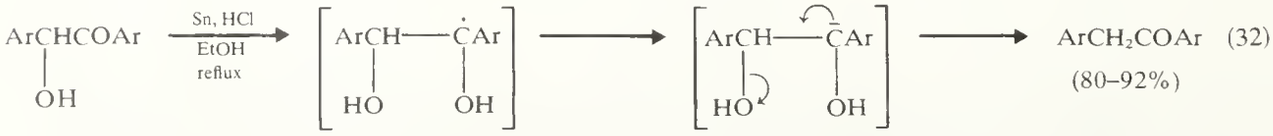
$$\underset{\underset{\displaystyle OH}{|}}{ArCHCOAr'} \xrightarrow[100\,^{\circ}C,\,1\,h]{Bi_2O_3,\,AcOH} \underset{(88\text{–}97\%)}{ArCOCOAr'} \qquad (31)$$

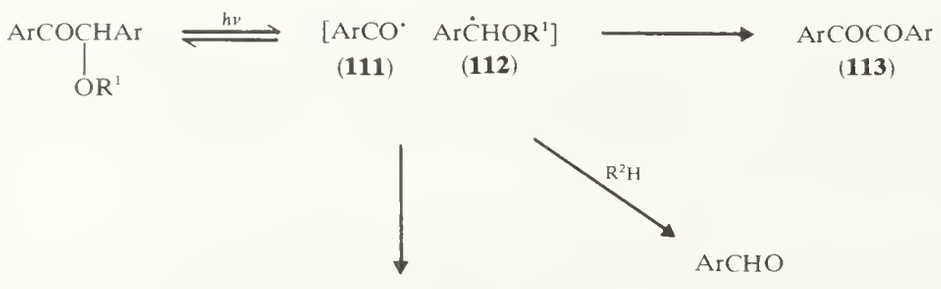
Under anhydrous conditions the lead tetra-acetate oxidation of benzoins gives α-diketones with very little cleavage, yet in the presence of a hydroxylic solvent, cleavage to the acid (**109**) and aldehyde (**110**) take place,[141] presumably *via* formation of a hydrate or hemiacetal (Scheme 23). Other reagents which induce cleavage are periodate and cerium(IV) ammonium nitrate.[142]



SCHEME 23

Reduction of the carbonyl group of benzoins takes place with typical metal hydride reagents, although with dissolving metals, reduction to deoxybenzoins takes place *via* the mechanism depicted (equation 32).[143] Photoreduction of the carbonyl group, however, does not take place owing to the ease of cleavage of the CO—C(OH) bond, and it is this property which has enabled benzoins — and their ethers — to be used as photoinitiators. The photocleavage of benzoin which takes place from the excited n,π^* triplet yields the radicals (**111**) and (**112**), which in the absence of other substrates dimerize to give the benzil (**113**) and pinacol (**114**) or transfer hydrogen to give two molecules of benzaldehyde (Scheme 24).[144] This latter process is the reverse of the photoproduction of radicals (**111**) and (**112**) from benzaldehyde (see Section 5.3.10). The radicals have been characterized by CIDNP experiments and trapped as nitroxides for e.s.r. examination.[145] For benzoin ethers the cleavage occurs extremely rapidly from the excited n,π^* singlet, competing favourably with intersystem crossing to the triplet state.[144] These highly efficient reactions of benzoin ethers have been developed to initiate the polymerization of methyl methacrylate (MMA), 1250 molecules of MMA being polymerized per quantum of 366 nm radiation.[145] The process is used in the production of acrylate-based printing plates and in unsaturated polyester varnishes.

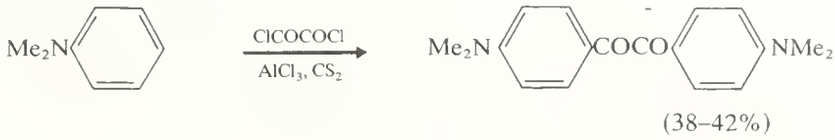




SCHEME 24

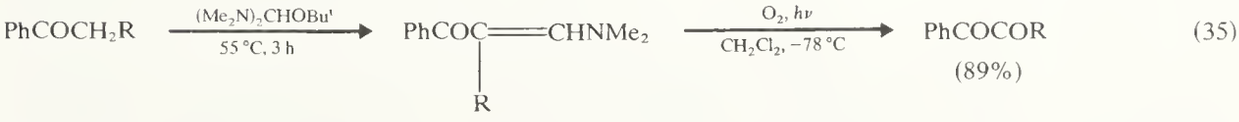
5.4.10 AROMATIC DIKETONES

Aromatic α-diketones, often called benzils after the parent diketone (PhCOCOPh), are stable crystalline compounds, useful in organic synthesis and as photosensitizers.[146] The simplest member of the series, benzil itself, m.p. 95 °C, b.p. 346–348 °C, behaves similarly to aliphatic diketones (Section 5.2.10) but undergoes additional interesting reactions. α-Diketones are readily available by the oxidation of benzoins (Section 5.4.9) but, for compounds which cannot be prepared *via* the benzoin condensation, alternative routes are available. Friedel–Crafts reaction using oxalyl chloride gives moderate yields of constitutionally symmetrical α-diketones (equation 33),[147] whereas the oxidation of monoketones is the best method for constitutionally unsymmetrical diketones. In the past, selenium dioxide[148] has been the preferred reagent for oxidation of the methylene group of a ketone in good yields; two modern procedures (equations 34 and 35),[149,150] however, provide useful alternatives. Aromatic α-diketones are also available by the oxidation of arylethynes with *N*-bromosuccinimide–dimethyl sulphoxide.[151]



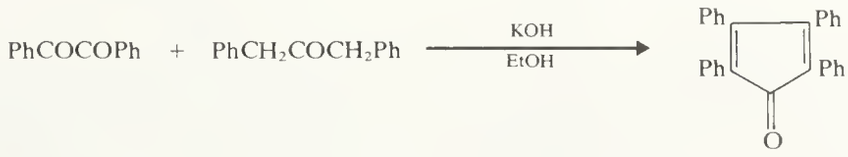
(38–42%) (33)

(80%) (34)



(89%) (35)

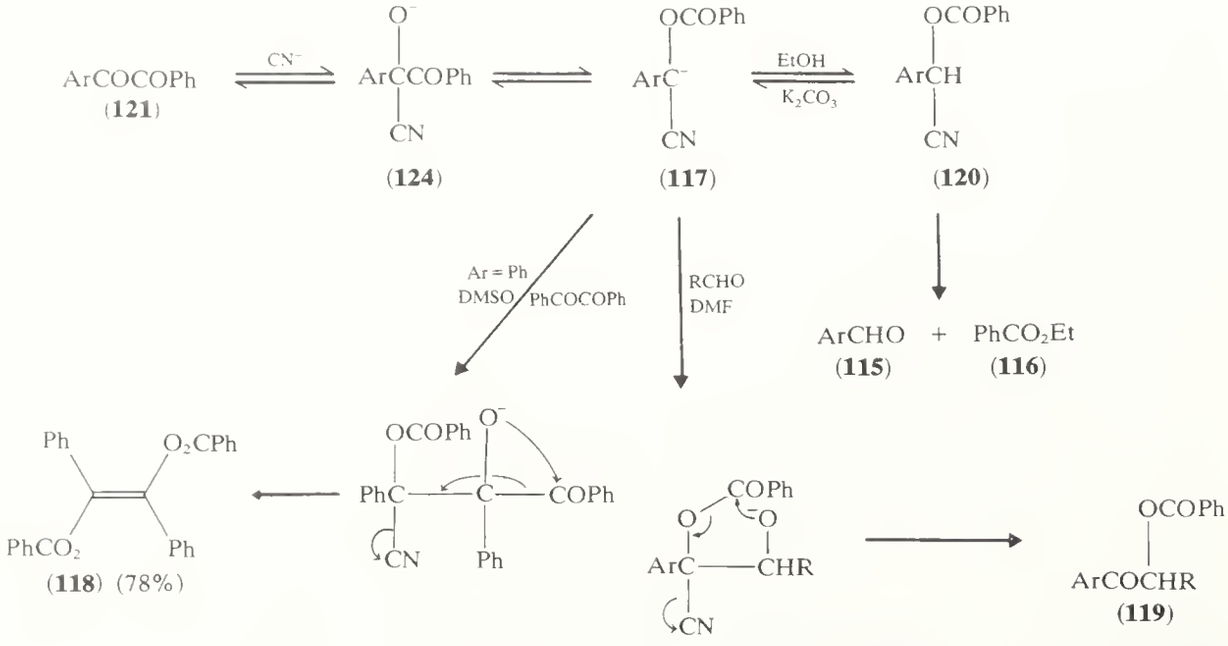
Aromatic α-diketones are readily reduced to benzoins (*e.g.* using vanadium(II) chloride)[152] and to the enediol dianion (see Section 5.4.9) using Grignard reagents.[136] With strong bases, benzilic acid rearrangement[153] takes place (see Section 5.2.17.5), and with active methylene groups, bis condensation often occurs (equation 36).[154]



(36)

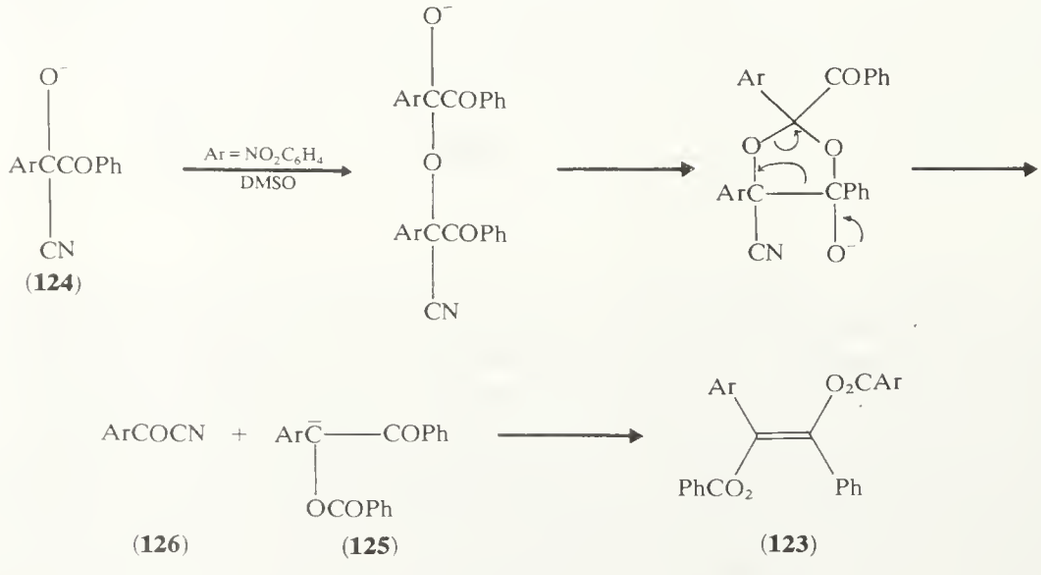
The reaction of aromatic α-diketones with cyanide ion has been widely studied recently owing to the similarity with the benzoin condensation and the renewed interest in reactions which generate protected cyanohydrins for use in nucleophilic acylation[155] (see Section 5.3.8). In alcoholic solvents, cleavage to give the aldehyde (**115**) and the ester (**116**) takes place, probably *via* the mechanism shown in Scheme 25.[156] In D_2O, deuterioaldehydes are formed in excellent yield and 98% isotopic purity, indicating the intermediacy of the anion (**117**).[157] Additional evidence for (**117**) has been obtained by conducting the reaction in aprotic solvents; the major product (**118**; 78%) can be envisaged to arise by attack of the anion (**117**) on a second molecule of diketone (Scheme 25).[158] In the presence of aldehydes the intermediate is trapped, giving the

acylated benzoin (**119**);[159] generation of the anion (**117**) from the protected cyanohydrin (**120**) using potassium carbonate in the presence of aldehydes also leads to a similar product (**119**) with migration of the benzoyl group.[160] Finally, reaction of the constitutionally unsymmetrical diketone (**121**; Ar=NO_2) with 1 equivalent of cyanide in DMSO yielded only the product (**120**; 58%) after acidification.[161]



SCHEME 25

In spite of an abundance of evidence in favour of the intermediate (**117**) in these reactions, recent work[162,163] suggests that an alternative mechanism may operate, at least under some conditions. In a study of the reactions of constitutionally unsymmetrical α-diketones with cyanide in aprotic solvents, the benzil (**121**) yielded the stilbene (**123**) when small amounts of cyanide ion were used.[162] This cannot be formed by the mechanism previously proposed (Scheme 25) and a more plausible explanation (Scheme 26) is that attack on the diketone by the oxygen of anion (**124**) takes place, yielding eventually the intermediate (**125**) and the aroyl nitrile (**126**) which, in separate

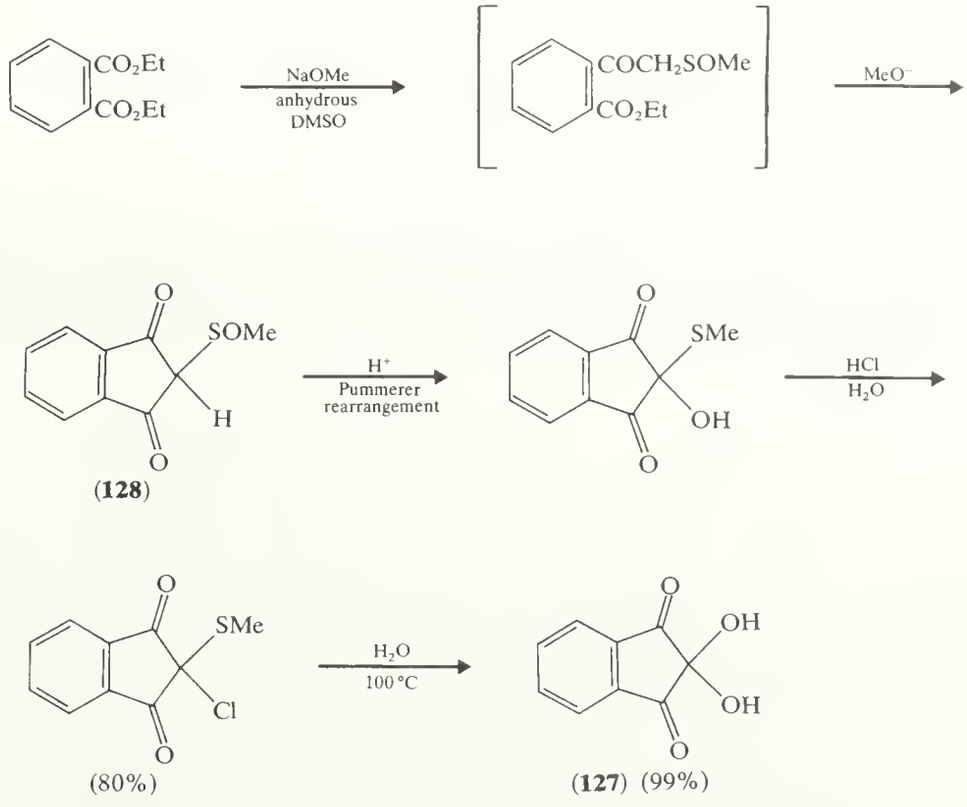


SCHEME 26

experiments, have been shown to yield the stilbene (**123**; 25%).[162,163] Further work is clearly necessary to clarify the mechanisms involved in these reactions and to explore the synthetic potential of the protected acyl anion equivalents[155] which appear to be generated in these reactions.

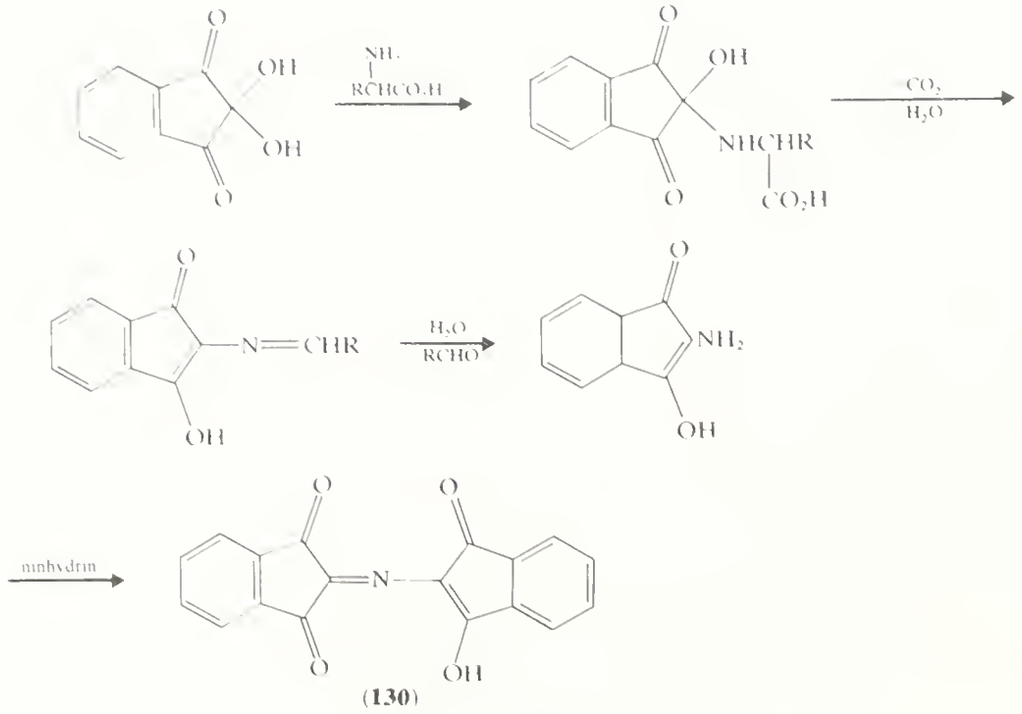
5.4.11 AROMATIC TRIKETONES[164]

The best known aromatic vicinal triketone is indane-1,2,3-trione, which, as its 'monohydrate', 2,2-dihydroxyindane-1,3-dione (ninhydrin) (**127**), was first used as a colour test for amino acids in 1910.[165] 1,2,3-Triketones can generally be synthesized from β-diketones by selenium dioxide oxidation or *via* bromination followed by Kornblum oxidation with DMSO.[166] The best method for the synthesis of ninhydrin, however, is by reaction of diethyl phthalate with the sodium salt of DMSO followed by Pummerer rearrangement of the intermediate sulphoxide (**128**) (Scheme 27).[167]



SCHEME 27

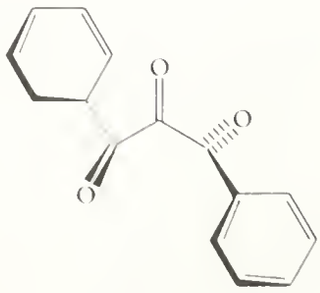
The central carbonyl group of vicinal triketones is highly activated owing to the unfavourable juxtaposition of three dipolar carbonyl groups. In acyclic compounds, such as 1,3-diphenylpropane-1,2,3-trione, a helical conformation (**129**) is adopted both in solution and in the crystal to minimize these interactions.[168,169] In cyclic vicinal triketones such as indane-1,2,3-trione, however, the molecule is fixed in a planar conformation.[170] Reaction at the central carbon atom therefore takes place extremely readily to try to remove the maximum number of unfavourable vicinal dione interactions. Thus 'hydration' to the *gem*-diol (**127**) takes place on standing in air;[171] the red triketone is transformed into the colourless 'hydrate' (ninhydrin) and this process is reversed by heating. The reactions of ninhydrin are identical to those of the dehydrated form; thus with α-amino acids reaction at 100 °C and pH 5 gives the well-known purple-coloured product (**130**) which has been used not only to identify α-amino acids, but also for quantitative analysis. Carbon dioxide is also quantitatively liberated and this again has been used to estimate free amino acids in protein digests. The mechanism of this reaction, correctly interpreted



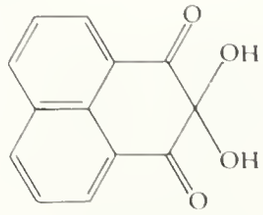
(**130**)

SCHEME 28

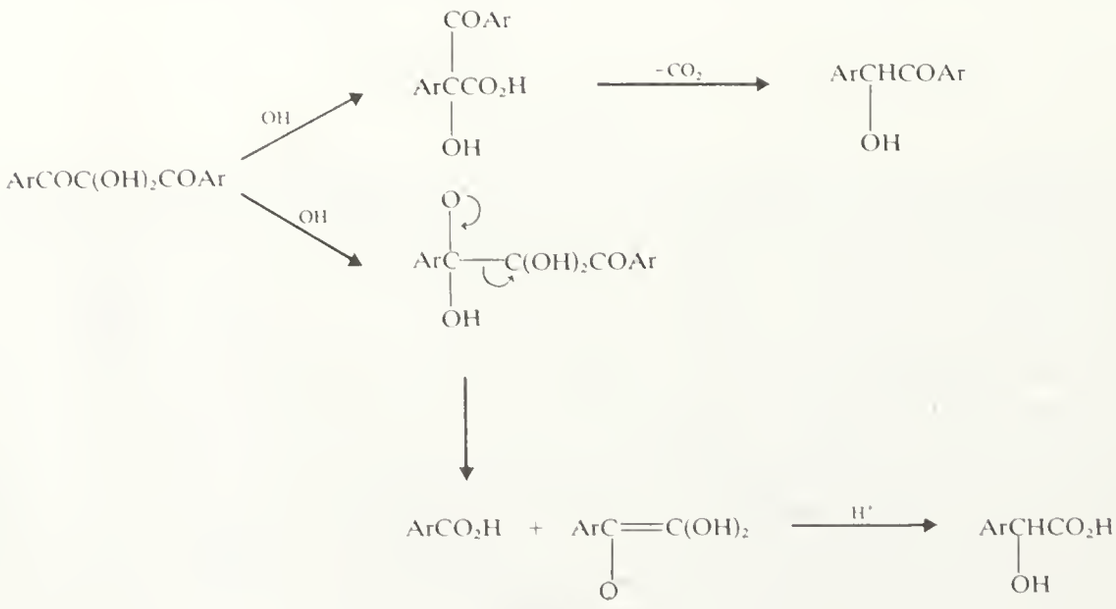
by Ruhemann in 1910, is summarized in Scheme 28.[165] Other aromatic triketones, *e.g.* phenalene-1,2,3-trione hydrate (**131**), however, behave in a slightly different manner, liberating both carbon dioxide and ammonia quantitatively.[172,173]



(**129**)



(**131**)

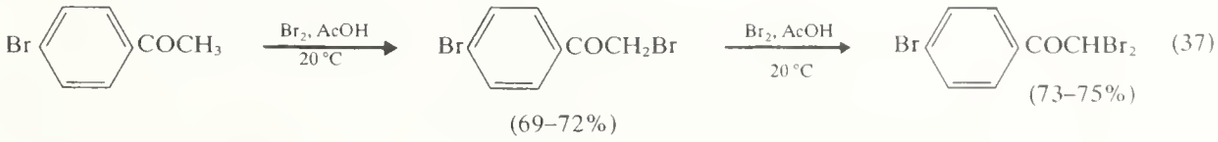


SCHEME 29

Vicinal triketones undergo acyl migration in base, formally equivalent to the benzilic acid rearrangement, although cleavage can also occur, depending on substituents (Scheme 29).[174]

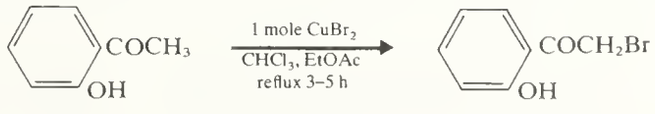
5.4.12 AROMATIC α-HALOKETONES

α-Halo- and α,α′-dihalo-ketones in the aromatic series are usually prepared by direct reaction of one or two moles of halogen with the ketone in carbon tetrachloride, chloroform, or acetic acid (equation 37).[175,176] The reaction is acid-catalysed so that in chloroform or carbon tetrachloride there is often an induction period until some HX is formed (or added). The rate-determining step is the acid-catalysed enolization of the ketone and this is followed by fast electrophilic attack by halogen. When ether is used as solvent, aluminium chloride is often added to promote enolization,[177] but a large excess of Lewis acid complexes with the ketone prevents enolization, and nuclear halogenation may predominate (see Section 5.4.3).



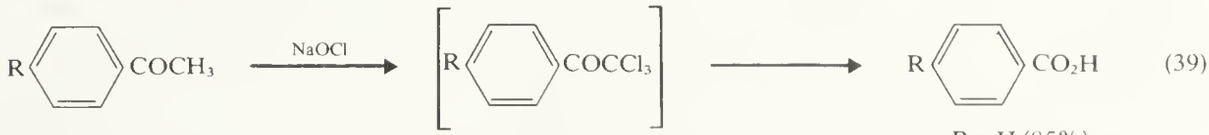
(69–72%) (73–75%) (37)

Cupric halides have occasionally been used to halogenate aromatic ketones, particularly if the use of free halogen caused nuclear halogenation, *e.g.* with phenolic ketones (equation 38).[178] The choice of solvent was critical: only when a chloroform–ethyl acetate mixture was used were high yields obtained. The copper(II) halide presumably catalyses enol formation, then transfers halogen to the enol, giving the α-haloketone.[178]



(100%) (38)

The presence of the α-halogen substituent renders acid-catalysed enolization more difficult so that further substitution becomes progressively slower. Thus it is possible to introduce one, two, or three halogen atoms simply by using one, two, or three moles of halogen. In base-catalysed halogenation, however, the halogen substituent increases the rate of further halogenation so that trihaloketones are often formed; hydrolysis of the trihaloketones, however, usually takes place under the basic conditions, leading to the corresponding carboxylate (haloform reaction) (equation 39). Acetylation of aromatic compounds followed by haloform reaction is thus a useful method of introducing a carboxylic acid group into an aromatic ring; only when NO_2 and OH groups are present does the reaction fail.[179]



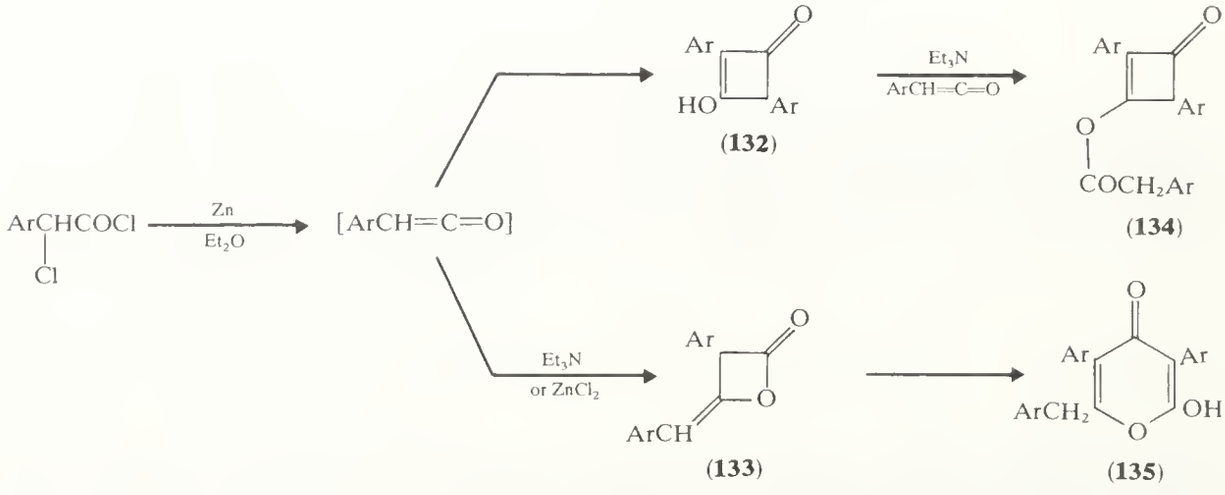
(39)

R = H (85%)
R = OMe (90%)
R = Cl (93%)
R = Br (91%)
R = Me (96%)

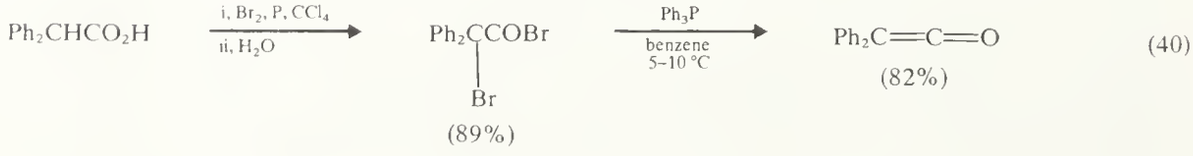
Aromatic α-haloketones are lachrymatory materials having low melting points and have been used in tear gas for riot control. The halogen atom is very easily displaced, and this governs the chemistry of aromatic α-haloketones; the important reactions have been described in Section 5.2.17.6 for aliphatic analogues.

5.4.13 ARYLKETENS

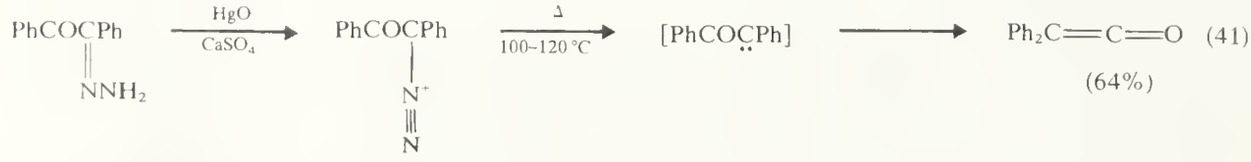
Arylketens, ArC(R)=C=O, like their aliphatic counterparts, can be formally regarded as carbonyl compounds, yet their chemistry in some ways resembles that of olefins.[180] For example, the methods of synthesis (dehydrohalogenation) and cycloadditions are characteristic of olefins. The simplest arylketen, phenylketen (PhCH=C=O) is very unstable, is usually generated *in situ*, and dimerizes readily to the cyclobutanedione (**132**).[181] In the presence of catalysts such as zinc chloride or triethylamine, however, the lactone (**133**) is preferentially formed but may rearrange to the isomer (**132**) in base;[181] trimers (**134**) and (**135**) are also produced under certain conditions (Scheme 30). The chemistry of phenylketen has not been examined in great detail but the more stable diphenylketen has been widely studied since it was first discovered in 1905 by Staudinger.[180] Diphenylketen, b.p. 120 °C (3.5 mmHg), is stable in the absence of air but is readily oxidized. It shows a much lower tendency to polymerize compared with aliphatic ketens, possibly owing to steric factors. It is prepared by most of the general methods for keten synthesis, *e.g.* dehydrohalogenation of acid halides.[182] The best route, however, is *via* dehalogenation of α-halodiphenylacetyl halides with zinc or triphenylphosphine (equation 40).[183] A useful alternative is the oxidation of benzil monohydrazone (equation 41).[184]



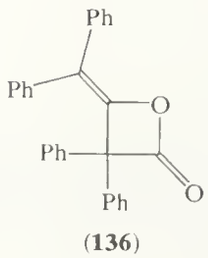
SCHEME 30



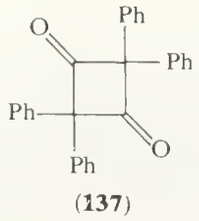
(40)



(41)



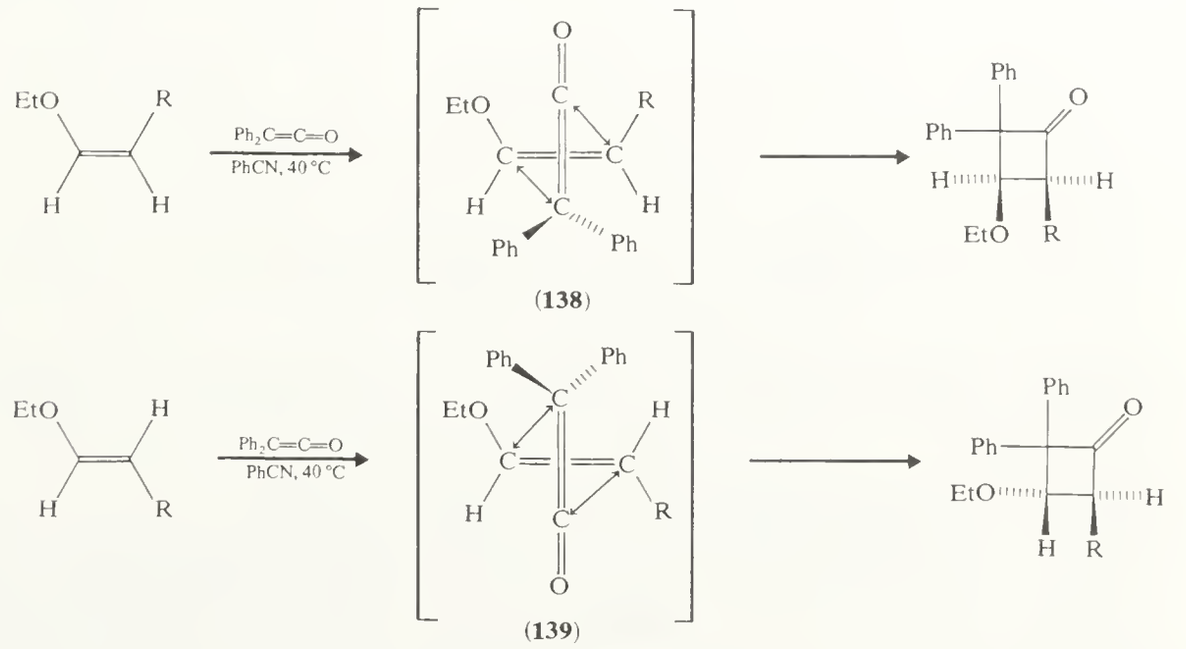
(136)



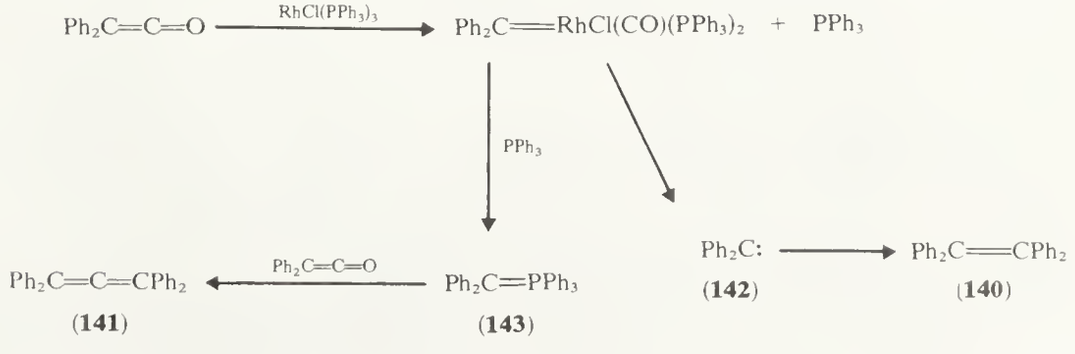
(137)

Diphenylketen has been reported to form both types of dimer; the β-lactone (**136**) is formed by heating the keten in HMPT[185] or with a catalytic quantity of sodium ethoxide in benzene,[186] whereas the cyclobutanedione (**137**), for which the structural evidence is lacking, is reported to be formed by heating the keten in quinoline at 180 °C.

The reactions of diphenylketen with nucleophiles to give diphenylacetic acid derivatives are analogous to those of aliphatic ketens and will not be discussed here. Cycloadditions of diphenylketen take place much more readily than with aliphatics and have been extensively studied.[187,188] Additions to C=C, C≡C, C=O, C=N, N=N, and N=O bonds are known;[188] they are fastest with the more electron-rich double bonds. The cycloadditions to olefins and, in particular, vinyl ethers have been examined in great detail and the latter will be used to exemplify diphenylketen [2+2] cycloadditions in general.[189] Diphenylketen adds to 1-ethoxyalkenes, giving high yields of the adducts expected by consideration of the dipolar characteristics of the reactants. Addition to *cis*- and *trans*-ethoxyalkenes takes place specifically to give 3-ethoxycyclobutanes in which the relative orientations of the alkyl and hydrogen have been retained (Scheme 31).[189] The exceptionally high negative entropy of activation ($\Delta S^{\ddagger} = -188\ JK^{-1}\ mol^{-1}$) indicates that a highly-oriented transition state is involved and a concerted $[{}_{\pi}2_a + {}_{\pi}2_s]$ mechanism with the orthogonal arrangement shown (Scheme 31) has been proposed. The *cis*-isomers react *ca.* 100 times faster than the *trans*-isomers, a factor unusual in olefin cycloadditions. This can be readily accounted for by examination of the orientation complexes (**138**) and (**139**); for the *cis*-isomer the phenyl group is involved in van der Waals repulsion only



SCHEME 31



SCHEME 32

with the olefinic hydrogen atom, whereas for the *trans*-isomer, interaction between a phenyl group and either an alkyl or ethoxy group will take place during bond formation (Scheme 31). Thus the *cis*-isomer reacts fastest; the effect becomes more pronounced as the size of R increases [$k_{cis}/k_{trans} = 84$ (R = Me), 107 (R = Et), 158 (R = Pr^i)].[189]

Diarylketens form complexes with many transition metals[190] and these can undergo decarbonylation on heating,[191] giving olefin (**140**) and allene (**141**), possibly *via* the mechanism shown in Scheme 32. In the presence of excess of triphenylphosphine the carbene (**142**) is trapped more effectively as the Wittig reagent (**143**), and the allene (**141**) becomes the major product.

References

1. M. Berthelot and C. Lawrence, *Canad. J. Chem.*, 1975, **53,** 993; K. K. Deb and W. L. Zielinski, Jr., *Spectroscopy Letters*, 1974, **7,** 193; A. M. de Roos, *Rec. Trav. chim.*, 1968, **87,** 1359.
2. P. J. Krueger, *Canad. J. Chem.*, 1973, **51,** 1362.
3. L. M. Jackman and S. Sternhell, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry', Pergamon, Oxford, 1969.
4. R. H. Martin, N. Defay and F. Geerts-Evrard; *Tetrahedron*, 1964, **20,** 1505.
5. P. H. Gore, in 'Friedel Crafts and Related Reactions', ed. G. A. Olah, Interscience, New York, 1964, vol. III, chapter 31; G. A. Olah, 'Friedel–Crafts Chemistry', Wiley-Interscience, New York, 1973; C. W. Schellhammer, in 'Methoden der Organischen Chemie (Houben-Weyl)', ed. E. Müller, Thieme Verlag, Stuttgart, 1973, volume VII/2a, part I.
6. F. Effenberger and G. Epple, *Angew. Chem. Internat. Edn.*, 1972, **11,** 300; J. O. Morley, *Synthesis*, 1977, 54.
7. F. P. Boer, *J. Amer. Chem. Soc.*, 1968, **90,** 6706.
8. G. A. Olah, S. J. Kuhn, S. H. Flood, and B. A. Hardie, *J. Amer. Chem. Soc.*, 1964, **86,** 2203.
9. S. E. Rasmussen and N. C. Broch, *Chem. Comm.*, 1965, 289.
10. L. Friedman and R. Koca, *J. Org. Chem.*, 1968, **33,** 1255.
11. R. B. Girdler, P. H. Gore, and C. K. Thadani, *J. Chem. Soc.* (*C*), 1967, 2619.
12. G. Baddeley, *J. Chem. Soc.*, 1949, S99.
13. P. H. Gore and J. A. Hoskins, *J. Chem. Soc.* (*C*), 1970, 517.
14. G. A. Olah and S. Kobayashi, *J. Amer. Chem. Soc.*, 1971, **93,** 6964.
15. F. Effenberger and G. Epple, *Angew. Chem. Internat. Edn.*, 1972, **11,** 299.
16. E. Rothstein and W. G. Schofield, *J. Chem. Soc.*, 1965, 4566.
17. H. A. Bruson and H. L. Plant, *J. Org. Chem.*, 1967, **32,** 3356.
18. R. Huisgen and I. Ugi, *Chem. Ber.*, 1960, **93,** 2693.
19. F. Uhlig and H. R. Snyder, *Adv. Org. Chem.*, 1960, **1,** 35.
20. W. Ruske, in 'Friedel–Crafts and Related Reactions', ed. G. A. Olah, Interscience, New York, 1964, vol. III, chapter 32.
21. P. E. Spoerri and A. S. du Bois, *Org. Reactions*, 1951, **5,** 387.
22. E. A. Jeffrey and D. P. N. Satchell, *J. Chem. Soc.* (*B*), 1966, 579.
23. B. Graffe, M. C. Sacquet, and P. Maitte, *J. Heterocyclic Chem.*, 1975, **12,** 247.
24. J. Houben, *Ber.*, 1926, **59,** 2878.
25. A. H. Blatt, *Org. Reactions*, 1942, **1,** 342; H. Henecka, in 'Methoden der Organischen Chemie (Houben-Weyl), ed. E. Müller, Thieme Verlag, Stuttgart, 1973, vol. VII/2, p. 379.
26. A. Gerecs, in 'Friedel–Crafts and Related Reactions', ed. G. A. Olah, Interscience, New York, 1964, vol. III, chapter 33.
27. K. W. Rosenmund and W. Schnurr, *Annalen*, 1928, **460,** 56.
28. F. Effenberger, H. Klenk, and P. L. Reiter, *Angew. Chem. Internat. Edn.*, 1973, **12,** 775.
29. M. J. S. Dewar and L. S. Hart, *Tetrahedron*, 1970, **26,** 973.
30. R. Martin, *Bull. Soc. chim. France*, 1974, 1519.
31. D. Bellus, *Adv. Photochem.*, 1971, **8,** 109.
32. H. Kobsa, *J. Org. Chem.*, 1962, **27,** 2293.
33. A. S. Kende, J. Belletire, T. J. Bentley, E. Hume, and J. Airey, *J. Amer. Chem. Soc.*, 1975, **97,** 4425.
34. D. A. Plank, *Tetrahedron Letters*, 1968, 5423.
35. C. E. Kalmus and D. M. Hercules, *J. Amer. Chem. Soc.*, 1974, **96,** 449.
36. D. H. Carlsson, L. H. Gan, and D. M. Wiles, *Canad. J. Chem.*, 1975, **53,** 2337.
37. A. Basha, S. S. Ahmed, and T. A. Farooqui, *Tetrahedron Letters*, 1976, 3217.
38. D. Seebach and M. Kolb, *Chem. and Ind.* (*London*), 1974, 687.
39. G. Stork and L. Maldonado, *J. Amer. Chem. Soc.*, 1971, **93,** 5286.
40. M. F. Semmelhack, H. T. Hall, M. Yoshifuji, and G. Clark, *J. Amer. Chem. Soc.*, 1975, **97,** 1247.
41. M. F. Semmelhack and H. T. Hall, *J. Amer. Chem. Soc.*, 1974, **96,** 7091, 7092.
42. M. F. Semmelhack and G. Clark, *J. Amer. Chem. Soc.*, 1977, **99,** 1675.

43. J. W. Baker and W. G. Moffitt, *J. Chem. Soc.*, 1931, 314.
44. D. E. Pearson, H. W. Pope, W. W. Hargrove, and W. E. Stamper, *J. Org. Chem.*, 1958, **23,** 1412; D. E. Pearson, H. W. Pope, and W. W. Hargrove, *Org. Synth. Coll. Vol. 5*, 1973, 117.
45. E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, 1965, **87,** 1345.
46. W. Wayne and H. Adkins, *Org. Synth. Coll. Vol. 3*, 1955, 367.
47. G. Wittig, *Topics Current Chem.*, 1976, **67,** 1.
48. G. Charles, *Bull. Soc. chim. France*, 1963, 1573.
49. W. S. Johnson and W. P. Schneider, *Org. Synth. Coll. Vol. 4*, 1963, 132.
50. E. C. Ashby, J. T. Laemmle, and H. M. Neumann, *Accounts Chem. Res.*, 1974, **7,** 272.
51. T. Holm, *Acta Chem. Scand.*, 1973, **27,** 1552.
52. C. Blomberg and H. S. Mosher, *J. Organometallic Chem.*, 1968, **13,** 519.
53. T. Holm and I. Crossland, *Acta Chem. Scand.*, 1971, **25,** 59.
54. E. C. Ashby and T. L. Wiesemann, *J. Amer. Chem. Soc.*, 1974, **96,** 7117.
55. E. C. Ashby, I. G. Lopp, and J. D. Buhler, *J. Amer. Chem. Soc.*, 1975, **97,** 1964.
56. I. Crossland and T. Holm, *Acta Chem. Scand.*, 1971, **25,** 1158.
57. J. F. Favarge and E. Rouget, *Compt. rend.*, 1968, **267,** 1355.
58. R. C. Fuson, *Adv. Organometallic Chem.*, 1964, **1,** 222.
59. E. C. Ashby, T. L. Wiesemann, J. S. Bowers, and J. T. Laemmle, *Tetrahedron Letters*, 1976, 21.
60. N. Hirota, in 'Radical Ions', ed. E. T. Kaiser and L. Kevan, Interscience, New York, 1968, chapter 2.
61. G. O. Schenck and G. Matthias, *Tetrahedron Letters*, 1967, 699.
62. V. Kalyanaraman and M. V. George, *J. Organometallic Chem.*, 1973, **47,** 225.
63. M. R. Rifi, in 'Technique of Chemistry', ed. N. L. Weinberg, Wiley, New York, vol. 5, chapter 8.
64. P. T. Lansbury and J. O. Peterson, *J. Amer. Chem. Soc.*, 1963, **85,** 2236.
65. J. D. Morrison and H. S. Mosher, 'Asymmetric Organic Reactions', Prentice-Hall, Englewood Cliffs, New Jersey, 1970.
66. O. Cervinka and O. Belovsky, *Coll. Czech. Chem. Comm.*, 1967, **32,** 3897.
67. S. Yamaguchi and H. S. Mosher, *J. Org. Chem.*, 1973, **38,** 1870.
68. S. R. Landor, B. J. Miller, and A. R. Tatchell, *J. Chem. Soc. (C)*, 1967, 197; 1966, 2280.
69. G. P. Giacomelli, R. Menicagli, and L. Lardicci, *J. Amer. Chem. Soc.*, 1975, **97,** 4009; D. Nasipuri, C. K. Ghosh, P. R. Mukherjee, and S. Venkataraman, *Tetrahedron Letters*, 1971, 1587.
70. A. I. Meyers and P. M. Kendall, *Tetrahedron Letters*, 1974, 1337.
71. S. Yamaguchi, F. Yasuhara, and K. Kabuto, *J. Org. Chem.*, 1977, **42,** 1578.
72. D. Seebach and H. Daum, *Chem. Ber.*, 1974, **107,** 1748.
73. J. E. McMurry, *Accounts Chem. Res.*, 1974, **7,** 281.
74. T. Mukaiyama, T. Sato, and J. Hanna, *Chem. Letters*, 1973, 1041; S. Tyrlik and J. Wolochowicz, *Bull. Soc. chim. France*, 1973, 2147.
75. J. E. McMurry and M. P. Fleming, *J. Amer. Chem. Soc.*, 1974, **96,** 4708; *J. Org. Chem.*, 1976, **41,** 896.
76. A. L. Baumstark, E. J. H. Bechara, and M. J. Semigran, *Tetrahedron Letters*, 1976, 3265.
77. J. E. McMurry and L. R. Krepski, *J. Org. Chem.*, 1976, **41,** 3929.
78. C. Willgerodt, *Ber.*, 1887, **20,** 2467.
79. E. V. Brown, *Synthesis*, 1975, 358; M. Carmack and M. A. Spielman, *Org. Reactions*, 1946, **3,** 83; R. Wegler, E. Kühle and W. Schäfer, in 'Newer Methods of Preparative Organic Chemistry', ed. W. Foerst, Academic, New York, 1964, vol. 3, p. 1.
80. E. V. Brown, E. Cerwonka, and R. C. Anderson, *J. Amer. Chem. Soc.*, 1951, **73,** 3735.
81. J. A. King and F. H. McMillan, *J. Amer. Chem. Soc.*, 1946, **68,** 2029.
82. E. Cerwonka, R. C. Anderson, and E. V. Brown, *J. Amer. Chem. Soc.*, 1953, **75,** 30.
83. F. Asinger, W. Schäfer, K. Halcour, A. Saus, and H. Triem, *Angew. Chem. Internat. Edn.*, 1964, **3,** 19.
84. W. G. Dauben and J. B. Rogan, *J. Amer. Chem. Soc.*, 1956, **78,** 4135.
85. A. McKillop, B. P. Swann, and E. C. Taylor, *J. Amer. Chem. Soc.*, 1973, **95,** 3340.
86. A. McKillop and E. C. Taylor, *Endeavour*, 1976, **35,** 88.
87. A. McKillop, *Pure Appl. Chem.*, 1975, **43,** 463.
88. E. C. Taylor, R. L. Robey, K. T. Liu, B. Favre, H. T. Bozimo, R. A. Conley, C. S. Chiang, A. McKillop, and M. E. Ford, *J. Amer. Chem. Soc.*, 1976, **98,** 3037.
89. E. C. Taylor, C. S. Chiang, A. McKillop, and J. F. White, *J. Amer. Chem. Soc.*, 1976, **98,** 6750.
90. 'Photochemistry', Specialist Periodical Reports, The Chemical Society, London, 1970–1977, volumes 1–8.
91. P. J. Wagner, *Topics Current Chem.*, 1976, **66,** 1.
92. J. A. Barltrop and J. D. Coyle, 'Excited States in Organic Chemistry', Wiley, Chichester, 1975, chapter 7.
93. W. M. Horspool, 'Aspects of Organic Photochemistry', Academic, London, 1976, chapter 6.
94. H. G. Heine, W. Hartmann, D. R. Kory, J. G. Magyar, C. E. Hoyle, J. K. McVey, and F. D. Lewis, *J. Org. Chem.*, 1974, **39,** 691.
95. P. S. Engel, *J. Amer. Chem. Soc.*, 1970, **92,** 6074.
96. W. K. Robbins and R. H. Eastman, *J. Amer. Chem. Soc.*, 1970, **92,** 6076, 6077.
97. H. G. Heine, H. J. Rosenkranz, and H. Rudolph, *Angew Chem. Internat. Edn.*, 1972, **11,** 974; H. G. Heine, *Tetrahedron Letters*, 1972, 4755.
98. A. Schonberg and A. Mustafa, *Chem. Rev.*, 1947, **40,** 181.
99. J. C. Scaiano, *J. Photochem.*, 1973, **2,** 81.
100. G. Ciamician and P. Silber, *Ber.*, 1900, **33,** 2911; *ibid.*, 1901, **34,** 1530.

101. N. Filipescu and F. L. Minn, *J. Amer. Chem. Soc.*, 1968, **90,** 1544; S. A. Weiner, *ibid.*, 1971, **93,** 425.
102. J. Chilton, L. Giering, and C. Steel, *J. Amer. Chem. Soc.*, 1976, **98,** 1865.
103. S. G. Cohen, A. Parola, and G. H. Parsons, *Chem. Rev.*, 1973, **73,** 141.
104. R. F. Bartholomew, R. S. Davidson, P. F. Lambeth, J. F. McKellar, and P. H. Turner, *J.C.S. Perkin II*, 1972, 577.
105. J. C. Scaiano, *J. Amer. Chem. Soc.*, 1977, **99,** 1494.
106. F. D. Lewis, R. W. Johnson, and D. E. Johnson, *J. Amer. Chem. Soc.*, 1974, **96,** 6090.
107. D. S. Weiss, N. J. Turro, and J. C. Dalton, *Mol. Photochem.*, 1970, **2,** 91.
108. F. D. Lewis and R. A. Ruden, *Tetrahedron Letters*, 1971, 715.
109. P. J. Wagner and R. G. Zepp, *J. Amer. Chem. Soc.*, 1971, **93,** 4958.
110. A. G. Schultz, C. D. DeBoer, W. G. Herkstroeter, and R. H. Schlessinger, *J. Amer. Chem. Soc.*, 1970, **92,** 6086.
111. H. J. Roth and M. H. El Raie, *Tetrahedron Letters*, 1970, 2445.
112. R. Breslow, *Chem. Soc. Rev.*, 1972, **1,** 553.
113. M. A. Winnik, R. E. Trueman, G. Jackowski, D. S. Saunders, and S. G. Whittington, *J. Amer. Chem. Soc.*, 1974, **96,** 4843.
114. R. Breslow, S. Balwin, T. Flechtner, P. Kalicky, S. Liu, and W. Washburn, *J. Amer. Chem. Soc.*, 1973, **95,** 3251.
115. R. L. Wife, D. Prezant, and R. Breslow, *Tetrahedron Letters*, 1976, 517.
116. P. G. Sammes, *Tetrahedron*, 1976, **32,** 405; K. Uji-Ie, K. Kikuchi, and H. Kokobun, *Chem. Letters*, 1977, 499.
117. G. Porter and M. F. Tchir, *J. Chem. Soc.* (*A*), 1971, 3772.
118. F. Nerdel and N. Brodowski, *Chem. Ber.*, 1968, **101,** 1398.
119. B. J. Arnold, S. M. Mellows, P. G. Sammes, and T. W. Wallace, *J.C.S. Perkin I*, 1974, 401.
120. B. J. Arnold, S. M. Mellows and P. G. Sammes, *J.C.S. Perkin I*, 1973, 1266.
121. W. Oppolzer and K. Keller, *Angew. Chem. Internat. Edn.*, 1972, **11,** 728.
122. R. Dessauer and J. P. Paris, *Adv. Photochem.*, 1963, **1,** 275. G. H. Brown, 'Photochromism', in 'Techniques of Chemistry, Vol. III', Wiley Interscience, New York, 1971.
123. W. A. Henderson and E. F. Ullman, *J. Amer. Chem. Soc.*, 1965, **87,** 5424.
124. D. R. Arnold, *Adv. Photochem.*, 1968, **6,** 301.
125. R. A. Caldwell, G. W. Sovocool, and R. P. Gajewski, *J. Amer. Chem. Soc.*, 1973, **95,** 2549.
126. N. J. Turro and P. A. Wriede, *J. Amer. Chem. Soc.*, 1970, **92,** 320.
127. N. C. Yang, M. Kimura, and W. Eisenhardt, *J. Amer. Chem. Soc.*, 1973, **95,** 5058.
128. D. Bichan and M. Winnik, *Tetrahedron Letters*, 1974, 3857.
129. S. R. Kurowsky and H. Morrison, *J. Amer. Chem. Soc.*, 1972, **94,** 507.
130. H. Polman, A. Mosterd, and H. J. T. Bos, *Rec. Trav. Chim.*, 1973, **92,** 845.
131. J. J. Bloomfield, D. C. Owsley, and J. M. Nelke, *Org. Reactions*, 1976, **23,** 259; S. M. McElvain, *ibid.*, 1948, **4,** 256. J. J. Bloomfield, D. C. Owsley, C. Ainsworth, and R. E. Robertson, *J. Org. Chem.*, 1975, **40,** 393.
132. C. A. Buehler, *Chem. Rev.*, 1964, **64,** 7.
133. A. Metz, *Angew. Chem. Internat. Edn.*, 1977, **16,** 467.
134. K. Ruhlmann, *Synthesis*, 1971, 236.
135. J. C. Sheehan and F. S. Guziec, Jr., *J. Amer. Chem. Soc.*, 1972, **94,** 6561.
136. D. P. Bauer and R. S. Macomber, *J. Org. Chem.*, 1976, **41,** 2640.
137. S. Shinkai, T. Kunitake, and T. C. Bruice, *J. Amer. Chem. Soc.*, 1974, **96,** 7140.
138. H. T. Clarke and E. E. Dreger, *Org. Synth. Coll. Vol. 1*, 1941, 87.
139. W. Rigby, *J. Chem. Soc.*, 1951, 793.
140. R. A. El-Zaru and A. A. Jarrar, *Chem. and Ind.* (*London*), 1977, 741.
141. E. Baer, *J. Amer. Chem. Soc.*, 1940, **62,** 1597.
142. T.-L. Ho, *Synthesis*, 1972, 560.
143. P. H. Carter, J. C. Craig, R. E. Lack, and M. Moyle, *Org. Synth. Coll. Vol. 5*, 1973, 339.
144. F. D. Lewis, R. T. Lauterbach, H.-G. Heine, W. Hartmann, and H. Rudolph, *J. Amer. Chem. Soc.*, 1975, **97,** 1519.
145. A. Ledwith, P. J. Russell, and L. H. Sutcliffe, *J.C.S. Perkin II*, 1972, 1925.
146. N. Shizimu and P. D. Bartlett, *J. Amer. Chem. Soc.*, 1976, **98,** 4193.
147. C. Tuzun, M. Ogliaruso, and E. I. Becker, *Org. Synth. Coll. Vol. 5*, 1973, 111.
148. N. Rabjohn, *Org. Reactions*, 1976, **24,** 261.
149. K. Oka and S. Hara, *Tetrahedron Letters*, 1977, 695.
150. H. H. Wasserman and J. L. Ives, *J. Amer. Chem. Soc.*, 1976, **98,** 7868.
151. S. Wolfe, W. R. Pilgrim, T. F. Garrard, and P. Chamberlain, *Canad. J. Chem.*, 1971, **49,** 1099.
152. T.-L. Ho and G. A. Olah, *Synthesis*, 1976, 815.
153. S. Selman and J. F. Eastham, *Quart. Rev.*, 1960, **14,** 221.
154. J. R. Johnson and O. Grummitt, *Org. Synth. Coll. Vol. 3*, 1955, 806; T. J. Clark, *J. Org. Chem.*, 1973, **38,** 1749.
155. O. W. Lever, Jr., *Tetrahedron*, 1976, **32,** 1943.
156. H. Kwart and M. M. Baevsky, *J. Amer. Chem. Soc.*, 1958, **80,** 580.
157. A. W. Burgstahler, D. E. Walker, Jr., J. P. Kuebrich, and R. L. Schowen, *J. Org. Chem.*, 1972, **37,** 1272.

158. J. C. Trisler and J. L. Frye, *J. Org. Chem.*, 1965, **30,** 306.
159. J. P. Kuebrich and R. L. Schowen, *J. Amer. Chem. Soc.*, 1971, **93,** 1220.
160. M. Hamana, T. Endo, and S. Saeki, *Tetrahedron Letters*, 1975, 903.
161. W. C. Reardon, J. E. Wilson, and J. C. Trisler, *J. Org. Chem.*, 1974, **39,** 1596.
162. A. Kawasaki and Y. Ogata, *J. Org. Chem.*, 1977, **42,** 2506.
163. Y. Ogata, A. Kawasaki, and A. Akutagawa, *J.C.S. Perkin II*, 1976, 1021.
164. M. B. Rubin, *Chem. Rev.*, 1975, **75,** 177.
165. D. J. McCaldin, *Chem. Rev.*, 1960, **60,** 39.
166. F. Dayer, J. Lê Dao, H. Gold, H. Rode-Gowal, and H. Dahn, *Helv. Chim. Acta*, 1974, **57,** 2201.
167. H.-D. Becker and G. A. Russell, *J. Org. Chem.*, 1963, **28,** 1896.
168. L. Horner and F. Maurer, *Chem. Ber.*, 1968, **101,** 1783.
169. S. Wolfe, J. E. Berry, and M. R. Peterson, *Canad. J. Chem.*, 1976, **54,** 210.
170. W. Bolton, *Acta Cryst.*, 1965, **18,** 5.
171. A. P. Lepley and J. P. Thelman, *Tetrahedron*, 1966, **22,** 101.
172. W. I. Awad, S. Nashed, S. S. M. Hassan, and R. F. Zakhary, *J.C.S. Perkin II*, 1976, 128.
173. A. Schönberg and R. Moubacher, *Chem. Rev.*, 1952, **50,** 261.
174. H. Lê Dao, F. Dayer, L. Duc, J. Rode-Gowal, and H. Dahn, *Helv. Chim. Acta*, 1974, **57,** 2215.
175. W. D. Langley, *Org. Synth. Coll. Vol. 1*, 1941, 127.
176. J. J. Klingenberg, *Org. Synth. Coll. Vol. 4*, 1963, 110.
177. R. M. Cowper and L. H. Davidson, *Org. Synth. Coll. Vol. 2*, 1943, 480.
178. L. C. King and G. K. Ostrum, *J. Org. Chem.*, 1964, **29,** 3459; D. P. Bauer and R. S. Macomber, *ibid.*, 1975, **40,** 1990.
179. A. M. Van Arendonk and M. E. Cupery, *J. Amer. Chem. Soc.*, 1931, **53,** 3185.
180. R. N. Lacey, in 'The Chemistry of Alkenes', ed. S. Patai, Interscience, New York, 1964, chapter 14.
181. D. G. Farnum, J. R. Johnson, R. E. Hess, T. B. Marshall, and B. Webster, *J. Amer. Chem. Soc.*, 1965, **87,** 5191; J. E. Baldwin and J. D. Roberts, *ibid.*, 1963, **85,** 2444.
182. E. C. Taylor, A. McKillop, and G. H. Hawks, *Org. Synth.*, 1972, **52,** 36; D. N. Harpp, L. Q. Bao, C. J. Black, J. G. Gleason, and R. A. Smith, *J. Org. Chem.*, 1975, **40,** 3420.
183. S. D. Darling and R. L. Kidwell, *J. Org. Chem.*, 1968, **33,** 3974.
184. L. I. Smith and H. H. Hoehn, *Org. Synth. Coll. Vol. 3*, 1955, 356.
185. A. Baba, S. Kitano, Y. Ohshiro, and T. Agawa, *Synthesis*, 1975, 537.
186. R. Anet, *Chem. and Ind. (London)*, 1961, 1313.
187. R. W. Holder, *J. Chem. Educ.*, 1976, **53,** 81.
188. H. Ulrich, 'Cycloaddition Reactions of Heterocumulenes', Academic, New York, 1967.
189. R. Huisgen and H. Mayr, *Tetrahedron Letters*, 1975, 2965; N. S. Isaacs and E. Rannala, *J.C.S. Perkin II*, 1975, 1555.
190. W. A. Herrmann, *Angew. Chem. Internat. Edn.*, 1974, **13,** 335.
191. T. Tsuji, in 'Organic Syntheses via Metal Carbonyls', ed. I. Wender and P. Pino, Wiley-Interscience, 1977, vol. 2, p. 624.

5.5

Quinones

T. LAIRD

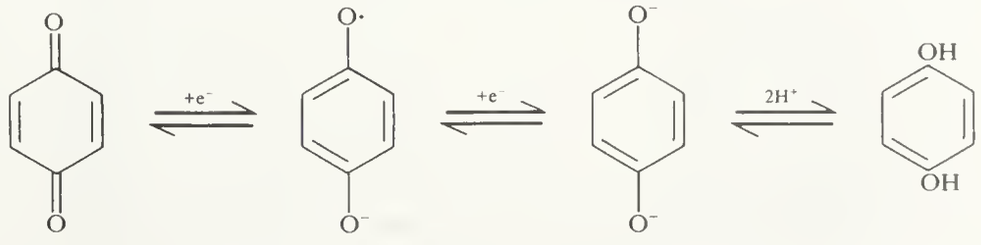
Imperial Chemical Industries Ltd., Blackley, Manchester

5.5.1 INTRODUCTION 1213
5.5.2 SYNTHESIS OF QUINONES 1216
5.5.3 QUINONES AS OXIDIZING OR DEHYDROGENATING AGENTS 1219
5.5.4 SUBSTITUTIONS AND ADDITIONS 1221
5.5.5 PHOTOCHEMISTRY OF QUINONES 1225

5.5.1 INTRODUCTION

Quinones are an important class of compounds in industry (*e.g.* anthraquinone dyestuffs), in organic synthesis as dehydrogenating agents, and in Nature, where they have a vital role in electron transport in the respiratory and photosynthetic elements of biological systems. 1,4-Quinones, *e.g.* (**1**), are a special example of cross-conjugated enediones whereas 1,2-quinones, *e.g.* (**2**), can be compared with dienediones. Although the charged or cyclic resonance forms (**3**) and (**4**) were at one time considered to contribute to the structure, it is now realized that quinones have little aromatic character; X-ray crystallographic data show that the bond lengths correspond to the values expected for the classical diketone structures.[1]

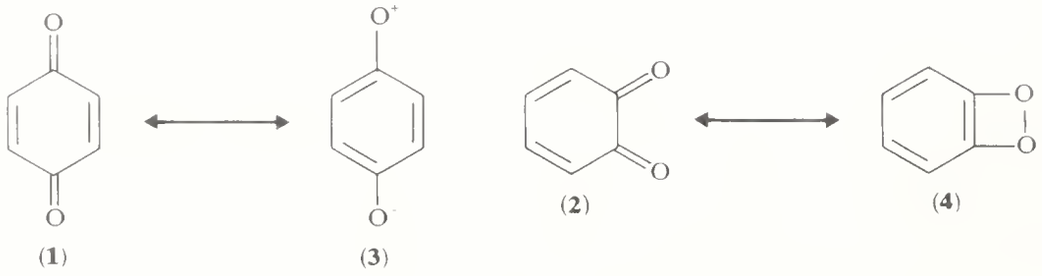
The significant difference between quinones and their acyclic counterparts is the ease of reduction, the driving force being the formation of a fully aromatic system. This ability to accept firstly one electron, forming the semiquinone anion radical, followed by a further electron to give the dianion, is the dominant feature of quinone chemistry (equation 1).



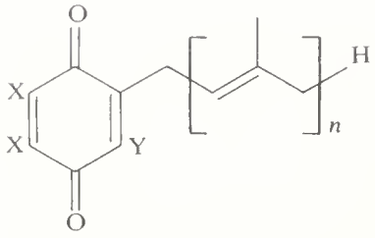
(1)

It is this reversible reduction process which accounts for the biological and industrial importance of quinones. *In vivo*, the reversible reduction of ubiquinones (**5**) and plastoquinones (**6**) is linked to the formation of adenosine triphosphate (ATP) during photosynthesis and respiration.[2] In the dyestuffs industry, the reduction and re-oxidation of quinones form the basis of the method of application of vat dyes to fibres.[3] The insoluble

quinone dye, usually an anthraquinone derivative, is reduced by sodium dithionite and base to the dihydro compound, which dissolves, as the sodium salt, in the basic solution. The solution is applied to the fibre and, in this ionic form, has a high affinity; when exposed to air, oxidation takes place, regenerating the quinonoid dye which remains attached to the fibre.[3]

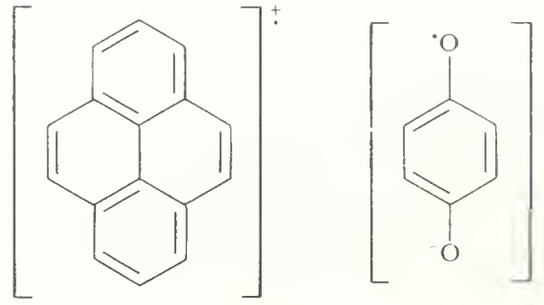


(1) (3) (2) (4)



(5) X = MeO, Y = Me, n = 0–10

(6) X = Me, Y = H, n = 0–10



(7)

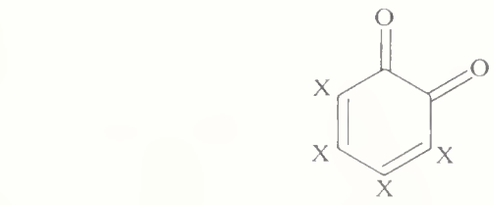
The ability to accept an electron to form the semiquinone anion radical can be measured polarographically as the halfwave potential ($E^{1/2}$).[4] Table 1 gives the values for some common quinones and shows the change in electron affinity with structure. The high electron affinity and the stability of the resulting anion radicals are responsible for the large numbers of charge-transfer complexes, some of them isolable, crystalline compounds, which are formed between quinones and electron donors.[5] An example which has been examined in detail is the 1 : 1 pyrene–1,4-benzoquinone complex (**7**) which forms as red crystals on mixing petroleum solutions of the two components.[6]

TABLE 1

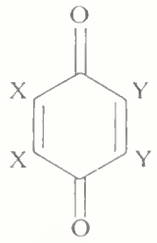
Physical Properties of Quinones

Quinone	*M.p.* (°C)	$E^{1/2}$ (V)[a]	$E°$ (V)[b]
1,2-Benzoquinone (**2**)	60–70 (d)	−0.31	0.795[c,d]
1,4-Benzoquinone (**1**)	116	−0.51	0.711[e,f,g]
2,3,4,5-Tetrachloro-1,2-benzoquinone (**8**)	133	—	0.830[c,d]
2,3,5,6-Tetrachloro-1,4-benzoquinone (**9**)	290	+0.01	0.742[e,f,h]
2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (**10**)	213	+0.51	*ca.* 1.00[f,i]
4,4′-Diphenoquinone (**11**)	165	−0.24	0.954[i]
1,2-Naphthoquinone (**12**)	145	−0.56	0.576[k]
1,4-Naphthoquinone (**13**)	125	−0.71	0.484[k]
1,2-Anthraquinone (**14**)	185–190	−0.49	0.490[k]
1,4-Anthraquinone (**15**)	218	−0.75	0.401[k]
9,10-Anthraquinone (**16**)	286	−0.94	0.154[k]
9,10-Phenanthraquinone (**17**)	206–208	−0.66	0.460[k]

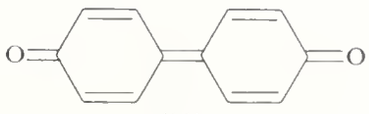
[a] MeCN solvent, $Et_4N^+ClO_4^-$ as supporting electrolyte, 25 °C; see Ref. 4. [b] EtOH solvent unless otherwise stated. [c] H. Musso, K. Figge, and D. J. Becker, *Chem. Ber.*, 1961, **94**, 1107. [d] H_2O solvent. [e] W. M. Clark, 'Oxidation–Reduction Potentials in Organic Systems', Williams and Wilkins, Baltimore, 1960. [f] C_6H_6 solvent. [g] $E° = 0.650$ V in AcOH.[e] [h] $E° = 0.675$ V in AcOH.[e] [i] L. M. Jackman, *Adv. Org. Chem.*, 1960, **2**, 329. [j] AcOH as solvent; L. Horner and E. Geyer, *Chem. Ber.*, 1965, **98**, 2016. [k] 'Encyclopaedia of Chemical Technology (Kirk-Othmer)', Interscience, New York, 1968, vol. 16, p. 899.



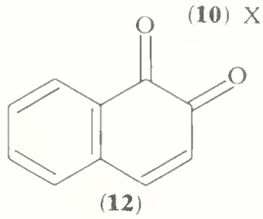
(**2**) X = H
(**8**) X = Cl



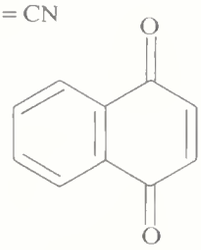
(**1**) X = Y = H
(**9**) X = Y = Cl
(**10**) X = Cl, Y = CN



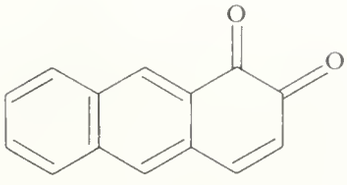
(**11**)



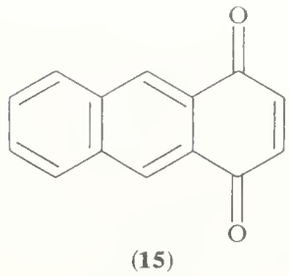
(**12**)



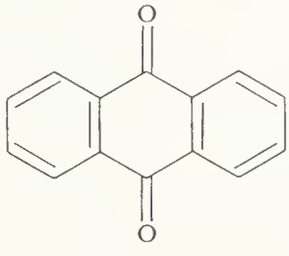
(**13**)



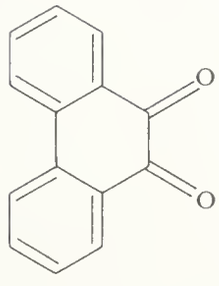
(**14**)



(**15**)



(**16**)

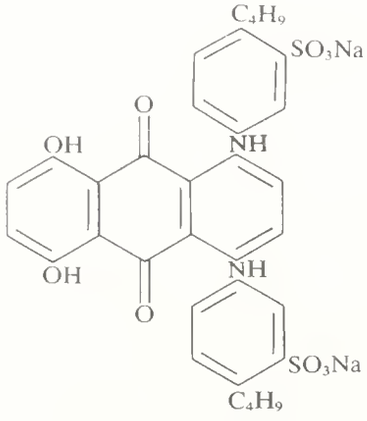


(**17**)

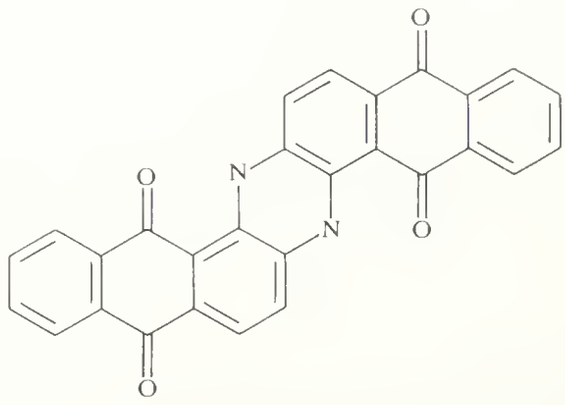
The ease of reduction of quinones to hydroquinones and therefore the ability of quinones to act as oxidizing or dehydrogenating agents is characterized by the redox potential ($E°$), which can be measured potentiometrically. The redox potentials of common quinones, some of which are used as oxidizing agents, are listed in Table 1. In general, 1,2-quinones have higher potentials than comparable 1,4-quinones but are rarely used as oxidizing agents, being less stable and more difficult to handle. Electron-withdrawing groups increase the oxidizing ability, and it is this factor coupled with high selectivity and versatility which has led to the widespread use of quinones as oxidizing and dehydrogenating agents in synthetic chemistry (see Section 5.5.3). Polycyclic quinones are much less readily reduced (Table 1), 9,10-anthraquinone (**16**) being the most resistant to reduction of the common quinones, and the chemical properties of these quinones tend to resemble those of aromatic ketones as the redox potential is lowered.

The simplest 1,4-quinone, 1,4-benzoquinone (**1**), forms yellow prisms, m.p. 116 °C, from water or petroleum ether; it is slightly soluble in cold water. The solid sublimes readily, has a pungent odour, and is harmful to skin and eyes, causing dermatitis and conjunctivitis. It is used as an oxidizing agent in photography and in the manufacture of dyestuffs.

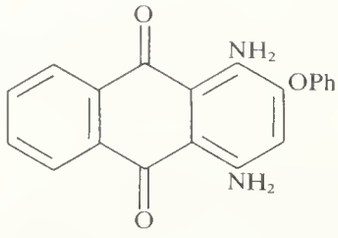
1,2-Benzoquinone (**2**) forms unstable bright red plates, m.p. 60–70 °C, having similar toxicological properties to the 1,4-isomer. Naphthoquinones (**12**) and (**13**) are volatile solids, but much less reactive than benzoquinones. 9,10-Anthraquinone is a very stable pale yellow compound, m.p. 286 °C, which is only slightly soluble in common organic solvents. Its derivatives (*e.g.* aminoanthraquinones, anthraquinonesulphonic acids) are used as the basis for the synthesis of a vast number of important dyestuffs, which have found extensive use because of their brightness, chemical, photochemical, and thermal stability, and applicability to all types of fibres.[7] Examples of anthraquinone dyes are shown in formulae (**18**)–(**20**).



(**18**) Wool dye (green)



(**19**) Cotton dye (blue)



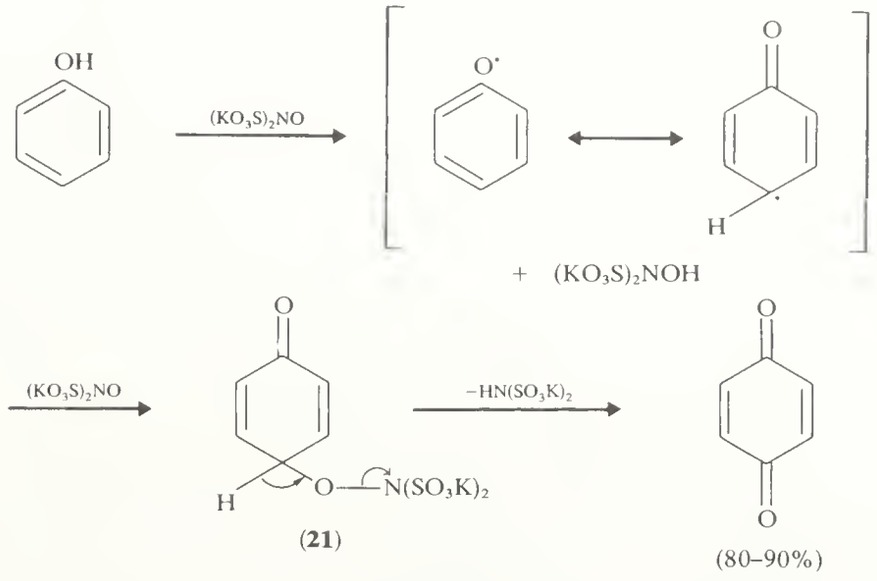
(**20**) Polyester dye (brilliant red)

The spectroscopic properties of quinones resemble those of α,β-unsaturated ketones. The infrared spectra of 1,4-quinones show two carbonyl bands due to Fermi resonance at 5.98 and 6.05 μm, whereas 1,2-quinones are characterized by a low-intensity absorption at 5.95 μm and a higher intensity one at 6.02 μm. In the ^{1}H n.m.r. spectrum the quinone protons (*e.g.* for 1,2- and 1,4-benzoquinone) appear at *ca.* δ 6.7, thus confirming the non-aromatic character of quinones.

5.5.2 SYNTHESIS OF QUINONES

Quinones are easily prepared by oxidation of phenols, quinols, aromatic amines, or diamines.[8] The Teuber reaction,[9] which uses Fremy's salt (potassium nitrosodisulphonate) as oxidizing agent, has been the most widely used method, since it gives excellent yields and proceeds under mild conditions. For example, monohydric phenols or aromatic amines are oxidized rapidly using two equivalents of the reagent in aqueous alcohol or

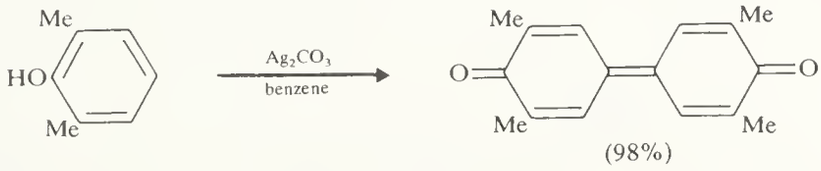
acetone, buffered with phosphate or acetate (Scheme 1). The mechanism of the reaction has been confirmed using [^{18}O]Fremy's salt, and, in some cases, by isolation of the intermediate (**21**).[10] If the position *para* to the phenol is blocked, oxidation with Fremy's salt then leads to a 1,2-quinone, although in some cases a halo or t-butyl group may be eliminated.[11] The Teuber reaction is useful for the synthesis of heterocyclic quinones, where other oxidizing agents fail.[11]



(**21**) (80–90%)

SCHEME 1

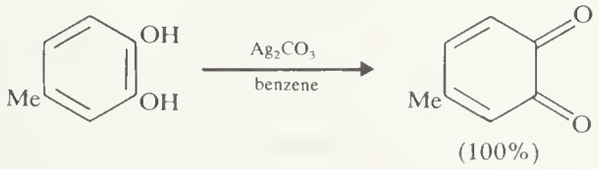
Chromic acid has often been used to oxidize phenols but gives lower yields than Fremy's salt when the phenol has no *para* substituent.[12] Thallium trifluoroacetate also gives excellent yields with *p*-chloro- or *p*-t-butyl-phenols, but the scope of this reagent has not yet been examined fully.[13] With one-electron oxidizing agents, the most notable being silver carbonate on celite,[14] phenols are oxidized to extended quinones, presumably *via* a radical dimerization mechanism (equation 2).



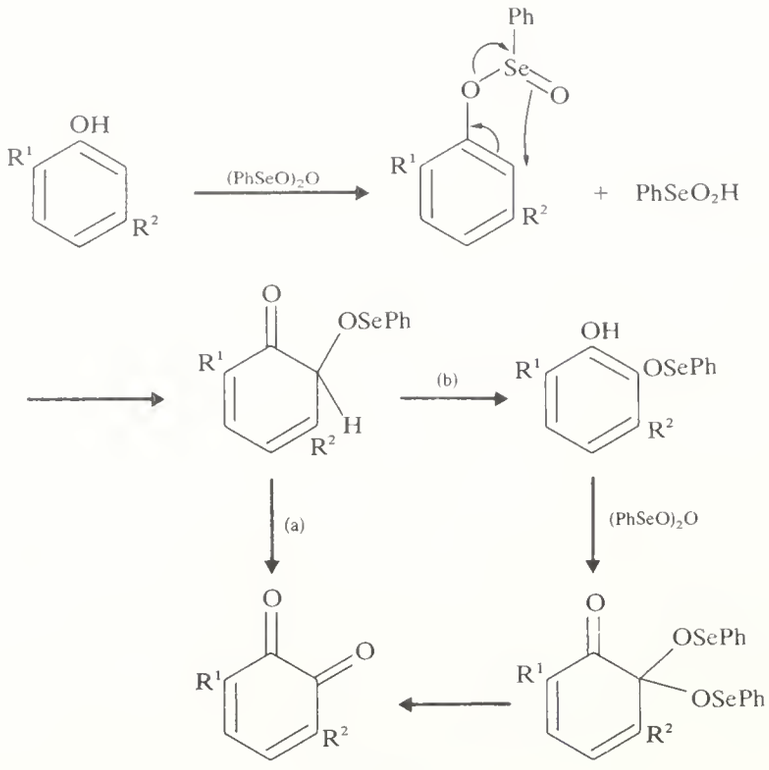
(98%) (2)

The potentially most useful reagent to be introduced for the formation of 1,2-quinones from phenols is diphenylseleninic anhydride, which is unique in its reaction with phenols containing an unblocked *para* position.[15] Only the *ortho*-quinone (*ca.* 60% yield) is formed, with virtually no *para* oxidation taking place (Scheme 2). Two mechanisms — (a) and (b) in Scheme 2 — have been proposed to account for this high selectivity; to date, there are insufficient data available to distinguish between them.

The oxidation of dihydric phenols to quinones is a very simple reaction but its synthetic utility is limited by the availibility of starting materials. The normal oxidizing agents are CrO_3, Fe^{3+} ions or Ag_2O, although many others have been used. Silver carbonate on celite[14] is very useful for sensitive compounds (equation 3). Quinones having high redox potentials, *e.g.* (**10**), can be used for oxidizing dihydric phenols to quinones provided that the redox potential of the product is lower than that of the oxidizing agent.[16]

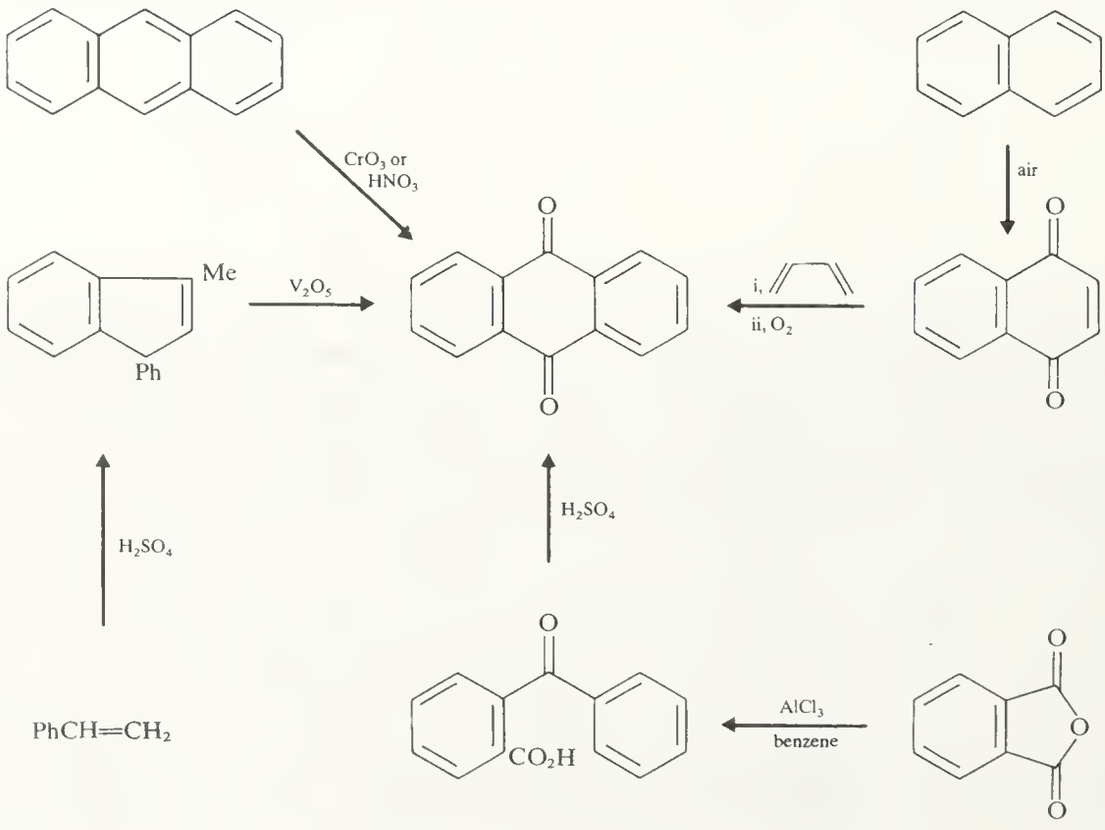


(100%) (3)



SCHEME 2

The oxidative demethylation of dimethoxy aromatics is a useful method of quinone synthesis, the usual reagents being silver oxide[17] or cerium(IV) ammonium nitrate.[18] In both cases it has been shown by performing the reaction in ^{18}O-enriched water that the oxidation proceeds *via* aryl–oxygen cleavage.



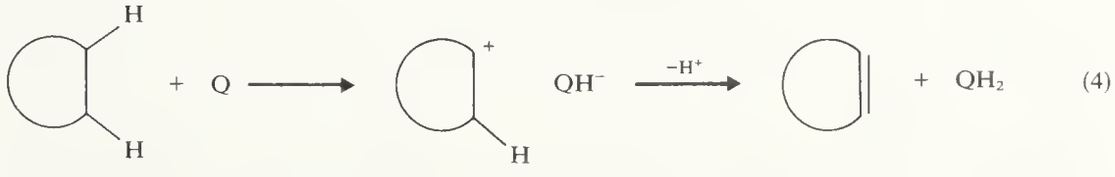
SCHEME 3

Although the previously described methods are applicable to the synthesis of a variety of quinones, they are unsuitable for the industrially important 9,10-anthraquinones and 1,4-naphthoquinones.[7] In Britain, anthraquinone is manufactured by oxidation of anthracene, available from coal tar, whereas in the U.S. the phthalic anhydride route[19] is favoured (Scheme 3). The oxidation of naphthalene to 1,4-naphthoquinone followed by cycloaddition to butadiene and further oxidation is an attractive route which Cyanamid developed, but technical problems have so far hindered its use on a large scale. Finally, the B.A.S.F. route involves dimerization of styrene to 1-phenyl-3-methylindane, followed by vapour-phase oxidation over a vanadium pentoxide catalyst. Since costs of styrene have risen sharply, however, this route (Scheme 3) has become uneconomic. In the laboratory, the phthalic anhydride route[19] is the most versatile, although the vigorous conditions used may occasionally lead to the formation of isomeric mixtures of anthraquinones.[20]

5.5.3 QUINONES AS OXIDIZING OR DEHYDROGENATING AGENTS

The ease of reduction of quinones to quinols by a variety of substrates is the significant difference between quinones and their acyclic counterparts. This has enabled synthetic chemists to explore the use of quinones as dehydrogenating agents,[21,22] the most common reagents being the quinones with higher redox potentials (see Table 1). Although *o*-quinones have higher redox potentials than analogous *p*-quinones they are, apart from *o*-chloranil (**8**), very rarely used as oxidizing agents owing to the ease with which they undergo Diels–Alder additions and the more difficult experimental handling required. The most common dehydrogenating agents are DDQ (**10**), *o*-chloranil (**8**), and *p*-chloranil (**9**); the relative rates of dehydrogenation of, for example, 1,2-dihydronaphthalene are 5500 : 4200 : 1, respectively.

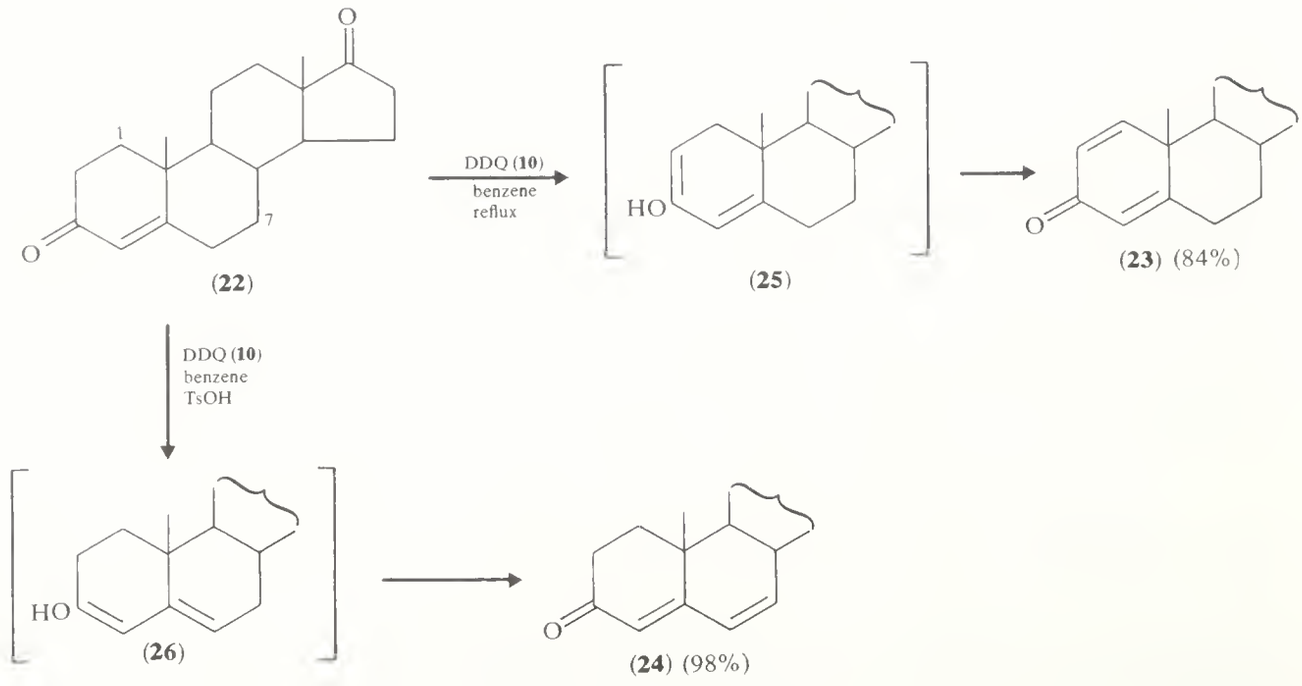
Dehydrogenation reactions using quinones are normally carried out by heating the substrate with one equivalent of quinone in benzene, when the insoluble quinol by-product precipitates out and this can be used to follow the reaction. The mechanism is by initial hydride abstraction by the quinone (Q) to give a carbenium ion, which, by further proton transfer, is dehydrogenated (equation 4). Carbenium ion rearrangements, such as alkyl migration, are therefore encountered occasionally.



(4)

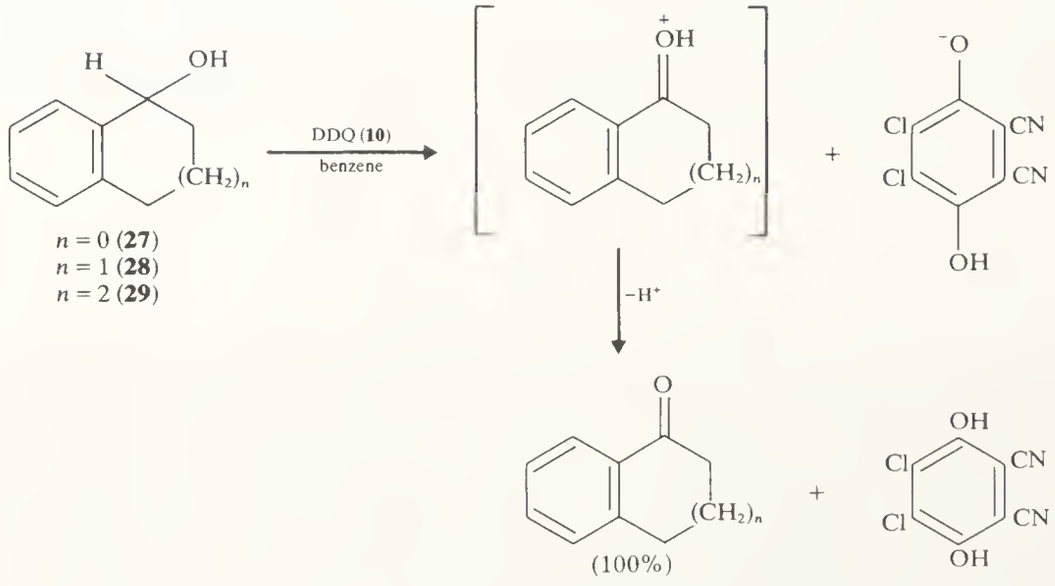
One of the most useful applications of dehydrogenations by quinones has been in steroid chemistry, particularly for the synthesis of ring A cyclohexadienones.[22] An interesting example is shown in Scheme 4; reaction of the α,β-unsaturated ketone (**22**) with DDQ (**10**) under neutral conditions leads to the product (**23**), whereas in the presence of anhydrous acid the isomer (**24**) was the sole product.[23] It has been shown that the regioselectivity depends on the relative rates of formation and stabilities of the enol intermediates (**25**) and (**26**), which are dehydrogenated by DDQ (Scheme 4). The enol (**25**) is formed faster and leads to the cyclohexadienone (**23**) under neutral conditions. However, in the presence of acid, equilibration of the enols takes place so that the major product (**24**) arises from the more stable enol (**26**). In each case it is the axial or pseudo-axial hydrogen (at C-1 or C-7, respectively) which is abstracted preferentially by the quinone, since this allows overlap of the developing carbenium ion by the existing π-system.

This explanation has also been used to account for the relative rates of oxidation of the alcohols (**27**)–(**29**) (Scheme 5) to the corresponding ketones.[24] The angle which the



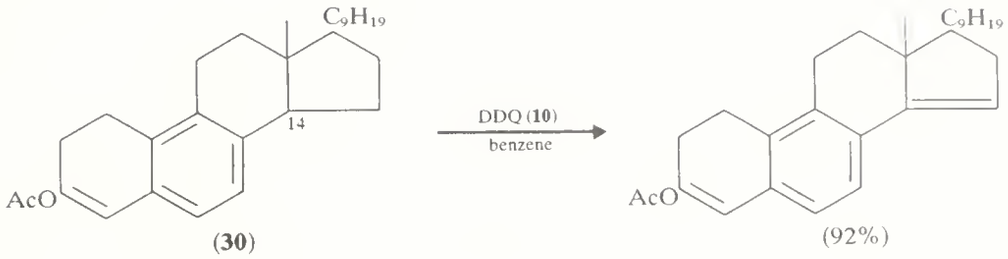
SCHEME 4

α-C—H bond makes with the plane of the aromatic ring is close to orthogonal for the alcohol (**28**) and this reacts fastest with DDQ (**10**). The relative rates (2.5 : 3.4 : 0.5) closely parallel the change in bond angle (72° : 83° : 48°) owing to the improvement in overlap of the developing carbenium ion with the aromatic π-system, optimal stabilization being achieved when the α-C—H bond is orthogonal to the aromatic ring.



SCHEME 5

DDQ is often the reagent of choice for the dehydrogenation of hydrocarbons activated by the presence of an aromatic ring or an olefinic bond. In the dehydrogenation of the neoergosterol derivative (**30**), hydride abstraction occurred exclusively at the C-14 α-position which is orthogonal to the π-system (equation 5); no dehydrogenation of ring A to a naphthalene was observed and the olefinic side chain remained unaffected, possibly owing to prior complexing of the DDQ with the aromatic B ring.[25]



(30) (92%) (5)

5.5.4 SUBSTITUTIONS AND ADDITIONS

The reactions of quinones with nucleophiles and electrophiles are similar to those of α,β-unsaturated ketones.[26] The main preparative use is that the addition products can be oxidized back to quinones, the total process being in effect a direct substitution of the quinone. These and other reactions of *p*-quinones are summarized in Scheme 6;[27–35] *o*-quinones react similarly in most cases. Quinones also undergo typical carbonyl group reactions, *e.g.* with hydroxylamine to give the expected oximes.

A reaction which is specific to quinones is the Thiele–Winter acetoxylation,[36] the introduction of an acyloxy group into the quinone nucleus with concomitant acylation. The reaction has been widely used for the introduction of oxygen functionality into aromatic rings and for the structural proof and to facilitate the isolation of natural products. The mechanism is shown in Scheme 7.

One of the more interesting reactions of *ortho*-quinones is the oxidative ring cleavage in, for example, methanol solution to give mono- or di-methyl (*Z,Z*)-muconate (equation 6). Several reagents, including lead tetra-acetate and oxygen in the presence of a cuprous chloride–pyridine–methanol catalyst, have been used.[37] In the latter case it has recently been shown that the ring is opened by the stable copper(II) species pyridine–CuClOMe and that oxygen serves only to oxidize cuprous to cupric ions.[38]

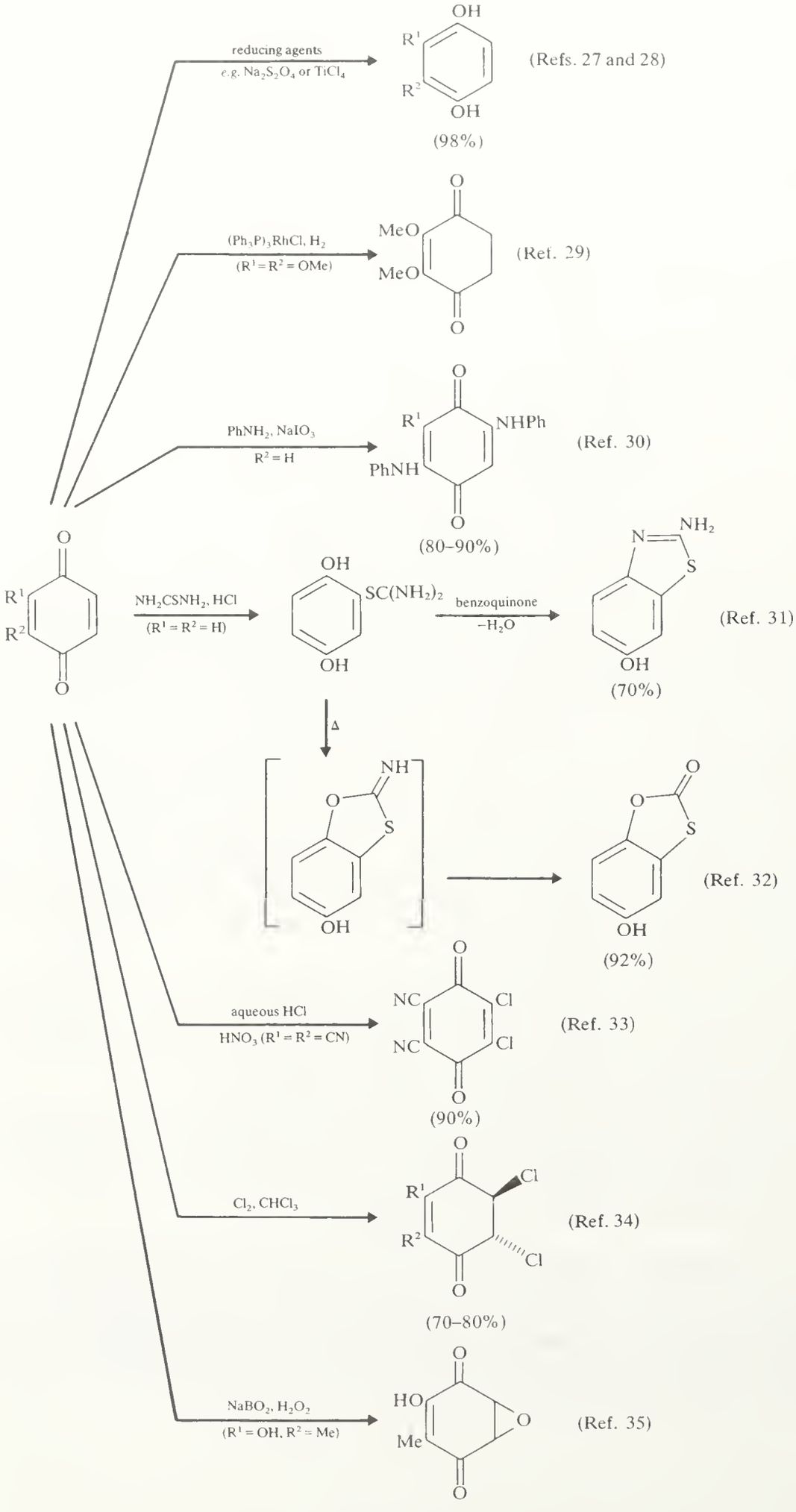
The Diels–Alder reactions of quinones have been one of the most intensely studied reactions.[26,39] In the 1950s several laboratories realized that the regio- and stereoselectivity of these cycloadditions could be applied to the synthesis of natural products and the early stages of many total syntheses (*e.g.* cholesterol, cortisone, oestrone, reserpine, terramycin, and yohimbine) incorporate a quinone cycloaddition. In Woodward's total synthesis of cholesterol (**31**) (Scheme 8), cycloaddition of the quinone (**32**) to butadiene gave a single isomer with the expected *cis* ring junction, which could be isomerized to the *trans* isomer by base.[40] This provided the correct stereochemistry for the C/D ring junction in the final product cholesterol (**31**).

The stereochemistry of the cycloaddition of cyclopentadiene to 1,4-benzoquinone has been studied in detail and illustrates the high selectivity of these reactions (Scheme 9). From a possible four isomers, only the predicted *endo-cis* 1 : 1 adduct (**33**) was formed initially, but this reacted with a second molecule of cyclopentadiene to give only the *endo-cis,anti,endo-cis* adduct (**34**) out of a possible 16 isomers.[41]

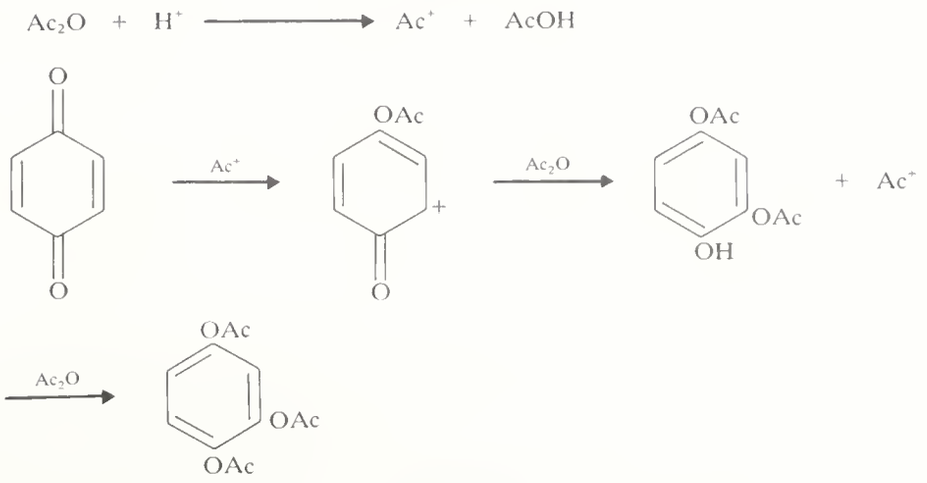
With substituted quinones, the position of addition depends on both steric and electronic factors. In general, an electron-withdrawing group on the quinone activates the dienophile, so that addition to the more substituted double bond is preferred. In contrast, electron-donating substituents deactivate and cycloaddition takes place to the least substituted double bond. The order of reactivity is:

$$CN > COMe > CO_2Me > CF_3 > H > F > Cl > Me > OAc > NMePh > OMe > SMe$$

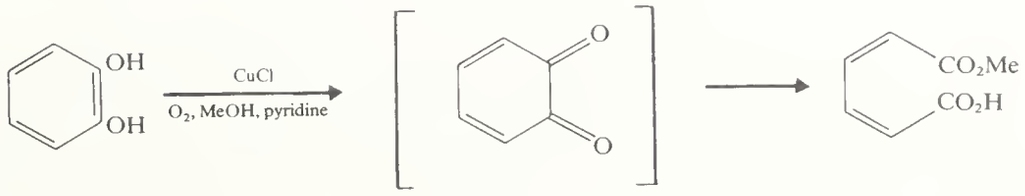
but there are many exceptions to these general rules, since the preferred *endo* transition states are subject to steric influence. When the diene is also constitutionally unsymmetrical, the factors are even more complex; yet, in practice, the reactions can be very selective[42] (equation 7).


reducing agents
e.g. $Na_2S_2O_4$ or $TiCl_4$
(Refs. 27 and 28)
(98%)
$(Ph_3P)_3RhCl$, H_2
$(R^1 = R^2 = OMe)$
(Ref. 29)
$PhNH_2$, $NaIO_3$
$R^2 = H$
(Ref. 30)
(80–90%)
NH_2CSNH_2, HCl
$(R^1 = R^2 = H)$
benzoquinone
$-H_2O$
(Ref. 31)
(70%)
Δ
(Ref. 32)
(92%)
aqueous HCl
HNO_3 $(R^1 = R^2 = CN)$
(Ref. 33)
(90%)
Cl_2, $CHCl_3$
(Ref. 34)
(70–80%)
$NaBO_2$, H_2O_2
$(R^1 = OH, R^2 = Me)$
(Ref. 35)

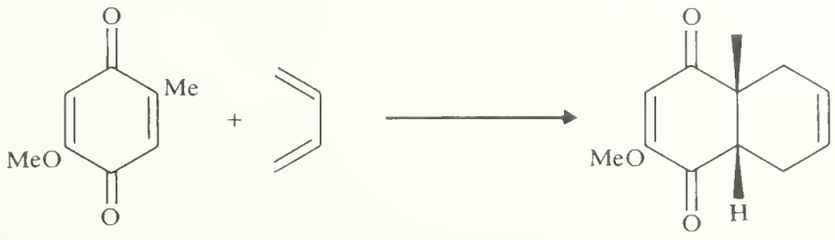
SCHEME 6



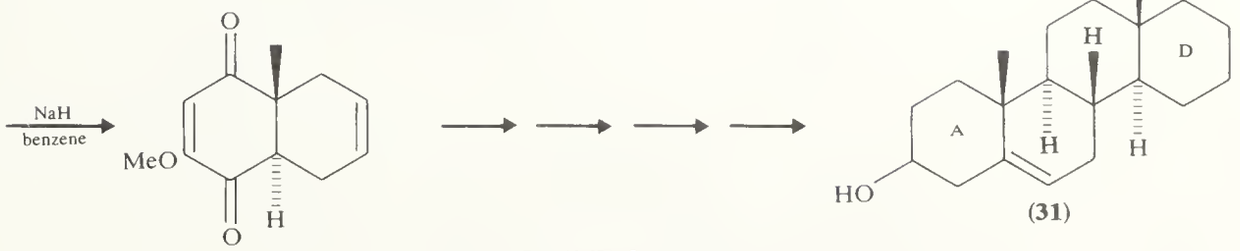
SCHEME 7



(6)

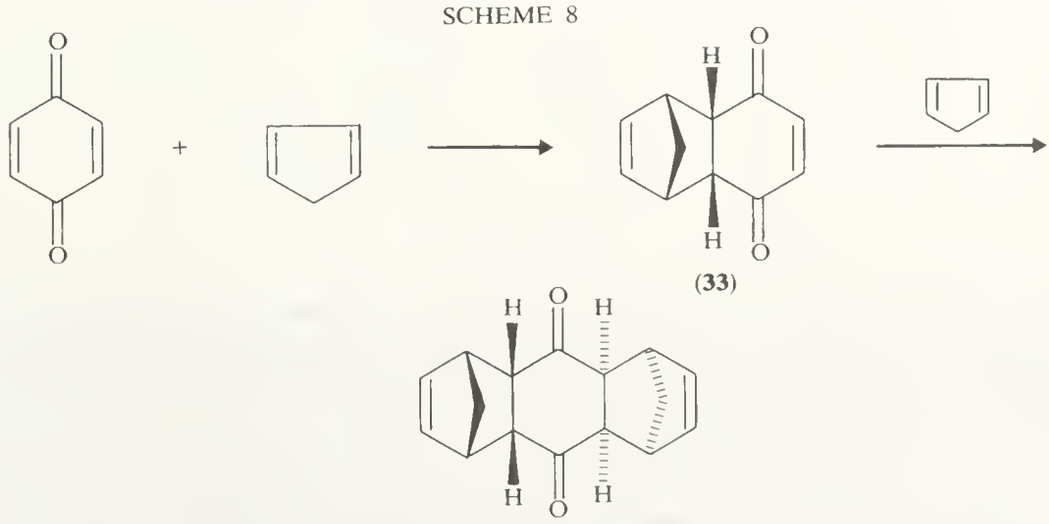


(**32**)



(**31**)

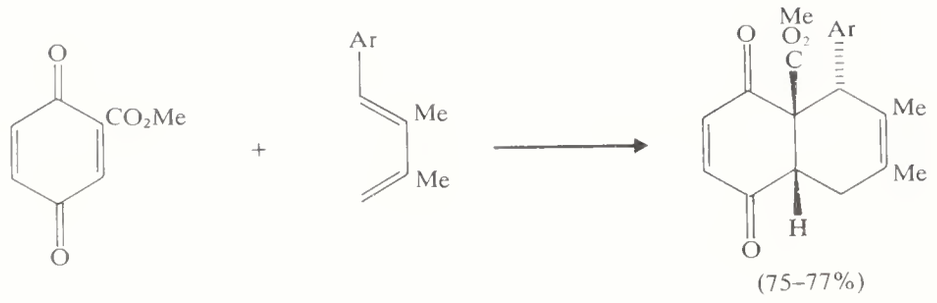
SCHEME 8



(**33**)

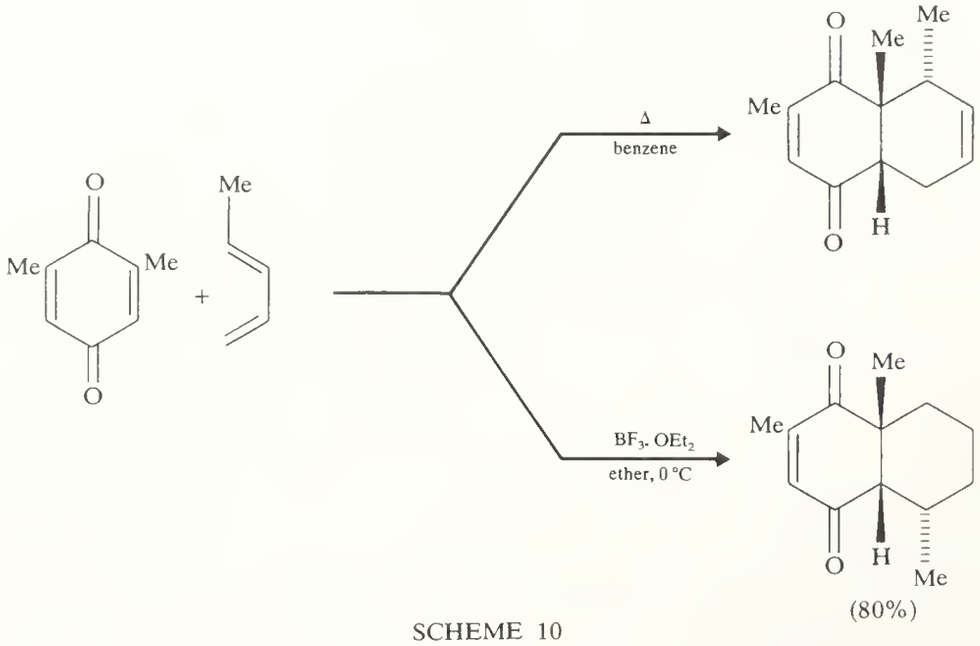
(**34**)

SCHEME 9

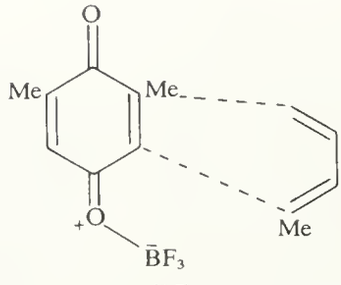


(75–77%) (7)

The most recent development in quinone cycloadditions has been the observation of a dramatic change of regioselectivity when the Diels–Alder reactions were carried out in the presence of Lewis acid catalysts (Scheme 10).[43] This discovery further increases the synthetic potential of quinone cycloadditions in the synthesis of natural products. The change in regioselectivity was attributed to selective complexing between the quinone and Lewis acid leading to complex (**35**), which added in the manner depicted.

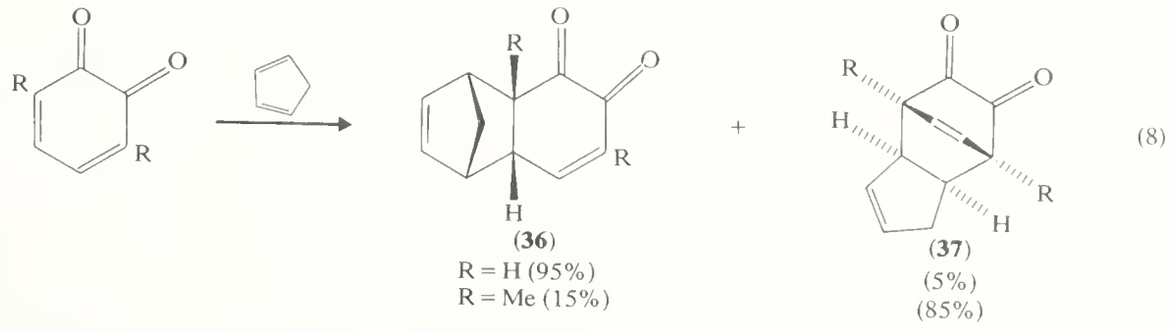


SCHEME 10



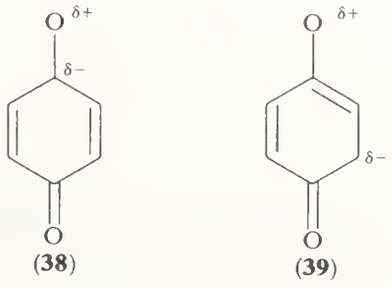
(**35**)

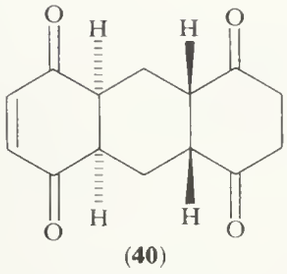
The cycloadditions of *ortho*-quinones are much more complex since the quinone can act either as diene or dienophile, *e.g.* with cyclopentadiene. The reaction of *o*-benzoquinone at room temperature gave, as major product, the adduct (**36**; 95%) formed by addition of cyclopentadiene to the dienophile. However, the major adduct (**36**) was quantitatively converted in refluxing benzene by a Cope rearrangement into the minor adduct (**37**) (equation 8). With substituted *o*-quinones the ratio of the adducts depends on steric and electronic factors, and often the quinone prefers to act as diene rather than dienophile (equation 8).[44] A further mode of reaction, cycloaddition to the carbonyl group, is also possible, but only usually occurs with tetrahalo-*o*-quinones.[45]

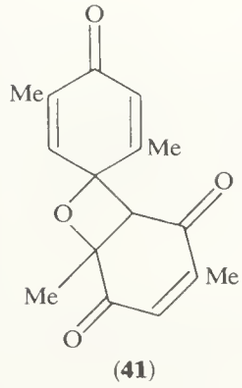


5.5.5 PHOTOCHEMISTRY OF QUINONES[46,47]

The most important band in the ultraviolet and visible spectra of 1,4-quinones lies in the region 400–500 nm (ε, 20–100), corresponding to the n,π^* singlet–singlet transition. Intersystem crossing to the first triplet (T_1) occurs rapidly with high efficiency and it is from T_1 that the subsequent reactions take place. For 1,4-benzoquinone (**1**), the energy of the first excited singlet (S_1) is 59 kcal mol^{-1} (248 kJ mol^{-1}) whereas T_1 is 6 kcal mol^{-1} (25 kJ mol^{-1}) lower. The corresponding triplets for 1,4-naphthoquinone (**13**) and 9,10-anthraquinone (**16**) are 58 kcal mol^{-1} (244 kJ mol^{-1}) and 63 kcal mol^{-1} (265 kJ mol^{-1}), respectively. The excited quinones have more electrophilic oxygens than the ground state owing to contributions from the structures (**38**) and (**39**). Similar structures can also be written for 1,2-quinones.



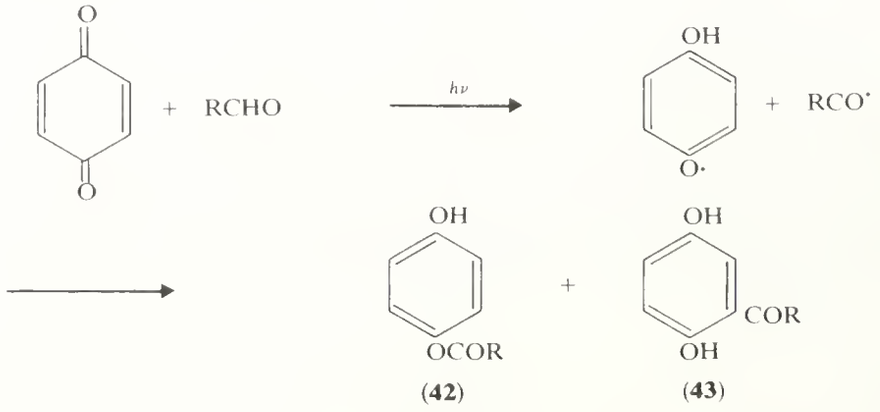




Irradiation of 1,4-benzoquinone in solution gives a low yield of the dimer (**40**), this reaction being similar to an α,β-unsaturated ketone dimerization.[48,49] However, when steric factors inhibit this process (for example, with 2,5-dimethyl-1,4-benzoquinone), the product is the spiro-oxetan (**41**).[50] Similar spiro-oxetans have been formed in the photoaddition of quinones to a variety of olefins, and in this respect the photochemistry parallels that of ordinary ketones.

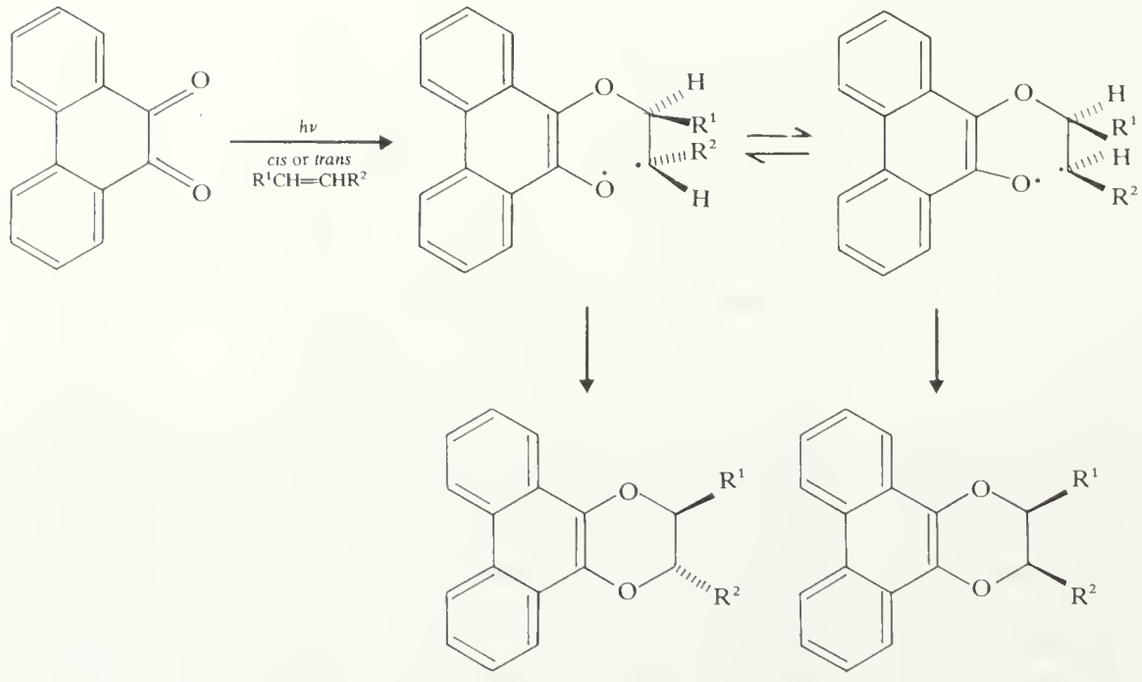
Although many of the photoreactions of quinones are similar to other carbonyl compounds (*e.g.* photoreduction), the photoaddition of aldehydes to quinones has no ketonic counterpart.[51] Irradiation of 1,4-benzoquinone in the presence of aldehydes leads

to moderate yields of either quinol monoesters (**42**) or acyl quinols (**43**). The mechanism shown in Scheme 11 has been substantiated by CIDNP experiments.[52] When aliphatic aldehydes were used, almost exclusive *C*-acylation took place, whereas with aromatic aldehydes, both *C*- and *O*-acylation products were isolated. With α,β-unsaturated aldehydes, only the esters (**42**) were obtained. The change in product with substituent depends on the nucleophilicity of the acyl radical (Scheme 11). Acyl radicals, owing to the contributions from structures such as $R—C{=}\overset{+}{\underset{\cdot}{O}}$, are nucleophilic and preferentially attack at carbon. Stabilization by aromatics containing electron-withdrawing groups, however, leads to a more electrophilic radical which attacks preferentially at oxygen. The photoacylation by aldehydes is a general reaction for most quinones; those with high oxidation potentials, however, give only the *O*-acylated product even with aliphatic aldehydes. 1,2-Quinones, which have higher oxidation potentials than analogous 1,4-quinones, also yield exclusively quinol monoesters.



SCHEME 11

The cycloaddition of 1,2-quinones to olefins, which proceeds thermally, can also be carried out photochemically at room temperature.[53] The products are similar, but the selectivity is lower in the photochemical reaction, presumably because triplet diradical intermediates are involved (Scheme 12).



SCHEME 12

References

1. M. J. S. Dewar and G. J. Gleicher, *J. Chem. Phys.*, 1966, **44,** 759.
2. R. A. Morton, *Biol. Rev. Camb. Phil. Soc.*, 1971, **46,** 47.
3. K. Venkataraman and V. N. Iyer, in 'Chemistry of Synthetic Dyes', ed. K. Venkataraman, Academic, New York, 1971, vol. 5, chapter 3.
4. M. E. Peover, *J. Chem. Soc.*, 1962, 4540.
5. R. Foster, 'Organic Charge Transfer Complexes', Academic, London, 1969.
6. J. Bernstein, H. Reger, F. H. Herbstein, P. Main, S. H. Rizvi, K. Sasvari, and B. Turcsanyi, *Proc. Roy. Soc.*, 1976, **A347,** 419.
7. C. W. Greenhalgh, *Endeavour*, 1976, **35,** 134.
8. R. H. Thomson, in 'Chemistry of Quinonoid Compounds', ed. S. Patai, Interscience, New York, 1974, chapter 3.
9. H. Zimmer, D. C. Lankin, and S. W. Horgan, *Chem. Rev.*, 1971, **71,** 229.
10. H. J. Teuber and O. Glosauer, *Chem. Ber.*, 1965, **98,** 2643.
11. I. Baxter and B. A. Davis, *Quart. Rev.*, 1971, **25,** 239.
12. J. Cason, *Org. Reactions*, 1948, **4,** 305.
13. A. McKillop, B. P. Swann, and E. C. Taylor, *Tetrahedron*, 1970, **26,** 4031.
14. V. Balogh, M. Fetizon, and M. Golfier, *J. Org. Chem.*, 1971, **36,** 1339.
15. D. H. R. Barton, A. G. Brewster, S. V. Ley, and M. N. Rosenfeld, *J.C.S. Chem. Comm.*, 1976, 985.
16. M. V. Gorelik, *Zhur. org. Khim.*, 1968, **4,** 501.
17. C. D. Snyder and H. Rapoport, *J. Amer. Chem. Soc.*, 1972, **94,** 227.
18. P. Jacob, III, P. S. Callery, A. T. Shulgin, and N. Castagnoli, Jr., *J. Org. Chem.*, 1976, **41,** 3627.
19. S. Sethna, in 'Friedel Crafts and Related Reactions', ed. G. A. Olah, Interscience, New York, 1964, vol. 3, chapter 35.
20. S. J. Cristol and M. L. Caspar, *J. Org. Chem.*, 1968, **33,** 2020.
21. H.-D. Becker, in 'Chemistry of Quinonoid Compounds', ed. S. Patai, Interscience, New York, 1974, chapter 7.
22. D. Walker and J. D. Hiebert, *Chem. Rev.*, 1967, **67,** 153.
23. A. B. Turner and H. J. Ringold, *J. Chem. Soc.* (*C*) 1967, 1720.
24. D. R. Brown and A. B. Turner, *J.C.S. Perkin II*, 1975, 1307.
25. W. Brown and A. B. Turner, *J. Chem. Soc.* (*C*) 1971, 2057.
26. K. T. Finlay, in 'Chemistry of Quinonoid Compounds', ed. S. Patai, Interscience, New York, 1974, chapter 17.
27. G. A. Reynolds and J. A. van Allen, *Org. Synth. Coll. Vol. 4*, 1963, 15.
28. L. C. Blaszczak and J. E. McMurry, *J. Org. Chem.*, 1974, **39,** 258.
29. A. J. Birch and K. A. M. Walker, *Tetrahedron Letters*, 1967, 3457.
30. W. Schäfer and A. Aguado, *Angew Chem. Internat. Edn.*, 1971, **10,** 405.
31. P. T. S. Lau and M. Kestner, *J. Org. Chem.*, 1968, **33,** 4426.
32. P. T. S. Lau and T. E. Gompf, *J. Org. Chem.*, 1970, **35,** 4103.
33. D. Walker and T. D. Waugh, *J. Org. Chem.*, 1965, **30,** 3240.
34. J. Y. Savoie and P. Brassard, *Canad. J. Chem.*, 1966, **44,** 2867.
35. A. Rashid and G. Read, *J. Chem. Soc.* (*C*), 1967, 1323.
36. J. F. W. McOmie and J. M. Blatchly, *Org. Reactions*, 1972, **19,** 199.
37. M. Weissler, *Tetrahedron Letters*, 1977, 233.
38. M. M. Rogic, T. R. Demmin, and W. B. Hammond, *J. Amer. Chem. Soc.*, 1976, **99,** 7441; J. Tsuji and H. Takayanagi, *Tetrahedron Letters*, 1976, 1365.
39. H. Wollweber, in 'Methoden der Organischen Chemie (Houben-Weyl)', ed. E. Müller, Thieme Verlag, Stuttgart, 1976, vol. VII/2b, p. 1765.
40. R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Amer. Chem. Soc.*, 1952, **74,** 4223.
41. R. C. Cookson, R. R. Hill, and J. Hudec, *J. Chem. Soc.*, 1964, 3043.
42. M. F. Ansell and A. H. Clements, *J. Chem. Soc.* (*C*), 1971, 269.
43. Z. Stojanac, R. A. Dickinson, N. Stojanac, R. J. Woznow, and Z. Valenta, *Canad. J. Chem.*, 1975, **53,** 616.
44. M. F. Ansell, A. F. Gosden, V. J. Leslie, and R. A. Murray, *J. Chem. Soc.* (*C*), 1971, 1401.
45. M. F. Ansell and V. J. Leslie, *J. Chem. Soc.* (*C*), 1971, 1423.
46. J. M. Bruce, in 'Chemistry of Quinonoid Compounds', ed. S. Patai, Interscience, New York, 1974, chapter 9.
47. J. M. Bruce, *Quart. Rev.*, 1967, **21,** 405.
48. D. Bryce-Smith and A. Gilbert, *J. Chem. Soc.*, 1964, 2428.
49. E. H. Gold and D. Ginsburg, *J. Chem. Soc.* (*C*), 1967, 15.
50. R. C. Cookson, J. J. Frankel, and J. Hudec, *Chem. Comm.*, 1965, 16.
51. J. M. Bruce and K. Dawed, *J. Chem. Soc.* (*C*), 1970, 645.
52. L. Maruyama and Y. Miyagi, *Bull. Chem. Soc. Japan*, 1974, **47,** 1303.
53. Y. L. Chow and T. C. Joseph, *Chem. Comm.*, 1968, 604.