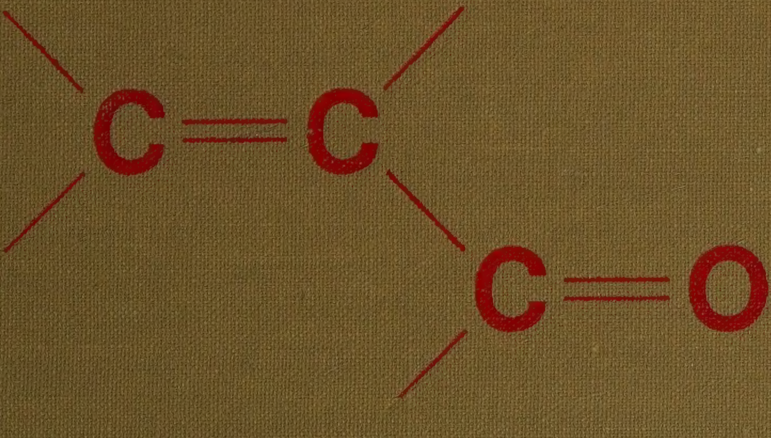


The chemistry of
enones

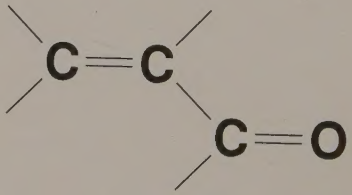
Part 1

THE CHEMISTRY OF FUNCTIONAL GROUPS

A series of advanced treatises under the general editorship of
Professor Saul Patai

The chemistry of alkenes (2 volumes)
The chemistry of the carbonyl group (2 volumes)
The chemistry of the ether linkage
The chemistry of the amino group
The chemistry of the nitro and nitroso groups (2 parts)
The chemistry of carboxylic acids and esters
The chemistry of the carbon–nitrogen double bond
The chemistry of amides
The chemistry of the cyano group
The chemistry of the hydroxyl group (2 parts)
The chemistry of the azido group
The chemistry of acyl halides
The chemistry of the carbon–halogen bond (2 parts)
The chemistry of the quinonoid compounds (2 volumes, 4 parts)
The chemistry of the thiol group (2 parts)
The chemistry of the hydrazo, azo and azoxy groups (2 parts)
The chemistry of amidines and imidates
The chemistry of cyanates and their thio derivatives (2 parts)
The chemistry of diazonium and diazo groups (2 parts)
The chemistry of the carbon–carbon triple bond (2 parts)
The chemistry of ketenes, allenes and related compounds (2 parts)
The chemistry of the sulphonium group (2 parts)
Supplement A: The chemistry of double-bonded functional groups (2 parts)
Supplement B: The chemistry of acid derivatives (2 parts)
Supplement C: The chemistry of triple-bonded functional groups (2 parts)
Supplement D: The chemistry of halides, pseudo-halides and azides (2 parts)
Supplement E: The chemistry of ethers, crown ethers, hydroxyl groups
and their sulphur analogues (2 parts)
Supplement F: The chemistry of amino, nitroso and nitro compounds
and their derivatives (2 parts)
The chemistry of the metal–carbon bond (4 volumes)
The chemistry of peroxides
The chemistry of organic selenium and tellurium compounds (2 volumes)
The chemistry of the cyclopropyl group
The chemistry of sulphones and sulphoxides
The chemistry of organic silicon compounds (2 parts)

UPDATES
The chemistry of α-haloketones, α-haloaldehydes and α-haloimines
Nitrones, nitronates and nitroxides
Crown ethers and analogs
The formation of carbon–halogen bonds



The chemistry of enones

Part 1

Edited by

SAUL PATAI

and

ZVI RAPPOPORT

The Hebrew University, Jerusalem

1989

JOHN WILEY & SONS
CHICHESTER–NEW YORK–BRISBANE–TORONTO–SINGAPORE

An Interscience® Publication

Library of Congress Cataloging-in-Publication Data:

The Chemistry of enones / edited by Saul Patai and Zvi Rappoport.
p. cm. — (The Chemistry of functional groups)
'An Interscience publication.'
ISBN 0 471 91563 7 (Part 1)
ISBN 0 471 92289 7 (Part 2)
ISBN 0 471 92290 0 (set)
1. Carbonyl compounds. 2. Olefins. I. Patai, Saul.
II. Rappoport, Zvi. III. Series.
QD305.A6C46 1989
547′.036—dc19 88-27713
CIP

British Library Cataloguing in Publication Data:

The Chemistry of Enones.
1. Enones
I. Patai, Saul II. Rappoport, Zvi
III. Series
547′.036

ISBN 0 471 91563 7 (Part 1)
ISBN 0 471 92289 7 (Part 2)
ISBN 0 471 92290 0 (set)

Printed and bound in Great Britain by
Courier International Ltd, Tiptree, Essex

Contributing authors

M. M. Baizer (deceased)	Department of Chemistry, University of California, Santa Barbara, California 93106, USA
C. L. Bevins	Department of Chemistry, The University of Maryland Baltimore County, Baltimore, Maryland 21228, USA
P. L. Bounds	Department of Chemistry, The University of Maryland Baltimore County, Baltimore, Maryland 21228, USA
G. V. Boyd	Department of Organic Chemistry, The Hebrew University of Jerusalem, Jerusalem 91904, Israel
B. Capon	Department of Chemistry, University of Hong Kong, Pokfulam Road, Hong Kong
M. Dizdaroglu	Center for Chemical Physics, National Bureau of Standards, Gaithersburg, Maryland 20899, USA
D. Duval	Laboratoire de Chimie Physique Organique, Université de Nice, Parc Valrose, 06034 Nice Cédex, France
A. A. Frimer	Department of Chemistry, Bar-Ilan University, Ramat Gan 52100, Israel
J. K. Gawronski	Faculty of Chemistry, Adam Mickiewicz University, Grunwaldzka 6, 60780 Poznań, Poland
S. Géribaldi	Laboratoire de Chimie Physique Organique, Université de Nice, Parc Valrose, 06034 Nice Cédex, France
H. E. Gottlieb	Department of Chemistry, Bar-Ilan University, Ramat-Gan 52100, Israel
N. Greenspoon	Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot, Israel
J. A. S. Howell	Department of Chemistry, University of Keele, Keele, Staffordshire, ST5 5BG, UK
C. R. Johnson	Department of Chemistry, Wayne State University, Detroit, Michigan 48202, USA
E. Keinan	Department of Chemistry, Technion–Israel Institute of Technology, Technion City, Haifa 32000, Israel
J. F. Liebman	Department of Chemistry, The University of Maryland Baltimore County, Baltimore, Maryland 21228, USA
R. D. Little	Department of Chemistry, University of California, Santa Barbara, California 93106, USA

A. Y. Meyer	Department of Organic Chemistry, The Hebrew University of Jerusalem, Jerusalem 91904, Israel
K. Müllen	Department of Organic Chemistry, University of Mainz, J. J. Becher-Weg 18–20, D-6500 Mainz, FRG
P. Neta	Center for Chemical Physics, National Bureau of Standards, Gaithersburg, Maryland 20899, USA
M. R. Peel	Department of Chemistry, Wayne State University, Detroit, Michigan 48202, USA
R. M. Pollack	Department of Chemistry, The University of Maryland Baltimore County, Baltimore, Maryland 21228, USA
G. A. Russell	Department of Chemistry, Iowa State University, Ames, Iowa 50011, USA
D. I. Schuster	Department of Chemistry, Faculty of Arts and Science, New York University, 4 Washington Place, Room 514, New York, NY 10003, USA
B. Schweizer	ETH Laboratorium für Organische Chemie, Universitätstrasse 16, ETH-Zentrum, CH-8092 Zürich, Switzerland
K. J. Shea	Department of Chemistry, University of California, Irvine, California 92917, USA
C. Thebtaranonth	Department of Chemistry, Faculty of Science, Mahidol University, Rama 6 Road, Bangkok 10400, Thailand
Y. Thebtaranonth	Department of Chemistry, Faculty of Science, Mahidol University, Rama 6 Road, Bangkok 10400, Thailand
C. R. Theocharis	Department of Chemistry, Brunel University, Uxbridge, Middlesex, UB8 3PH, UK
F. Tureček	The Jaroslav Heyrovsky Institute of Physical Chemistry and Electrochemistry, Machova 7, 12138 Prague 2, Czechoslovakia
P. Wolf	Department of Organic Chemistry, University of Mainz, J. J. Becher-Weg 18–20, D-6500 Mainz, FRG
R. I. Zalewsky	Department of General Chemistry, Academy of Economy, 60–967 Poznań, Poland

Foreword

The present volume in 'The chemistry of functional groups' series presents material on ketones and aldehydes containing also a carbon–carbon double bond, i.e. on enones and enals. The two (in the large majority of cases conjugated) functional groups involved, i.e. C=C and C=O influence one another profoundly and their properties and reactions in enones and enals are by no means identical to those which occur alone in simple alkenes or carbonyl compounds. Hence we believed that a separate volume on the C=C—C=O system would be a desirable addition to the series and we are very pleased that we succeeded in securing the collaboration of an international team of authors, scattered widely over three continents.

Two subjects were intended to be covered in this volume, but did not materialize. These were on biochemistry and on enones with strained double bonds. We hope to include these chapters in one of the forthcoming supplementary volumes of the series. A third chapter, on cycloadditions, will be included in Supplement A2, to be published in a few months' time.

Literature coverage in most chapters is up to late 1987 or early 1988.

Jerusalem
December 1988

SAUL PATAI
ZVI RAPPOPORT

The Chemistry of Functional Groups
Preface to the Series

The series 'The Chemistry of Functional Groups' is planned to cover in each volume all aspects of the chemistry of one of the important functional groups in organic chemistry. The emphasis is laid on the functional groups treated and on the effects which it exerts on the chemical and physical properties, primarily in the immediate vicinity of the group in question and secondarily on the behaviour of the whole molecule. For instance, the volume *The Chemistry of the Ether Linkage* deals with reactions in which the C—O—C group is involved, as well as with the effects of the C—O—C group on the reactions of alkyl or aryl groups connected to the ether oxygen. It is the purpose of the volume to give a complete coverage of all properties and reaction of ethers in as far as these depend on the presence of the ether group but the primary subject matter is not the whole molecule, but the C—O—C functional group.

A further restriction in the treatment of the various functional groups in these volumes is that material included in easily and generally available secondary or tertiary sources, such as Chemical Reviews, Quarterly Reviews, Organic Reactions, various 'Advances' and 'Progress' series as well as in textbooks (i.e. in books which are usually found in the chemical libraries of universities and research institutes) should not, as a rule, be repeated in detail, unless it is necessary for the balanced treatment of the subject. Therefore each of the authors is asked not to give an encyclopaedic coverage of his subject, but to concentrate on the most important recent developments and mainly on material that has not been adequately covered by reviews or other secondary sources by the time of writing of the chapter, and to address himself to a reader who is assumed to be at a fairly advanced postgraduate level.

With these restrictions, it is realized that no plan can be devised for a volume that would give a complete coverage of the subject with no overlap between chapters, while at the same time preserving the readability of the text. The Editor set himself the goal of attaining reasonable coverage with moderate overlap, with a minimum of cross-references between the chapters of each volume. In this manner, sufficient freedom is given to each author to produce readable quasi-monographic chapters.

The general plan of each volume includes the following main sections:

(a) An introductory chapter dealing with the general and theoretical aspects of the group.

(b) One or more chapters dealing with the formation of the functional group in question, either from groups present in the molecule, or by introducing the new group directly or indirectly.

(c) Chapters describing the characterization and characteristics of the functional groups, i.e. a chapter dealing with qualitative and quantitative methods of determination including chemical and physical methods, ultraviolet, infrared, nuclear magnetic resonance and mass spectra: a chapter dealing with activating and directive effects exerted by the group and/or a chapter on the basicity, acidity or complex-forming ability of the group (if applicable).

(d) Chapters on the reactions, transformations and rearrangements which the functional groups can undergo, either alone or in conjunction with other reagents.

(e) Special topics which do not fit any of the above sections, such as photochemistry, radiation chemistry, biochemical formations and reactions. Depending on the nature of each functional group treated, these special topics may include short monographs on related functional groups on which no separate volume is planned (e.g. a chapter on 'Thioketones' is included in the volume *The Chemistry of the Carbonyl Group*). In other cases certain compounds, though containing only the functional group of the title, may have special features so as to be best treated in a separate chapter, as e.g. 'Polyethers' in *The Chemistry of the Ether Linkage*, or 'Tetraaminoethylenes' in *The Chemistry of the Amino Group*.

This plan entails that the breadth, depth and thought-provoking nature of each chapter will differ with the views and inclinations of the author and the presentation will necessarily be somewhat uneven. Moreover, a serious problem is caused by authors who deliver their manuscript late or not at all. In order to overcome this problem at least to some extent, it was decided to publish certain volumes in several parts, without giving consideration to the originally planned logical order of the chapters. If after the appearance of the originally planned parts of a volume it is found that either owing to non-delivery of chapters, or to new developments in the subject, sufficient material has accumulated for publication of a supplementary volume, containing material on related functional groups, this will be done as soon as possible.

The overall plan of the volumes in the series 'The Chemistry of Functional Groups' includes the titles listed below:

The chemistry of alkenes (two volumes)
The chemistry of the carbonyl group (two volumes)
The chemistry of the ether linkage
The chemistry of the amino group
The chemistry of the nitro and nitroso groups (two parts)
The chemistry of carboxylic acids and esters
The chemistry of the carbon–nitrogen double bond
The chemistry of the cyano group
The chemistry of amides
The chemistry of the hydroxyl group (two parts)
The chemistry of the azido group
The chemistry of the acyl halides
The chemistry of the carbon–halogen bond (two parts)
The chemistry of the quinonoid compounds (two volumes, four parts)
The chemistry of the thiol group (two parts)
The chemistry of the hydrazo, azo and azoxy groups (two parts)
The chemistry of amidines and imidates
The chemistry of cyanates and their thio derivatives (two parts)
The chemistry of diazonium and diazo groups (two parts)
The chemistry of the carbon–carbon triple bond (two parts)
The chemistry of ketenes, allenes and related compounds (two parts)
The chemistry of the sulphonium group (two parts)
Supplement A: The chemistry of double-bonded functional groups (two parts)
Supplement B: The chemistry of acid derivatives (two parts)
Supplement C: The chemistry of triple-bonded functional groups (two parts)

Supplement D: The chemistry of halides, pseudo-halides and azides (two parts)
Supplement E: The chemistry of ethers, crown ethers, hydroxyl groups and their sulphur analogues (two parts)
Supplement F: The chemistry of amino, nitroso and nitro compounds and their derivatives (two parts)
The chemistry of the metal–carbon bond (four volumes)
The chemistry of peroxides
The chemistry of organic selenium and tellurium compounds (two volumes)
The chemistry of the cyclopropyl group
The chemistry of sulphones and sulphoxides
The chemistry of organic silicon compounds (two parts)

Titles in press:

Supplement A2: The chemistry of double-bonded functional groups

Titles in preparation:

The chemistry of enols
The chemistry of sulphinic acids, esters and derivatives
The chemistry of sulphenic acids, esters and derivatives

Advice or criticism regarding the plan and execution of this series will be welcomed by the Editor.

The publication of this series would never have been started, let alone continued, without the support of many persons. First and foremost among these was the late Dr Arnold Weissberger, whose reassurance and trust encouraged me to tackle this task. The efficient and patient co-operation of several staff members of the Publisher also rendered me invaluable aid (but unfortunately their code of ethics does not allow me to thank them by name). Many of my friends and colleagues in Israel and overseas helped me in the solution of various major and minor matters, and my thanks are due to all of them, especially to Professor Zvi Rappoport. Carrying out such a long range project would be quite impossible without the non-professional but none the less essential participation and partnership of my wife.

The Hebrew University
Jerusalem, ISRAEL

SAUL PATAI

Contents

List of abbreviations used

Ac	acetyl (MeCO)
acac	acetylacetone
Ad	adamantyl
All	allyl
An	anisyl
Ar	aryl
Bz	benzoyl (C_6H_5CO)
Bu	butyl (also *t*-Bu or Bu^t)
CD	circular dichroism
CI	chemical ionization
CIDNP	chemically induced dynamic nuclear polarization
CNDO	complete neglect of differential overlap
Cp	η^5-cyclopentadienyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulphoxide
ee	enantiomeric excess
EI	electron impact
ESCA	electron spectroscopy for chemical analysis
ESR	electron spin resonance
Et	ethyl
eV	electron volt
Fc	ferrocene
FD	field desorption
FI	field ionization
FT	Fourier transform
Fu	furyl(OC_4H_5)
Hex	hexyl(C_6H_{11})
c-Hex	cyclohexyl(C_6H_{11})
HMPA	hexamethylphosphortriamide
HOMO	highest occupied molecular orbital

i-	iso
Ip	ionization potential
IR	infrared
ICR	ion cyclotron resonance
LCAO	linear combination of atomic orbitals
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
M	metal
M	parent molecule
MCPBA	*m*-chloroperbenzoic acid
Me	methyl
MNDO	modified neglect of diatomic overlap
MS	mass spectrum
n	normal
Naph	naphthyl
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
Pen	pentyl(C_5H_{11})
Pip	piperidyl($C_5H_{10}N$)
Ph	phenyl
ppm	parts per million
Pr	propyl (also *i*-Pr or Pr^i)
PTC	phase transfer catalysis
Pyr	pyridyl (C_5H_4N)
R	any radical
RT	room temperature
s-	secondary
SET	single electron transfer
SOMO	singly occupied molecular orbital
t-	tertiary
TCNE	tetracyanoethylene
THF	tetrahydrofuran
Thi	thienyl(SC_4H_3)
TMEDA	tetramethylethylene diamine
Tol	tolyl(MeC_6H_4)
Tos	tosyl (*p*-toluenesulphonyl)
Trityl	triphenylmethyl(Ph_3C)
Xyl	xylyl($Me_2C_6H_3$)

In addition, entries in the 'List of Radical Names' in *IUPAC Nomenclature of Organic Chemistry*, 1979 Edition, Pergamon Press, Oxford, 1979, pp. 305–322, will also be used in their unabbreviated forms, both in the text and in structures.

We are sorry for any inconvenience to our readers. However, the rapidly rising costs of production make it absolutely necessary to use every means to reduce expenses—otherwise the whole existence of our Series would be in jeopardy.

The Chemistry of Enones
Edited by S. Patai and Z. Rappoport

CHAPTER 1

General and theoretical

A. Y. MEYER

Department of Organic Chemistry, The Hebrew University of Jerusalem, Jerusalem 91904, Israel

I. INTRODUCTION

In this chapter we concentrate on those features of the enone system that have most attracted the attention of computational chemists. Methods that have served and serve in theoretical studies of enones will be reviewed against the relevant experimental background.

Nowadays, the term 'computational chemistry' implies, first and foremost, *ab initio* quantum-chemical calculations[1]. A rival approach is molecular mechanics[2,3]. In both options, results are easy to come by. Computer programs are available, and there are manuals and guides[4] that tell the user how to run the programs and how to exploit the output. But up to 20 years ago, even as late as the early seventies, most calculations of organic molecules were 'semiempirical quantum-chemical'[5,6]. Those who had calculations in mind started by building up their own program. There was no guarantee that any version of the program would produce meaningful results. Frequent checks and fitting to experimental data were required and performed. Questions of principle were frequently encountered, and experts rather than manuals had to be consulted. To some of the innates, the advent of *ab initio* methods brought disillusionment. As Boggs has put it[7], 'The old-timers questioned approximate mathematical models; nowadays we can question Nature herself'. For the disillusioned, it is probably the standardization of questioning Nature that hurts.

Simultaneously with the rise and decline of semiempirical methods, there rose and dwindled the interest of theoreticians in the systematic analysis of enones. Unsaturated carbonyl compounds had everything with which the semiempiricist wanted to grapple. Their atomic orbitals can be separated into σ orbitals and π orbitals, and the properties of most interest depend almost exclusively on the latter. Once σ electrons are left aside, the residual system $C{=}C\cdots C{=}\ddot{O}$ can be partitioned into two simple 'chromophores' ($C{=}C$, $C{=}\ddot{O}$). Interaction between the two can be 'switched on and off' by mathematical tricks. The number of molecular orbitals (MOs) is very small: for $C{=}C$, one π and one π^* MO; for $C{=}\ddot{O}$, one π, one π^* and the n orbital that houses the nonbonding electron pair on oxygen. Of these, the $C{=}C$ MOs are determined by symmetry, and the n MO is identifiable with the corresponding atomic orbital (AO). To make matters even more fortunate, the two absorption bands of enones in the near ultraviolet (near UV) are well separated and widely different in shape: π–π^*, strong and sharp, occurs close to 200 nm; n–π^*, weak and wavy, occurs around 300 nm. As to the ground molecular state, the computed distribution of π charges could be superposed[8] on a computed distribution of σ charges, and the sum checked against experimental dipole moments.

The UV spectrograph and the dipolemeter are no longer in vogue. A similar fate has befallen quantum-chemical studies of enones. It is symptomatic that Schäfer's *ab initio* screening of organic molecules[9] does not include one sole unsaturated carbonyl compound. Supplement 5 (1985) to the *Quantum Chemistry Literature Data Base*[10] contains only two references which vaguely touch our topic. Volume 3 of Robin's *Higher Excited States of Polyatomic Molecules*[11] (published in 1985) glides over two references, the later dating back to 1979. Just confront this meager crop with the 20 pages of heavy analysis that Suzuki devoted to the vinyl–carbonyl system in his 1967 monograph[12]!

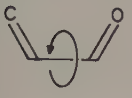
Unsaturated carbonyl compounds, while serving as objects for computation, provided also testing grounds for various concepts in theoretical organic chemistry: effect of heteroatoms on conjugation, chromophore interaction, interaction through bonds and through space, and more. This chapter is a retrospective view of theoretical procedures, quantum chemical and molecular mechanical, that have been applied to $C{=}C\cdots C{=}O$ systems. The methods to be discussed or referenced are: *ab initio* (Section IV), building-block interaction (VI), CNDO/S-CI (X), configurational interaction (VII), π-electronic SCF-CI (X), HAM/3 (X), INDO (IV), molecules in molecules (VIII), MINDO and MNDO (IV), molecular mechanics (IV) and VESCF (X).

The organic chemist's kcal and nm are related to other units (to be used below) through the following conversion factors:

$$1\ \text{kcal mol}^{-1} = 4.336 \times 10^{-2}\ \text{eV molecule}^{-1}$$
$$1\ \text{kcal mol}^{-1} = 349.8\ \text{cm}^{-1}\ \text{molecule}^{-1}$$
$$\lambda\ (\text{nm}) = 10^7/8068 \times (\text{energy in eV})$$

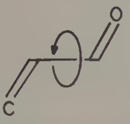
II. CONFORMATIONAL SPACE OF ACROLEIN DERIVATIVES

In $C^4{=}C^3{-}C^2{=}O^1$, internal rotation about $C^2{-}C^3$ spans a continuum of rotamers. Conceivable conformers, that is, rotamers corresponding to energy minima, are of four types. In two of them, the $C{=}C{-}C{=}O$ moiety is coplanar, with C^4 either as close as possible to O^1 (**1**, $\omega \equiv 0°$) or as far from it as possible (**2**, $\omega = 180°$). The other eventualities are close to **1** and **2**, but the four-atom sequence $C{=}C{-}C{=}O$ is not coplanar (**3** and **4**). **1** and **2** have a local plane of symmetry; **3** and **4** do not, and each should be understood as one representative of an enantiomeric pair. In a given molecule, if **3** happens to be a conformer, so is its enantiomer, and species **1** is a transition state along the course of internal rotation. This is more properly called a 'saddle point' since, at the barrier, the molecule is relaxed in most degrees of freedom, excepting the dihedral angle 1–2–3–4. An analogous statement applies to **4** and **2**: if **4** happens to be a conformer, its enantiomer is also a conformer, and **2** is a saddle point.



SP($\omega \equiv 0°$)

(1)

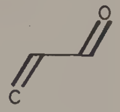


AP($\omega \equiv 180°$)

(2)

S

(3)



A

(4)

Disregarding chiral multiplicity, enones have two conformers. One is either **1** or **3**, the other is either **2** or **4**. The two, again, are separated by a barrier. Thus, in the most eventful case, the energy-versus-dihedral angle $E(\omega)$ curve has 8 singular points: 4 minima and 4 maxima. Of these, only two—**1** and **2**—are determined by symmetry: since the symmetry at **1** and **2** goes up from C_1 to C_s, they must correspond to extrema. A sketch of the most general $E(\omega)$, with arbitrary extrema, is provided in Figure 1.

By molecular mechanics[13], $Me_2C{=}CMeCHO$ is one such case. The lower minima occur at the enantiomeric dispositions of $\omega_1 = 173$ and $\omega_2 = 187°$ (**4**). The higher minima occur at the enantiomeric dispositions of $\omega_3 = 22$ and $\omega_4 = 338°$ (**3**). **1** and **2** must constitute saddle points. A third saddle must lie somewhere between ω_3 and ω_1, and a fourth between ω_2 and ω_4. By calculation, the molecule spans a range of *ca* 5.3 kcal mol^{-1} along its course of internal rotation.

The simplest case, of course, is when the conformers are **1** and **2**. In terms of Figure 1, each of the two enantiomeric pairs merges into a *meso* form. These are minima that submerge the maxima at 0° and 180°. As shown in Figure 2, four singular points are left. Acrolein is an example. By molecular mechanics[13], the energy range spanned amounts to *ca* 6.6 kcal mol^{-1}. Two other eventualities can be envisaged. In these, only one of the two

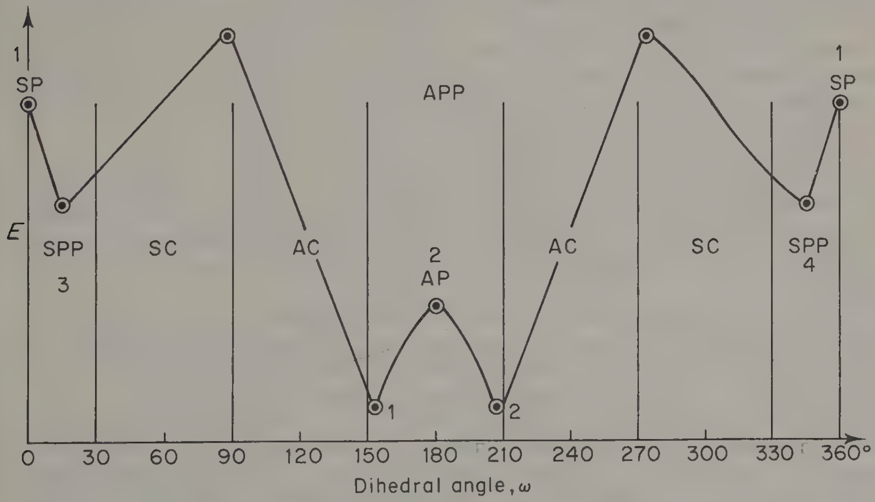


FIGURE 1. $E(\omega)$ curve for internal rotation about $C^2{-}C^3$ in $C^4{=}C^3{-}C^2{=}O^1$ in the most eventful case (schematic). In particular cases, some of the sketched features disappear

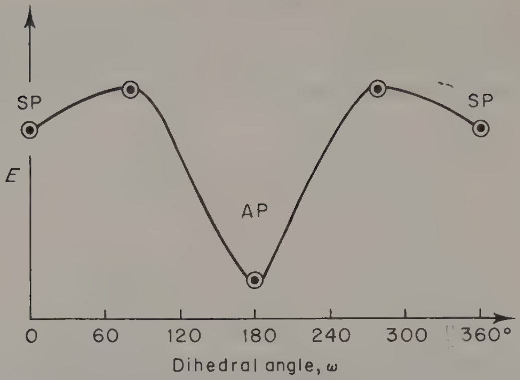


FIGURE 2. $E(\omega)$ curve for internal rotation about C^2—C^3 in C^4=C^3—C^2=O^1 in the least eventful case (schematic)

enantiomeric pairs merges into a *meso* form. Such cases have also been encountered (see below).

For the sake of perspective, it is worthwhile to recall[14] that the major conformer of butadiene is of symmetry C_{2h} (analogous to **2**, not to **4**), and that the minor must be very close to C_{2v} (**1**, not **3**).

As for stereochemical designations, species **1** has been variously called *cis*, *syn* or s-*cis*; **2**, *trans*, *anti*, or s-*trans*; **3**, cisoid or '*gauche*' (French for awkward, because of its seemingly precarious nature[15]); **4**, transoid. For $\omega \sim 90°$, the term 'skew' has been used. By Klyne and Prelog's labelling of sextants[16], **1** and **3** are both '*syn*' (S), **2** and **4** are both '*anti*' (A). If the deviation from coplanarity does not exceed 30°, *syn* rotamers are '*syn* periplanar' (SPP) and *anti* rotamers are '*anti* periplanar' (APP). Otherwise, they are '*syn* clinal' (SC) and '*anti* clinal' (AC). Since a term is not provided for strictly coplanar dispositions, we shall add to this list the terms '*syn* planar' (SP) and '*anti* planar' (AP). Also, since qualitative arguments need not contend with the demarcations at 30° and 330°, we shall occasionally use the loose term '*syn*' (S) for **3** and '*anti*' (A) for **4**. In Figures 1 and 2, those abbreviations that contain the letter S refer to range S, and those containing A refer to range A.

Using again the results from molecular mechanics[13], the conformers and conformational energies of methylated acroleins are listed in Table 1. It is seen that steric hindrance dictates the preferences. If not appreciable, the more stable conformer is *anti* planar, and the secondary conformer is *syn* planar. As steric hindrance becomes more severe, conformers depart from planarity, *anti* and *syn* exchange roles and periplanarity yields to clinality.

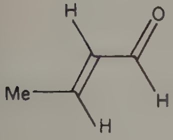
To illustrate the gradation in steric effects, let us examine two pairs of π diastereomers (formulas **5–12**). (π Diastereomers are isomers of the type formerly referred to as '*cis–trans* isomers about double bonds'. In the *E* diamer of XCH=CHCHO, X and CHO are on opposing sides of C=C ('entgegen'); in the *Z* diamer, they are on the same side ('zusammen')). In *E*-MeCH=CHCHO, there is no crowding. *anti* Planar (**5**) is the preferred conformer, and the other conformer is *syn* planar (**6**). In its *Z* diamer, Me···O interaction intervenes. The preferred conformer is still *anti* planar (**7**), but the other conformer is now *syn* nonplanar (**8**). *E*-MeCH=CHCOMe (**9, 10**) has the same conformers as *E*-MeCH=CHCHO (**5, 6**), but the energy difference is lower. Its diastereomer, however, is utterly different: in *Z*-MeCH=CHCOMe, both Me···O and

TABLE 1. Conformers of methylated acrolein derivatives[a]

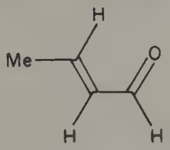
More favored	Less favored	Molecule and energy difference[b]
AP	SP	CH_2=CHCHO (1.64, 1.60)
		CH_2=CMeCHO (3.06, 3.07)
		CH_2=CHCOMe (0.56, 0.56)
		E-MeCH=CHCHO (1.82, 1.93)
		CH_2=CMeCOMe (1.57)
		E-MeCH=CHCOMe (0.71, 0.59)
AP	SPP	*Z*-MeCH=CHCHO (1.34)
		Z-MeCH=CMeCHO (2.65)
		CH_2=CMeCHO (1.41)
APP	SPP	*E*-MeCH=CMeCHO (3.26)
		E-MeCH=CMeCOMe (1.70)
		Me_2C=CMeCOMe (3.06)
SPP	APP	*Z*-MeCH=CHCOMe (1.74)
		Me_2C=CHCOMe (1.74)
SC	AC	*Z*-MeCH=CMeCOMe (1.47)
		Me_2C=CMeCOMe (0.60)

[a] As calculated by molecular mechanics[13]. Energy differences in kcal mol^{-1}. When an experimental number is known, it is cited as the second parenthetic entry. Data for the first three compounds served to parametrize the field.
[b] Energy difference between the more favored and less favored conformers.

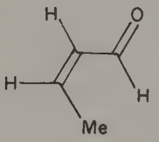
Me···Me interactions intervene. One consequence is that *syn* (**12**) is preferred to *anti* (**11**). Another consequence is that both conformers are clinal.



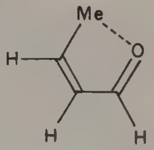
(5)



(6)

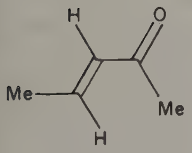


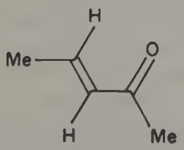
(7)



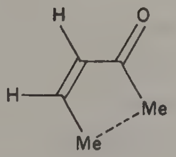
(8)

(9)

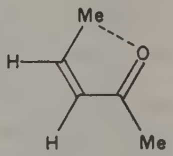




(10)



(11)



(12)

III. WHY *anti* AND NOT *syn*?

The foregoing considerations imply that electronic factors stabilize the *anti* range with respect to the *syn* range.

Acrolein figures among the few examples that Eyring and coworkers invoked in 1958 to illustrate the 'principle of minimum bending'[17]. Since 'electrons hate to go around corners', they would prefer to haunt the less edgy *anti* skeleton. Bingham's modern

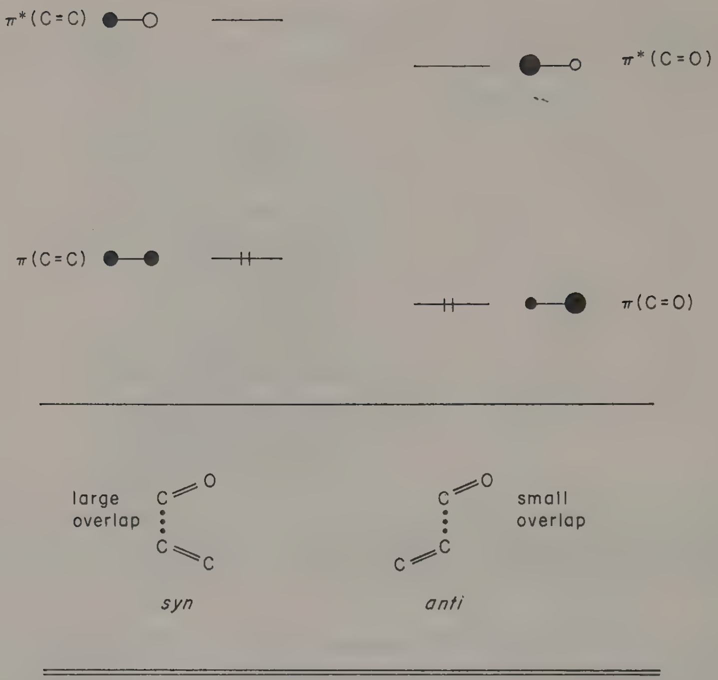


FIGURE 3. Top: Molecular orbitals of the π type in C=C (left) and C=O (right). Bottom: Disposition of fragments in the *syn* and *anti* varieties of C=C⋯C=O

rendering of the principle[18] states that electron delocalization in extended π systems should be greater for *anti* than for *syn* conformers. Therefore, as long as no antibonding MOs are occupied, electron delocalization stabilizes *anti* with respect to *syn*. Occupation of antibonding orbitals would destabilize *anti*. For illustration, Bingham recalls that butadiene is essentially *anti*, but its dianion contains an appreciable amount of a *syn* conformer. To this we may add an example closer to our topic, namely that of acrolein itself. In the ground electronic state, *anti* is more stable than *syn*. From microwave spectroscopy[19], the zero-point levels of *anti* and *syn* differ by $700 \pm 40\,\mathrm{cm}^{-1}$, which corresponds to about $2.0\,\mathrm{kcal\,mol}^{-1}$. However, in the n–π* excited state, where an antibonding orbital becomes occupied, *syn* becomes lower in energy. The difference between zero levels is then $530 \pm 40\,\mathrm{cm}^{-1}$, that is $1.5\,\mathrm{kcal\,mol}^{-1}$, but this time in favor of *syn*. On theoretical grounds[20], inversion of the order of stability is also expected for the π–π* excited state.

Later applications of 'minimum bending' have been reported[21]. The principle, however, is controversial[22], and recent literature prefers to invoke perturbation theory[23,24]. Application to the planar varieties of unsubstituted acrolein is almost straightforward.

If sigma interactions are not dominant, reckoning can be limited to the four MOs of type π. These are shown in Figure 3. On the one hand, there are the bonding and antibonding π and π* MOs of the C=C fragment (Figure 3, top left). Each resides equally on the two ethylene carbons, the distinction being that π*(C=C) is noded while π(C=C) is not. On the other hand, there are the bonding and antibonding π and π* MOs of the C=O fragment (Figure 3, top right). Because oxygen is more electronegative than carbon, both are at a lower energy than their C=C counterparts. For the same reason, π(C=O) resides more on the oxygen while π^*(C=O) is concentrated on carbon. There are now three interactions to consider.

(a) The destabilizing 4-electron interaction between π(C=C) and π(C=O). Since the C=O/C=C overlap is larger in *syn* than in *anti* (Figure 3, bottom), the destabilization is more pronounced in *syn*.

(b) The stabilizing 2-electron interaction between π(C=C) and π^*(C=O). Since π^*(C=O) has a node, proximity of the fragments actually reduces electronic overlap between the fragments. Hence, *syn* is affected less by this interaction and *anti* is stabilized better.

(c) The stabilizing 2-electron interaction between π(C=O) and π^*(C=C). The conclusion is as in case (b), except that the culprit now is the noded π^*(C=C).

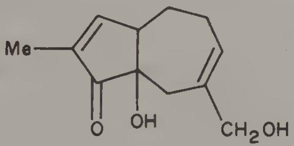
To summarize, stabilizing factors affect *anti* more than *syn*, while the destabilizing factor affects *syn* more than *anti*.

Electrostatic interactions between the termini, and destabilizing steric repulsions, have been proposed as contributing to the greater stability of the *anti* disposition in acrolein[25].

IV. COMPUTATION OF ENONE GEOMETRIES

Currently, both the quantum-chemical and molecular-mechanical pathways are being used to compute the geometry of organic molecules. The more commonly used quantum-chemical techniques are MINDO/3, MNDO and *ab initio* methods. All have recently been reviewed[4]. As for enones, conjugated[26,27] or unconjugated[28], it seems that some care should be taken in exploiting MINDO/3 results. This concerns, however, only delicate numerical details, and does not affect the use of MINDO/3 in interpreting the course of reactions[29,30]. Derivatives of acrolein have been calculated also by INDO[26].

4β-Hydroxyphorbol (**13**) may be cited as a case in which the MNDO geometry of a fairly complex molecule could be compared with the actual crystal structure[31]. Here, MNDO was found to 'inflate' the molecule: calculated bond angles are close to the crystal values, but many of the bonds come out longer. For example, the conjugated double bond is calculated as 1.359 Å long, whereas the measured value is only 1.341 Å.



(13)

Molecular mechanics was reviewed several times in recent years[3,4,32,33], also in *The Chemistry of Functional Groups*[34]. Still, the mode of treating conjugated systems has persistently evaded reviewers. Since this is a pivotal stage in calculating enones, and the original literature presents the material piecemeal, a brief overview is in place here.

In molecular mechanics (MM), any geometry of a given molecule defines a potential energy E_t (t for total). The computational process consists of constructing the E_t equation of the molecule, and of shifting the atoms in space so as to minimize E_t.

Quantity E_t comprises a sum of components. In current force fields, the main components are given by

$$E_t = E_s + E_b + E_{nb} + E_{es} + E_{tor}$$

where E_s (stretch) is the energy due to stretching or compression of bonds, E_b (bend) refers to the opening or closing of valence angles, E_{nb} (nonbonded) represents attraction and repulsion between nonbonded nongeminal atoms, E_{es} (electrostatic) stands for intramolecular electrostatic interaction and E_{tor} (torsion) is the energy due to torsion about bonds. Each of these components is itself a sum of subcomponents. For example, E_s is a sum of terms due to stretching of individual bonds, $E_s = \sum(\text{bonds } i)e_{s,i}$. Likewise, E_{tor} is a sum of terms due to individual dihedral angles, $E_{tor} = \sum(\text{dihedral angles } j)e_{tor,j}$.

The choice of components (E) and subcomponents (e) varies from one force field to another. In computer programs of the MM series[35]

$$e_{s,i} = \tfrac{1}{2}k_{s,i}(l_i - l_{0,i})^2 + k'_{s,i}(l_i - l_{0,i})^3$$

and, for internal rotation about a bond with a partial double-bond character[36].

$$e_{tor,j} = \tfrac{1}{2}V_{2,j}(1 - \cos 2\omega_j) + \text{minor terms}$$

Note that the parameters are of two types. Bond lengths (l_i), dihedral angles, etc., are the target of computation. Reference bond lengths ($l_{0,i}$), force constants ($k_{s,i}$, $k'_{s,i}$), torsional constants ($V_{2,j}$), etc., constitute the input and have to be assigned beforehand. This is done in a preliminary stage, by trial-and-error fitting of output to measured geometries and to conformational energies of selected sets of molecules.

In programs of the MM series, molecules with conjugated portions are treated as follows[37]. First, the built-in list of numerical constants (l_0, k_s, V_2, etc.) is used to characterize all structural features that are not decreed to depend on π-electron properties. If the conjugated portion of the molecule is coplanar, it is then subjected to a π-electronic VESCF calculation (Section X). This furnishes for each bond i a bond order p_i and a function β_i of the overlap between π orbitals on the bond terminals (β_i is the ratio β_{pq}/β_{rs} of the original publication[38]). The missing constants are then expressed as

$$l_{0,i} = 1.512 - 0.179p_i, \quad k_{s,i} = 5.0 + 4.6p_i, \quad V_{2,j} = 16.25p_i f \beta_i$$

where $f = 1$. Once all constants are assigned, minimization is performed in the usual way. If the geometry changes appreciably in this step, the process is re-iterated.

For noncoplanar unsaturation, VESCF calculations are conducted twice: once for the real geometry and once for a hypothetical coplanar system. The duplicity is required to estimate the energy lost by the disruption of conjugation, due to deviation from coplanarity. Quantum-chemically, the loss amounts to

$$\sum(\pi \text{ bonds})\{p_i\beta_i(\text{coplanar}) - p_i\beta_i(\text{real})\}$$

The corresponding mechanical expression is

$$\sum(\pi \text{ bonds})\{p_i\beta_i(\text{coplanar})(1 - \cos\omega_j)\}$$

where ω_j is the dihedral angle defined by atoms at the terminals of bond i. The ratio of the former expression to the latter is the factor f that intervenes in the expression for $V_{2,j}$. This done, $l_{0,i}$, $k_{s,i}$ and $V_{2,j}$ are evaluated and the process is run to completion.

In 1976, Liljefors and Allinger published a list of constants pertaining to C═C···C═O systems[13], then used them extensively[39]. Many of the constants were subsequently modified[40]. Unfortunately, this means that numerical details in the earlier report have to be updated; *a fortiori*, this pertains to figures published before the inclusion of π-electron properties in the MM process[41]. On top of this, dissatisfaction with the parameter f seems to be growing. Reasons have been advanced both in favor of replacing it by a better function[42], and in favor of eliminating it altogether[36]. To date, the new approaches have been checked only for unfunctionalized hydrocarbons. Obviously, if C═C and C═O are far in space and the skeleton is rigid, as in 7-norbornenone, results[43] cannot be affected significantly. A recent investigation, using the new constants but retaining the old formulation of *f*, concerns the configurations of 2-methyl-3-cyclohexene-1-carboxaldehyde[44].

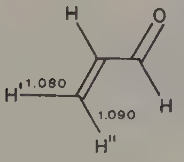
V. TWO PROTOTYPES

Two prototypes will serve to illustrate current computational activities.

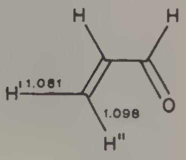
A. Propenal

Acrolein has been studied extensively[25], frequently together with some of its derivatives, or together with butadiene and glyoxal. In the ground state, it is certainly *anti* periplanar (APP, Figure 1), almost certainly *anti* planar (AP, Figure 2). Geometrical details are available from microwave[45,46] and electron-diffraction studies[47,48]. The *syn–anti* energy difference has been estimated as[19] 2.0 or[49] 1.6 kcal mol^{-1}. *Ab initio* calculations furnish[20,25,50] 0.4–0.5, 0.8, 1.20 and 1.70 kcal mol^{-1} at the levels of, respectively, STO-3G, 4-31G, 3-21G and 6-31G*//6-31G*. The barrier height is calculated in the range 5.4–8.9 kcal mol^{-1}, dependent on level. In molecular mechanics[13], the constants have been calibrated to yield 1.64 kcal mol^{-1} as the *syn–anti* energy difference.

Complete substitution structures of both conformers have been obtained[46]. The C=O and C=C bond lengths and the CCO angle are almost identical. The central C—C single bond and the CCC angle increase somewhat on going from *anti* (**14**) to *syn* (**15**). The most interesting feature is the difference in length between the two methylene C—H bonds (C—H′ and C—H″ in **14** and **15**): in both conformers, the *internal* C—H bond (C—H″) is longer, by 0.01 Å in **14** and by as much as 0.02 Å in **15**.



(14)



(15)

Examination of scale models does not reveal any prominent crowding that may contribute to the destabilization of the *syn* conformer. Figure 4 (top) shows a cut through the van der Waals body[51] of the *anti* conformer (AP) in its ED geometry[47]. It also shows (bottom) a cut through a hypothetical geometry of the *syn* conformer (SP), constructed from AP by rigid rotation. On the AP → SP transition, virtually no new overlapping is created between CH_2=CH and CH=O. The calculated volume of the van der Waals body is 63.0 Å^3 in both cases; the surface areas are 84.7 Å^2 for *anti* and 84.5 Å^2 for *syn*. Now, since electron delocalization in AP is more effective than in SP (Section III), the internal bond in SP is somewhat longer[46] than in the hypothetical geometry of Figure 4 (bottom). Hence, no extra overlapping of fragments is to be suspected.

The picture changes somewhat, but to a very small extent, if to each atom is appended the void volume in which it strives to encrust itself[51]. Computationally, this can be modelled by attributing to atoms radii that are longer than the usual van der Waals radii. The outcome, for AP acrolein, is shown in Figure 5. The inflated molecular volumes are 105.5 Å (*anti*) and 104.7 Å^3 (*syn*), and the molecular surface areas are 122.1 Å^2 (*anti*) and 121.5 Å^2 (*syn*). Even so, extra overlapping is negligible.

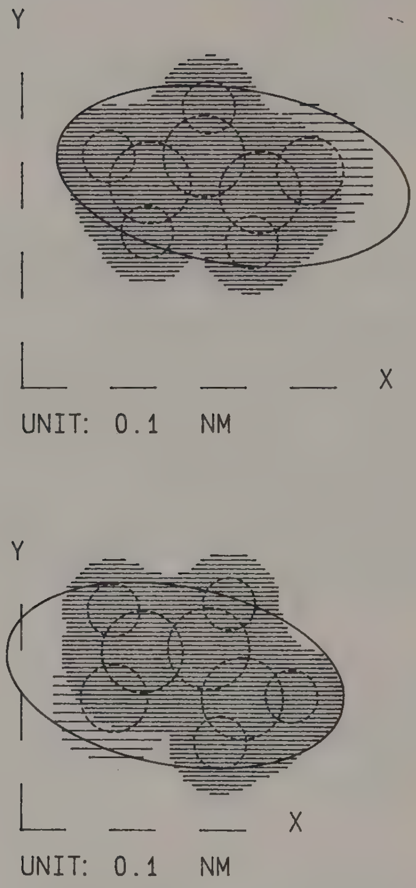


FIGURE 4. Cut through the van der Waals body of *anti* planar (top) and *syn* planar acrolein (bottom), in the first plane (*xy*) of their respective systems of principal coordinates. Circles represent atoms at half the van der Waals atomic radii. The hatched area cuts through the body, as defined by the overlapping atomic spheres at their full radii. Sparse hatching shows the protrusion of the oxygen atom out of the molecular body (transformation into principal coordinates places C=O on the right in *anti* planar and on the left in *syn* planar conformations)

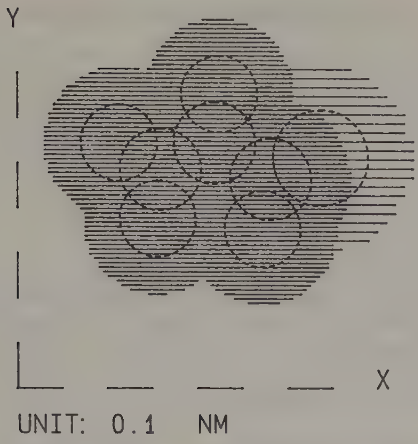
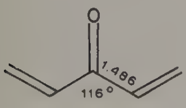


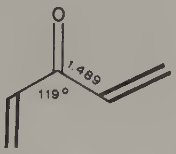
FIGURE 5. Cut through the ‘inflated body’ of *anti* planar acrolein. For details see caption to Figure 4

B. 1,4-Pentadien-3-one

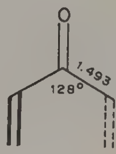
In divinyl ketone, $CH_2{=}CH{-}CO{-}CH{=}CH_2$, molecular mechanics[52] (MMPI version) and *ab initio* studies[53] have located several conformers and saddle points. Molecular mechanics detects three conformers, spanning an energy range of 1.2 kcal mol^{-1}. They are separated by barriers in the range 0.4–6.2 kcal mol^{-1}. The most stable species is the coplanar SP/SP conformer **16** (symmetry C_{2v}). Next come the nonplanar APP/SPP enantiomeric pair **17** (symmetry C_1), followed by the nonplanar APP/APP enantiomeric pair **18** (symmetry C_2). As the formulas show, the $CC({=}O)C$ angle is computed to open up along the sequence, from the normal value of 116° to 128°. Concurrently, the bond $C^2{-}C^3$ is computed to stretch, from 1.486 Å in **16** to 1.493 Å in **18**. The quantum-chemical calculations[53] predict the same order of stability, but favor a coplanar geometry for **17** and distinguish two separate minima for APP/APP.



(16)



(17)



(18)

One may care to compare these predictions with theoretical data on the carbon analog, 3-methylene-1,4-pentadiene[54]. According to *ab initio* results (6-31G), the most stable conformer of $CH_2{=}CH{-}C({=}CH_2)CH{=}CH_2$ is the coplanar variant of **17**. Next comes the coplanar variant of **18**, while **16** is the least favored.

Methyl and dimethyl derivatives of divinyl ketone have also been studied by molecular mechanics[52]. Their conformers are anticipated to correspond to those of the parent molecule.

VI. BUILDING-BLOCK INTERACTION

It is useful to regard an enone molecule as made up of several fragments, two of which are the vinyl moiety (C=C) and the carbonyl moiety (C=Ö). Properties of the *composite molecule* are then considered as the outcome of interaction between the *building blocks*, namely between a substituted ethylene and a substituted formaldehyde. In such an approach, no demarcation need be interposed between α,β-unsaturated carbonyl compounds and other molecules that simultaneously contain C=C and C=O. Simply, the nature of interaction is made to depend on the distance between the fragments and their relative orientation.

For many purposes, there is no harm in disregarding part of the σ framework of the building blocks. The atomic orbitals retained for consideration are those perpendicular to the fragment planes, and the nonbonding 'n-AO' on the carbonyl oxygen. We shall label these AOs as follows: χ_1 and χ_2 on C=C, χ_3 and χ_4 on C=O and χ_5 for n-AO. They are sketched in Figure 6. The subset χ_1–χ_4 constitutes the basis of π-type molecular orbitals (π MOs), and the entire set χ_1–χ_5 can be understood as a basis to a variant of the π-electron approximation[55].

The molecular orbitals (MOs) of the fragments, when expressed as linear combinations of the selected AOs, are as follows:

$$\begin{array}{lll}
\text{For C=C,} & \phi_1 = a(\chi_1 + \chi_2) & \pi \\
 & \phi_2 = a(\chi_1 - \chi_2) & \pi^* \\
\text{For C=O,} & \phi_3 = r\chi_3 + s\chi_4 & \pi \\
 & \phi_4 = s\chi_3 - r\chi_4 & \pi^* \\
 & \phi_5 = \chi_5 & \text{n}
\end{array}$$

Here, the numerical coefficients are $a \sim 0.7$ (exact value $2^{-\frac{1}{2}}$), $r \sim 0.6$ and $s \sim 0.8$. Estimates of r and s depend on the method of computation. To illustrate, one π-electron calculation[56] led to $r = 0.5649$ and $s = 0.8251$, another[57] led to 0.5472 and 0.8370, respectively. The essential point is that $s > r$, so that π(C=O) is more concentrated on O and π^*(C=O) is more concentrated on C. We have already used this conclusion in interpreting the electronic preference of the *anti* to the *syn* conformer (Section III, Figure 3).

An operational sequencing of the five MOs is shown in Figure 7 (which is modelled after Figure 8.3 in Reference 58). The points to note are that ϕ_3 is lower than ϕ_1, ϕ_5 higher than ϕ_1 and ϕ_4 lower than ϕ_2. The term 'operational' was used, because this is not the sequencing of vertical ionization energies in isolated ethylene and formaldehyde. By photoelectron spectroscopy, the orbital energy of ϕ_1 in $CH_2{=}CH_2$ is -10.5 eV, while the orbital energies of ϕ_3 and of ϕ_5 in $CH_2{=}O$ are[59] -14.1 and -10.9 eV. Substitution raises all orbitals. Using again data for vertical ionizations[59], the nonbonding ϕ_5 in

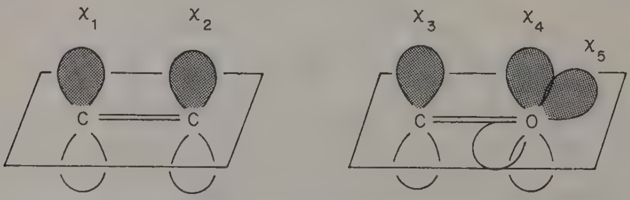


FIGURE 6. Basis set for component interaction in C=C···C=O. Atomic orbitals χ_1 to χ_4 are perpendicular to the skeletal planes. Orbital χ_5 is in plane

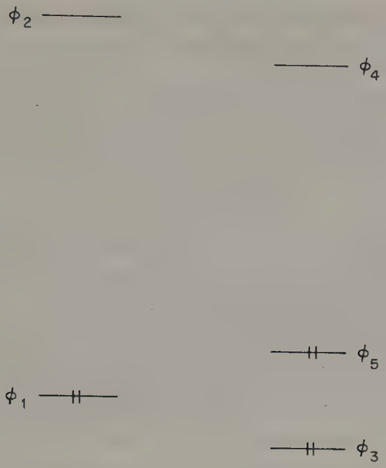


FIGURE 7. Sequencing of some molecular orbitals of C=C and C=O in C=C···C=O

CH_3CH_2CHO is already as high as −9.8 eV. The ethylenic π-MO ϕ_1 shifts also upwards. It gets to −9.7 and −9.6 eV in, respectively, propene and 1-butene[60].

All electronic levels of the constituting units, as computed by *ab initio* methods, have been reviewed[61]. The review analyzes also the location and nature of electronic transitions in ethylene and formaldehyde. It is interesting to note that, in both, the singlet $\pi \rightarrow \pi^*$ transition occurs at very high energies: *ca* 7.7 eV (161 nm) in ethylene, *ca* 11 eV (113 nm) in formaldehyde. The $n \rightarrow \pi^*$ transition of the latter is at *ca* 3.8 eV (326 nm). As for acrolein, it is almost certain (Reference 11, p. 271) that its lowest $\pi \rightarrow \pi^*$ transition[62] occurs at 6.32 eV (196 nm). This verges on the near UV. Substitution pushes the band into the near UV.

Theoretical analysis of a composite molecule, C=C···C=O in our case, can be initiated according to either of two strategies. In the first option, one views the enone as a unified system, and concentrates on obtaining molecular orbitals that extend inasmuch as possible over its entirety. Nowadays, this is the usual practice, since it can be confided to the computer and the investigator is not called upon to lend a hand. In the second option, one regards the enone as a system in which the two fragments have been brought into proximity, and concentrates on computational techniques that 'switch the interaction on'.

A simple example of arguing in terms of fragments has been cited in Section III. There, one distinguished stabilizing from destabilizing interactions between the units and attempted to assess their relative importance[23]. Another simple application[57] has to do with the electronic spectra of enones. It is based on the observation that ϕ_4 is closer in energy to ϕ_1 than ϕ_1 is to ϕ_2 (Figure 7). One expects, then, that the *inter*-fragment electronic transition $\phi_1 \rightarrow \phi_4$ requires a lower energy, and is observable at a longer wavelength, than the *intra*-fragment transition $\phi_1 \rightarrow \phi_2$. In other words, enones would show an intra-molecular charge-transfer absorption band, interlying the local excitations within the separate fragments. This transfer, indeed, is well-characterized experimentally[58,63].

More sophisticated realizations of the second option will be considered in Sections VII and VIII.

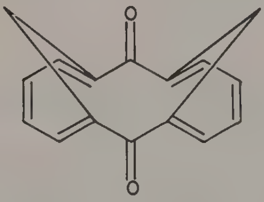
By vertical ionization potentials (IPs), the highest occupied MO of α,β-unsaturated aldehydes and ketones resides mainly in the nonbonding oxygen orbital. In the notation of

Section VI, this is ϕ_5. Next comes a π MO, the antibonding combination of ϕ_1 and ϕ_3. The next to come is a σ MO. The bonding combination of ϕ_1 and ϕ_3 has not been identified unambiguously.

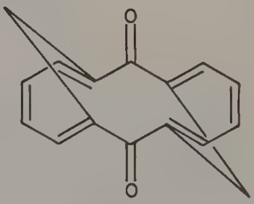
In acrolein, the first three ionization energies are[26] 10.11 (n), 10.93 (π) and 13.67 eV (σ). The fourth is 14.76 eV. As for the n orbital, substitution or strain decreases its energy, that is, pushes it higher. Examples are[26] $CH_3CH{=}CHCHO$, 9.75 eV, $(CH_3)_2C{=}CHCOCH_3$, 9.11 eV, and di-*tert*-butylcyclopropenone[64], 8.23 eV. In general, other orbitals shift up concurrently. An exception is cyclopropenone, for which the second IP has been reported[64] as 11.19 volt.

In cyclobutenediones, the n level splits in two, and these flank the π level[65]. According to the MINDO/3 calculation, the bonding combination of n orbitals comes above the antibonding, due to through-bond interaction. As an example, the sequence in dimethylcyclobutenedione is 9.10 (n_+), 10.18 (π), 11.05 (n_-).

Complications that can arise on σ/π interaction are illustrated by the two bishomoanthraquinones[66], **19** and **20**. In **19**, sequencing by MINDO/3 identifies the top orbital (8.6 eV) as π, with n_- following (8.76 eV); n_+ is characterized as too deep to be identified. In **20**, the first massif ($\sim$ 8.7 eV) has been assigned as due to mixing of π with n_-. It is followed by π (9.42 eV) and n_+ (9.7 eV).



(19)



(20)

VII. QUANTUM-CHEMICAL INTERLUDE

For later use, we now delineate relations between atomic orbitals (AOs, χ), molecular orbitals (MOs, ϕ), electronic configurations (Ψ) and electronic states (Θ). The emphasis is on fragment interaction within the π-electron context. Details and references can be found in Parr's monograph[67].

Suppose there is justification to limit attention to a few MOs in a chemical species, say, to ϕ_1, ϕ_3 and ϕ_5 in enones (Figure 7). Suppose also that these MOs are doubly occupied. Then, an electronic *configuration* Ψ_1 can be symbolically referred to as

$$\Psi_1 = (\phi_1\bar{\phi}_1\phi_3\bar{\phi}_3\phi_5\bar{\phi}_5) \qquad (1)$$

or, more simply, $\Psi_1 = (1\bar{1}3\bar{3}5\bar{5})$. This means that two electrons are allotted to ϕ_1, one with spin α (ϕ_1 or 1 unbarred) and one with spin β ($\bar{\phi}_1$ or $\bar{1}$ barred), and, likewise, two electrons with opposing spins are allotted to ϕ_3 and to ϕ_5 each. If one electron has been promoted from ϕ_1 to another MO, say ϕ_4, two equally probable situations ensue: $(4\bar{1}3\bar{3}5\bar{5})$ and $(1\bar{4}3\bar{3}5\bar{5})$. A symbolical representation of this configuration, say, Ψ_5, is

$$\Psi_5 = 2^{-\frac{1}{2}}\{(4\bar{1}3\bar{3}5\bar{5}) + (1\bar{4}3\bar{3}5\bar{5})\}$$

or, to further simplify the notation,

$$\Psi_5 = 2^{-\frac{1}{2}}\{A_{41} + A_{14}\} \qquad (2)$$

Here, $2^{-\frac{1}{2}}$ is the factor of normalization.

The energy E that characterizes a configuration Ψ is $\langle \Psi H \Psi \rangle$, where Ψ denotes the accurate mathematical formulation of the configuration in question. H is the Hamiltonian operator, and the enclosers $\langle$ and $\rangle$ indicate that the product enclosed has to be integrated over the coordinates of all electrons. For the configurations in equations 1 and 2, one has

$$E_1 = \langle \Psi_1 H \Psi_1 \rangle \tag{3}$$

$$E_5 = \langle A_{41} H A_{41} \rangle + \langle A_{41} H A_{14} \rangle \tag{4}$$

In equations 3 and 4, integrals are expressed in terms of electronic configurations. They can be reformulated (Reference 67, pp. 21–30) in terms of MOs ($\langle \phi_1 H \phi_1 \rangle$, $\langle \phi_2 H \phi_2 \rangle$, etc.). Now, the Hamiltonian H is itself a sum of components. Some components in H contain the coordinates of one sole electron, while others contain the coordinates of two electrons. Let us denote a typical term of the first type by h^1 (monoelectronic) and a typical term of the second type by h^2 (bielectronic). The sum that expresses E in terms of MOs contains three types of integral. Using subscripts i and j to refer to particular MOs (ϕ_i, ϕ_j), and indices μ and v to refer to particular electrons, the three types are as follows:

(a) I integrals (monoelectronic):

$$\begin{aligned} I_{ij} &= \langle \phi_i(\mu) h^1(\mu) \phi_j(\mu) \rangle \\ &= \langle i h^1 j \rangle \end{aligned} \tag{5}$$

(b) J integrals (bielectronic):

$$\begin{aligned} J_{ij} &= \langle \phi_i(\mu) \phi_i(\mu) h^2(\mu, v) \phi_j(v) \phi_j(v) \rangle \\ &= \langle i i h^2 j j \rangle \end{aligned} \tag{6}$$

(c) K integrals (also bielectronic):

$$\begin{aligned} K_{ij} &= \langle \phi_i(\mu) \phi_j(\mu) h^2(\mu, v) \phi_j(v) \phi_i(v) \rangle \\ &= \langle i j h^2 j i \rangle \end{aligned} \tag{7}$$

The definitions above are mathematically exact if the molecular orbitals are real, which is almost always the case. Particular cases are:

(a) $I_i = I_{ii} = \langle i h^1 i \rangle$; (5a)

(b) $J_{ii} = \langle i i h^2 i i \rangle$; (6a)

(c) $K_{ii} = \langle i i h^2 i i \rangle = J_{ii}$. (7a)

It is useful to have at hand expressions for the configurational energies (equations 3 and 4). By using the rules, one gets the following:

$$\begin{aligned} E_1 = {} & 2I_1 + 2I_3 + 2I_5 + J_{11} + J_{33} + J_{55} + 4J_{13} - 2K_{13} \\ & + 4J_{15} - 2K_{15} + 4J_{35} - 2K_{35} \end{aligned} \tag{8}$$

$$\begin{aligned} E_5 = {} & I_4 + I_1 + 2I_3 + 2I_5 + J_{33} + J_{55} + J_{14} + 2J_{43} - K_{43} \\ & + 2J_{45} - K_{45} + 2J_{13} - K_{13} + 2J_{15} - K_{15} \\ & + 4J_{35} - 2K_{35} + K_{14} \end{aligned} \tag{9}$$

In actual work, one may need an expression for the energy difference $\Delta E_{51} = E_5 - E_1$, that is, the energy required to promote an electron from ϕ_1 (in Ψ_1, equation 1) to ϕ_4 (in Ψ_5, equation 2). In subtracting equation 8 from equation 9, many terms cancel:

$$\begin{aligned} \Delta E_{51} &= E_5 - E_1 \\ &= I_4 - I_1 - J_{11} + J_{14} + 2J_{34} - K_{34} \\ &\quad + 2J_{45} - K_{45} - 2J_{13} + K_{13} - 2J_{15} + K_{15} + K_{14} \end{aligned} \tag{10}$$

In a specific case, some of the remaining terms may vanish. For enone MOs (Section VI and Figure 7), $K_{13} = K_{14} = K_{15} = 0$. Furthermore, some groups of terms may be taken to represent *per se* a numerical property of the molecule, whose experimental counterpart is known. Thus, if the ionization energy P_1 of an electron in ϕ_1 can be equated to the energy required to effect passage from the configuration $(1\bar{1})$ to the configuration $2^{-\frac{1}{2}}\{(1)+(\bar{1})\}$ (cf. equations 1 and 2), then $P_1 \doteq -I_1 - J_{11}$. By introducing P_1 and striking out the nul Ks, equation 10 reduces to

$$\Delta E_{51} = P_1 + I_4 + J_{14} + 2J_{34} - K_{34} + 2J_{45} - K_{45} - 2J_{13} - 2J_{15} \qquad (10a)$$

In this way, complicated expressions can be simplified. Also, quantities of different nature (transition energies, ionization potentials, electron affinities) can be related to each other, and each used in evaluating others.

In the next step, each MO is expressed explicitly as a linear combination of atomic orbitals. Referring to the combinations in Section VI, ϕ_1 (the orbital from which the electron jumps) is $a(\chi_1 + \chi_2)$, and ϕ_4 (the orbital in which it lands) is $s\chi_3 - r\chi_4$. Thus, the configurational change $\Psi_1 \rightarrow \Psi_5$ (equations 1, 2, 10 and 10a) represents the intramolecular electron transfer π(C=C)→π^*(C=O).

(a) To express I_1 (equation 10) in terms of atomic orbitals, use equations 5 and 5a:

$$\begin{aligned} I_1 &= a^2\langle(\chi_1 + \chi_2)h^1(\chi_1 + \chi_2)\rangle \\ &= 0.5\{\langle\chi_1 h^1 \chi_1\rangle + \langle\chi_1 h^1 \chi_2\rangle + \langle\chi_2 h^1 \chi_1\rangle + \langle\chi_2 h^1 \chi_2\rangle\} \end{aligned}$$

Traditionally, integrals of type $\langle\chi_a h^1 \chi_a\rangle$ are denoted by α_a, and integrals of type $\langle\chi_a h^1 \chi_b\rangle$ are denoted by β_{ab}. Since $\beta_{ab} = \beta_{ba}$,

$$I_1 = 0.5(\alpha_1 + \alpha_2) + \beta_{12} \qquad (11)$$

(b) To transform J_{14} (equations 10, 10a) over atomic orbitals, we use equation 6:

$$\begin{aligned} J_{14} &= \langle 11h^2 44\rangle \\ &= a^2\langle(\chi_1 + \chi_2)(\chi_1 + \chi_2)h^2(s\chi_3 - r\chi_4)(s\chi_3 - r\chi_4)\rangle \end{aligned}$$

To simplify the notation, one replaces the orbital symbol (χ_1, χ_2, $\cdots$) by its subscript ($1, 2, \cdots$), and the operator symbol h^2 by a comma. Also, simple parentheses are used, to avoid confusion with integrals over MOs. Thus,

$$\begin{aligned} J_{14} &= a^2\{(1+2)(1+2), (s3 - r4)(s3 - r4)\} \\ &= a^2 s^2(11, 33) - a^2 rs(11, 34) + \cdots \end{aligned}$$

In many contexts, it is admissible to retain only integrals of the type (aa, bb) (ZDO approximation[68]). Doing this, we obtain

$$J_{14} \sim a^2 s^2\{(11, 33) + (22, 33)\} + a^2 r^2\{(11, 44) + (22, 44)\} \qquad (12)$$

When the procedure, here illustrated for I_1 and for J_{14}, is applied to all components of expressions like equations 10 and 10a, some terms vanish and others add up. The final expressions are compact and easy to handle.

Estimates of transition energies can be improved by superposition of configurations, that is, by the technique of *Configurational Interaction*[69,70] (CI). It is reasonable to assume that the various electronic transitions of a molecule are not independent. In enones, for example, the charge-transfer transition $\Psi_1 \rightarrow \Psi_5$ may be affected by a local $\pi \rightarrow \pi^*$ excitation within the vinyl moiety. In the latter, an electron jumps from ϕ_1 to ϕ_2, yielding a configuration

$$\Psi_2 = 2^{-\frac{1}{2}}\{(2\bar{1}3\bar{3}5\bar{5}) + (1\bar{2}3\bar{3}5\bar{5})\} \qquad (13)$$

The interaction energy between $\pi(C{=}C)\rightarrow\pi^*(C{=}O)$ and $\pi(C{=}C)\rightarrow\pi^*(C{=}C)$ is $\langle\Psi_2 H\Psi_5\rangle$.

As before, there are rules to convert integrals of the type $\langle\Psi_i H\Psi_j\rangle$ to sums of integrals over MOs (Reference 67, pp. 21–30), and these in turn can be reduced to sums of integrals over AOs. When this is done for $\langle\Psi_2 H\Psi_5\rangle$, and the ZDO approximation invoked, a very simple expression ensues. All bielectronic components vanish, and one ends up with

$$\langle\Psi_2 H\Psi_5\rangle = 2^{-\frac{1}{2}}\{s(\beta_{13}+\beta_{23}) - r(\beta_{14}+\beta_{24})\} \tag{14}$$

Note that the expression contains only interfragment terms.

In the CI stage of a calculation, the investigator tries to anticipate which configurations are essential to an adequate description of the *electronic state*. Apart from the ground configuration (GC, Ψ_1 in our derivation), one defines local excitations (LE, like Ψ_2) and charge transfers (CT, like Ψ_5). Next one calculates all energies E_i (as in equations 3 and 4) and all interaction energies E_{ij} (as in equation 14), and a secular equation is written down. Resolution leads to *state energies* ε_i, each corresponding to a *state function* Θ_i. This is a linear combination of electronic configurations,

$$\Theta_i = \sum_j c_{ji}\Psi_j \tag{15}$$

The squared coefficient c_{ji}^2 is taken to represent the fractional contribution of configuration Ψ_j to state Θ_i. Usually, one of these squares is appreciably larger than the others, so that a state Θ can be characterized as 'virtually pure GC' (Θ_1), or 'mainly CT', or 'essentially LE'.

For example, in Nagakura's pioneering calculation of acrolein[57], the second state function was found to be

$$\Theta_2 = -0.1945\Psi_1 + 0.4851\Psi_2 - 0.2665\Psi_3 + 0.8098\Psi_5 \tag{16}$$

where Ψ_1, Ψ_2 and Ψ_5 are defined as before (GC, LE in C=C, C=C→C=O CT), and Ψ_3 is the carbonyl $\pi\rightarrow\pi^*$ LE. The term in Ψ_5 leads, contributing 66% to Θ_2 (i.e. 100×0.8098^2). One can say that the first excited *state* (Θ_2) is essentially a charge transfer, contaminated to about 30% by local excitations. In Nagakura's calculation, $\varepsilon_2 - \varepsilon_1 = 6.23$ eV, which is his estimate of the transition energy. The number corresponds to 199 nm.

VIII. MIM METHODS REVISITED

The method of 'Molecules in Molecules' (MIM, or 'method of composite molecules'[12]) may be described, perhaps somewhat loosely, as 'the quantitative theory of building molecules from fragments'.

It may seem disproportionate to devote a separate section to MIM. This technique has never belonged in the mainstream of quantum-chemical work. Also, few applications to enones have been reported. Moreover, the 'historical' applications had been carried out before dexterity was gained in handling atomic integrals (of the type entering equations 11, 12 and 14 of Section VII), and do not reflect the capabilities of the method.

Our case for MIM is that it moulds results in a way quite different from other MO methods, and that the MIM approach is closer than other approaches to the organic chemist's language. It is ideally suited to bring out the dependence of electronic properties, in a composite molecule, on the distance and mutual disposition of the building blocks. The method lacked popularity not because of inherent shortcomings, but probably because any structural type—sometimes even a particular molecule[71]—required a quantum-chemical derivation of its own. In π-electronic SCF–CI, the rival approach that superceded MIM (Section IX), one basic derivation serves all types. Hopefully, revisiting MIM here would contribute to its revival.

The basic idea may be traced back to a paper, published in 1955 by Longuet-Higgins and Murrell[72], and to a series of papers by Nagakura and coworkers[57,73]. Here we limit attention to the π-electron context, although the procedure has been exploited in a wider scope[74]

In brief, the species under consideration is viewed as an assembly of two subspecies. For each, a set of MOs is somehow obtained. Next, configurations are defined for the overall assembly, comprising GC, LEs and CTs (terms defined in Section VII, below equation 14). A CI treatment leads then to the characterization of states as the ground state 'GS', 'mainly LE in either unit', or 'mainly CT'. Eigenvalues serve to predict or interpret spectral bands and their response to changes in the relative orientation of the building blocks. For further details, see Suzuki's monograph[12]. Typical recorded applications are to the phenyl–carbonyl system[75], diones[76], a spiro-conjugated dione[77], and even to aromatic and other conjugated hydrocarbons[71,78].

In what follows, the terminology of the original publications has been replaced by that of Section VII.

For acrolein, Nagakura[57] considered only the π orbitals ϕ_1 to ϕ_4, disregarding ϕ_5 (Figure 7), and used them to construct four configurations: GC Ψ_1, LE(C=C) Ψ_2, LE(C=O) Ψ_3, and CT Ψ_5. Quantities E_2 and E_3 were estimated from spectroscopic data, and E_5 expressed in terms of C=C ionization potential, C=O electron affinity and atomic integrals. Interaction energies, of the type in equation 14 of Section VII, were also estimated. The CI procedure then yielded the electronic states (cf. equations 15 and 16) and the state energies. In the following tabulation of Nagakura's results, energies ε are expressed relative to E_1.

	Ψ_1	Ψ_2	Ψ_3	Ψ_5	ε(eV)
Θ_1	0.98	0.03	−0.02	0.21	−0.31
Θ_2	−0.19	0.49	−0.27	0.81	5.92
Θ_3	0.02	0.64	0.76	−0.13	7.79
Θ_4	0.09	−0.60	0.59	0.53	8.50

It is seen that the ground state Θ_1 is not pure GC. Contamination by CT depresses its energy by 0.31 eV (~7.1 kcal mol^{-1}). This is equivalent, in MO phraseology, to the organic chemist's statement that 'the resonance C=C—C=O (GC)↔$\overset{+}{\mathrm{C}}$—C=C—$\overset{-}{\mathrm{O}}$ (CT) stabilizes the system'. The first excited state, Θ_2, comes out as essentially CT (66% of Ψ_5). Its location above GS, 6.2 eV (199 nm), is close to an observed absorption of acrolein[79] (193 nm). The next two states, interpreted as mainly local, are placed 8.1 and 8.8 eV above GS. These energies are close to two of the observed transitions of acrolein.

Whether the two bands are really due to $\pi \rightarrow \pi^*$ and not to Rydberg transitions has not been settled to this day (Reference 11, p. 271). Edwards and Grinter, using somewhat different estimates of integrals, proposed another assignment[63]. In their work, the nonbonding electron pair on oxygen (χ_5 in Figure 6) was included. Strictly speaking, n electrons belong in the molecular σ system. However, earlier[56,76,80] and later[75] experience shows that they can be safely included in π-electron calculations. The n → π^* transition was computed at 325 nm, where it is actually observed. In the cited calculation, the ground-state depression (i.e. conjugative stabilization) amounted to 0.53 eV (12.2 kcal mol^{-1}).

Vay's work[81] has the unusual feature of taking *three* building blocks into the MIM construction. He aimed at calculating ground- and excited-state properties of acrylamides and crotonamides, $R^1CH{=}CH{-}CO{-}NR^1R^2$ ($R^1 = R^2 = R^3 = H$; $R^1 = R^2 = H$, $R^3 = Et$; $R^1 = H$, $R^2 = R^3 = Me$; $R^1 = R^2 = R^3 = Me$). The three components were C=C, C=O (χ_5 excluded) and $\dot{\mathrm{N}}$, and the effect of alkyl substituents was taken account of by modifying the atomic parameters of C and of $\dot{\mathrm{N}}$. Ground-state depressions were in the range 1.26–1.60 eV for the acrylamides (29–37 kcal mol^{-1}), and 1.62 eV (37 kcal mol^{-1}) for *N,N*-dimethylcrotonamide. The CT absorption bands of these compounds, observed in the range 220–240 nm (heptane solution), were consistently calculated too low energywise. For example, the crotonamide absorbs at *ca* 5.2 eV (240 nm), while calculation furnished 4.3 eV. At first sight, one might attribute the discrepancy to uncertainties as to the molecular conformation—the conformers may be SP, AP or intermediate. Yet, Vay's own results—as well as an earlier study of butadiene[72]—suggest that the computed spectrum can be affected but little by conformation. More probably, the trouble lies with the estimation of atomic integrals. Vay used the Nishimoto–Mataga approximation[82] which was popular at the time. In such a delicate balancing of three-block interactions, analytical integrals[75,76] should have done better.

The citations above explicate what happened to MIM. Precisely because it speaks the language of chemists—molecules as assemblies of components—it was resorted to too early in the development of theoretical methods. When reliable procedures for calculating geometries and integrals became available, other MO methods had already been taking the lead.

IX. ABSORPTION SPECTRA OF ENONES

The literature on UV spectral properties of enones—α,β-unsaturated[83], β,γ-unsaturated[58] and others—is enormous. Some of it constitutes nowadays textbook material[84,85], and much of it is to be reviewed in Chapter 3. Here we limit ourselves to a quick reminder and a few examples.

α,β-Unsaturated ketones show two typical absorptions. One, strong at 220–250 nm, reflects to a considerable extent the vinyl-to-carbonyl charge transfer. The other, weak and wavy, occurs just above 300 nm. This is the $n \rightarrow \pi^*$ transition, allowed by vibronic borrowing or due to the lack of overall coplanarity in the absorbing molecule[86].

Spectra are best recorded in a nonpolar solvent (hexane, cyclohexane), so as to increase the gap between the two bands of interest and conserve the fine structure of $n \rightarrow \pi^*$. A dilute solution (say, 5×10^{-5} M) is recommended for the intense $\pi \rightarrow \pi^*$, and a fairly concentrated solution (say, 5×10^{-3} M) should reveal the weak $n \rightarrow \pi^*$.

Figure 8, the spectrum of 4-methylbicyclo[3.2.1]oct-3-en-2-one[87] (**21**), is a typical

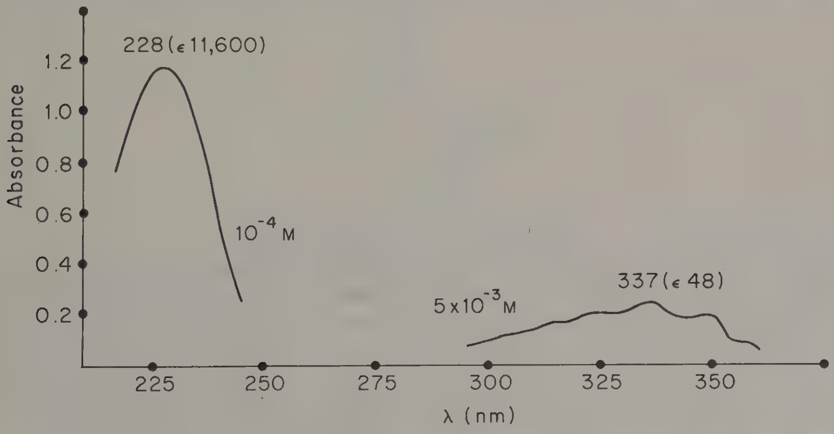
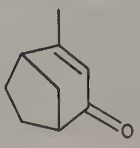
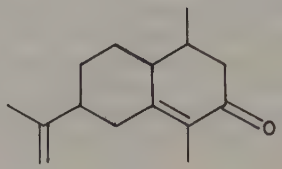


FIGURE 8. Ultraviolet spectrum of 4-methylbicyclo[3.2.1]oct-3-en-2-one (**21**) in cyclohexane

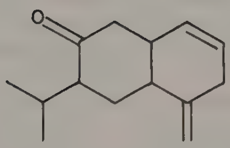
example. Maxima occur at 228 nm ($\pi \rightarrow \pi^*$; ε 11,600) and in the range 300–350 nm ($n \rightarrow \pi^*$; ε 48 at the 337 nm maximum). A polar protic solvent would shift the blue-side band to the red and the red-side band to the blue[84]. The combination of an intense band in the 210–250 nm region, a weak and wavy band just above 300 nm, and lack of features in between, is typical of enones and can be used in structure elucidation. Thus, formula **22** could be assigned to α-cyperone[83] because the absorption indicated an α,β-unsaturated ketone (eliminating alternative **23**), and the exact position of the maximum indicated three alkyl substituents on the C═C fragment (eliminating **24**).



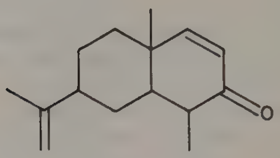
(21)



(22)



(23)



(24)

We take this opportunity and show in Figure 9 the UV spectrum of verbenone[87] (**25**). Our aim in this example is to recall that a four-membered ring, if contiguous to the C═C end of C═C—C═O, can extend conjugation[88]. In the terminology of building blocks, compound **25** should be considered as a superposition of three units. On passing from the compound with the 5-ring (**21**, Figure 8) to the compound with the 4-ring (**25**, Figure 9), the

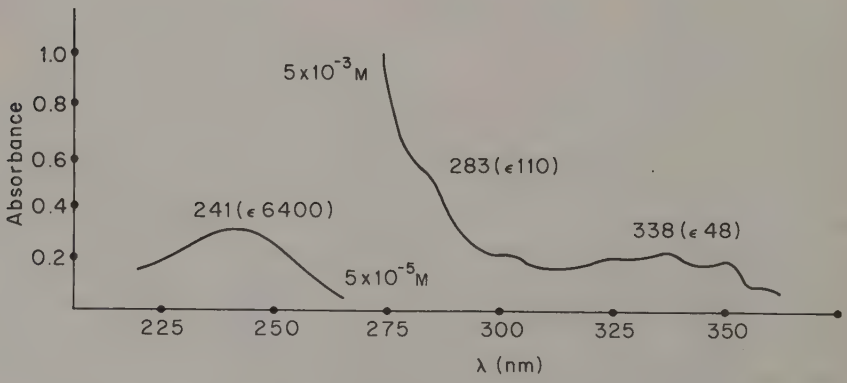
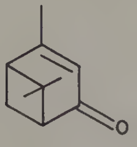
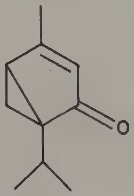


FIGURE 9. Ultraviolet spectrum of verbenone (**25**) in cyclohexane

$\pi \rightarrow \pi^*$ absorption maximum shifts bathochromically and hypochromically: from 228 nm (ε 11,600) to 241 nm (6400). Calculations suggest that the phenomenon is electronic in nature, and does not have to do with skeletal strain. The four-membered ring participates in the enone's π and π^* MOs, releases charge into C=C—C=O upon excitation and concurrently undergoes an internal charge redistribution. The effects are even more pronounced in umbellulone[89] (**26**), where the third building block is a *three*-membered ring.



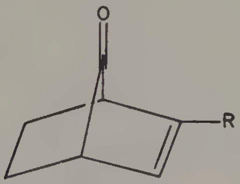
(25)



(26)

Obviously, occurrence of a CT band does not necessitate C=C/C=O conjugation in the classical sense. Enones, even if not α,β-conjugated, are expected to show the band to the extent that the C=C/C=O distance and mutual orientation permit. What the permissive ranges are has not been demarked, but a case is known[43] in which the typical spectrum is manifested even though π orbitals on C=C and C=O are almost orthogonal.

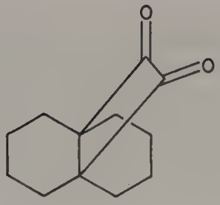
The compound in question is bicyclo[2.2.1]hept-2-en-7-one (7-norbornenone, **27**, R = H). In this and germane compounds, a strong absorption in the far UV tails into the near UV, and it was hard to tell whether the tail is practically smooth or carries a weak 'mystery band'. The problem was solved by measuring the circular dichroism spectrum (CD) of **27** (R = D or Me) in heptane solution[43]. CD spectroscopy is much more sensitive than UV to weak or hidden electronic transitions. The spectrum made fully manifest a weak transition at 225 nm. As for $n \rightarrow \pi^*$ transitions in derivatives of 7-norbornenone, they are weaker and at higher energies than those of α,β-unsaturated ketones. These absorptions occur at 270–275 nm (ε30–40).



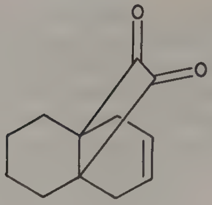
(27)

An exceptional dione spectrum was reported in 1968[90]. Three propellanes were prepared, **28–30**, and their UV spectra recorded in cyclohexane solution. The saturated dione **28** is yellow. It absorbs at 461 nm (ε 73) which, for diones, is not unusual[76]. By contrast, the diene-dione **30** is pink, and its absorption appreciably red-shifted: the band extends from *ca* 400 to 560 nm, peaking at 537 (ε72). The ene-dione **29** shows an intermediate behavior.

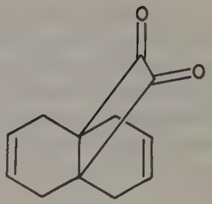
In the molecule **30**, the π AOs on unsaturated carbons are not orthogonal to the n AOs on oxygen. Neither are they orthogonal to the π AOs on carbonyls and to the C—C(=O) bonds in the four-membered ring. Therefore, through-bond and through-space interactions[23,91] can make of the entire molecule a unified absorbing system.



(28)



(29)



(30)

In order to gain more details on the electronic states of **30**, a series of calculations was undertaken[92]. The molecule was assumed to be in its crystallographic exo-exo C_{2v} conformation[93] (Figure 10) and its geometry optimized by molecular mechanics. The closer of the two (C=)C···O(=C) distances came out as 3.05 Å; the other (C=)C···O(=C) distance is 3.66 Å. Next, direction cosines were computed for bonds and for 2p AOs. π Orbitals of C=C are perpendicular to the CC=CC plane, and π orbitals of C=O are perpendicular to the O=C—C=O plane (plane σ in Figure 10). n Orbitals on the oxygens lie within the σ plane, and are perpendicular both to the C=O π orbitals and to the C=O σ bond. The calculated cosines for C and O on the foreground of Figure 10 are:

π(C)	0.6791	0	0.7340
π(O)	-1	0	0
n(O)	0	0.7340	0.6791
C—C(=O)	0	-0.0973	0.9952

(see Figure 10 for the definition of the axes). From these numbers, the estimated interorbital angles are:

(a) between the vinyl and the carbonyl π system, arccos(-1×0.7691) = 133° or 47°;

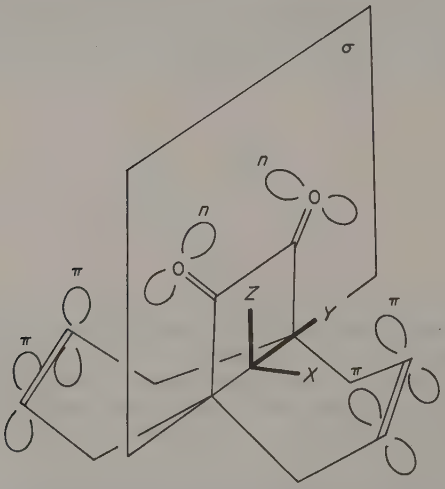


FIGURE 10. Conformation, orbitals (n and π) and symmetry plane (σ) in the calculation of the diene-dione **30**

(b) between a C=C π AO and an oxygen n AO, arccos $(0.7340 \times 0.6791) = 60°$;
(c) between the vinyl π system and the cyclobutanic C—C(=O) bond, arccos $(0.7340 \times 0.9952) = 43°$.

In other words, there is no symmetry restriction on any of the three interfragment interactions. From the experimental fact that interaction actually sets in, we also conclude that an interfragment distance of *ca* 3 Å is not prohibitive.

Moreover, in the exo-exo conformation of **30** (Figure 10), the —COCO— unit has two double bonds with which to interact. By simultaneously interacting with both, it forces them to interact with each other despite their distance (4.6 Å). The spectrum of **30** then provides an early manifestation of the '*relay effect*', where one part of the molecule bridges the electronic clouds of two others. The effect was later defined and theoretically investigated in relation to the electronic spectrum of barrelene[94].

Calculations[92] by an all-valence-electron SCF–CI method[95] reveal four subbands in the long-wave absorption of **30**. In the language of electronic states (Section VII), all transitions are very mixed, that is, the excited states constitute combinations of many configurations. The more prominent sources of electron jump are π(C=C), oxygen n and cyclobutanic σ bonds. In all four subbands, the electron lands in a state that contains *ca* 90% of π^*(C=O). The absorption is therefore very far from being a simple $n \rightarrow \pi^*$. It can be characterized as a very mixed n,π(C=C), $\sigma \rightarrow \pi^*$(C=O).

X. COMPUTATION OF ENONE SPECTRA

Sometimes, a theoretical calculation is required of the spectrum of an enone. The usual aim is not to predict the location of bands, for measurement is always more accurate. Rather, it is to assign them, that is, obtain the symmetry of MOs and the contribution of AOs.

Photoelectron spectroscopy (PES) measures the ionization energies of MOs. Theoreticians of PES have their own choice of computational methods[96]. Practising chemists prefer other methods[28,66], some of which have already been alluded to (Section IV).

One method, current though somewhat controversial[96], is the semiempirical HAM[97] ('Hydrogenic Atoms in Molecules'). It differs from other semiempirical methods in being based on an empirical description of atoms in their ground, excited and ionized states. The version last described, HAM/3, was parametrized mainly by fitting to a large number of measured ionization energies of many molecules. It is therefore expected to furnish satisfying characterizations of processes in which electrons in molecules change state: ionization energies (photoelectron spectra), excitation energies and electron affinities. Certain elements in the method have been criticized. Yet, for many molecules, computed ionization energies are close to the experimental or reproduce the results of advanced *ab initio* methods[96].

One of the first applications of HAM/3 has been to acrolein itself[62]. A very recent application is to bicyclic, tricyclic and tetracyclic unconjugated enones[28], for which it has proved definitely superior to MINDO/3.

As to calculating the absorption spectra of enones, one has to choose between an all-valence-electron and a π-electron calculation. If C=C and C=O are far from coplanar, σ–π interaction may be appreciable, and the former pathway is preferable. CNDO/S–CI[98] is the method now endorsed[28]. Otherwise, or if one is ready to ignore the interaction of C=C···C=O with the rest of the molecule, π-electronic SCF–CI is the path to choose. The series of algorithms that fall under this heading is sometimes referred to as 'PPP', after their first proponents: Parr, Pariser and Pople[99,100]. Among later developments, one may cite contributions by the Scandinavian school, who dealt specifically with α,β-unsaturated carbonyl compounds[101]. Users of molecular-mechanics programs of the MM series, MM2 and MMPI, have encountered VESCF–CI. This 'Variable Electronegativity' SCF–CI method was conceived by Brown and Heffernan[102]. It has been further developed by

Allinger and his collaborators for the calculation of electronic spectra, and applied extensively to α,β-unsaturated[13,39,103] and other unsaturated carbonyl compounds. The SCF portion of the procedure is incorporated in the MM programs, serving there to assign constants to the conjugated portion of molecules.

π-Electronic SCF–CI programs are readily available and easy to handle. For a brief outline of the method[5] let us go back to equation 8 of Section VII. The equation says that, if the Hamiltonian operator for the species has been defined and the molecular orbitals are known, the energy E_1 of the ground configuration can be calculated. Obviously, when one launches a calculation, MOs that extend over the entire system are not known. In the SCF stage of SCF–CI, one starts by guessing a set of MOs; in actual practice, the computer performs automatically the guesswork and all subsequent stages. Working backwards, the Hamiltonian operator is derived from the energy equation, rather than the energy from the operator. Once an expression has been constructed for the operator, the solution procedure is applied, now furnishing an improved guess of the MOs. The process is iterated to self-consistence. In the CI stage of SCF–CI, a series of excited configurations is defined. All energies E_i and interaction energies E_{ij} are evaluated, and the CI equation solved. Hence the electronic states are obtained. Their interpretation is not as straightforward as in MIM (Section VIII), since all MOs—to the extent that symmetry and distance allow—extend over the entire system.

To illustrate the application to enones, we shall cite subsequently two examples[104]: one in which calculation is in line with experiment, and one in which deviations due to σ–π interaction are encountered. The chosen variant of π-electronic SCF–CI[105] had been developed with noncoplanar π systems in mind. Both calculations were preceded by molecular-mechanical optimizations of geometry.

The first example is the C=C—C=O system of 4-methylbicyclo[3.2.1]oct-3-en-2-one (**21**, n electrons on oxygen included in the calculation). By molecular mechanics, the chromophore is somewhat distorted from coplanarity: dihedral angle C=C—C=O ~ 170°. This suffices to mix some of the n orbital (χ_5) into the π orbitals (χ_1 to χ_4), so that no MO is pure n or pure π. By major components, they are: ϕ_1 (deepest), π; ϕ_2, π; ϕ_3 (HOMO), n; ϕ_4 (LUMO), π^*; ϕ_5 (highest), π^*. The first computed excited state corresponds to a transition at 337 nm. It is interpreted as $n \rightarrow \pi^*$, comprising 29% of $\phi_3 \rightarrow \phi_4$ and 70% of $\phi_3 \rightarrow \phi_5$. The next computed transition is at 205 nm. This is $\pi \rightarrow \pi^*$, containing 94% of $\phi_2 \rightarrow \phi_4$, with an oscillator strength of 0.81. Agreement with the experimental spectrum is reasonable (see Figure 8), implying that the five-membered ring does not have a significant effect on transitions.

The second example is the C=C—C=O system in verbenone (**25**). Here, the skeleton is more rigid than before, and molecular mechanics indicates coplanarity of the enone fragment. Notwithstanding, σ is not separated from π. At the optimized geometry, $n \rightarrow \pi^*$ is predicted at 314 nm (33% of $\phi_3 \rightarrow \phi_5$, 67% of $\phi_3 \rightarrow \phi_4$), and $\pi \rightarrow \pi^*$ at 204 nm (oscillator strength 0.84, 95% of $\phi_2 \rightarrow \phi_5$). Thus (cf. Figures 8 and 9), the calculation erroneously anticipates an hypsochromic–hyperchromic shift on going from **21** to **25**. In actual fact, the shift is bathochromic–hypochromic. Also, for compound **21**, the theoretical $n \rightarrow \pi^*$ (337 nm) coincides with a peak in the midst of the band (Figure 8). For compound **25**, the theoretical $n \rightarrow \pi^*$ (314 nm) precedes the onset of absorption (Figure 9).

SCF–Cl has withstood many tests. Rather than label the results as suspicious, they should be taken to suggest that the four-membered ring in **25** partakes significantly of the chromophoric unit. It was indeed noted[88] that inclusion of ring orbitals in the calculation brings the computed spectrum into place.

XI. REFERENCES

1. W. J. Hehre, L. Radom, P.v.R. Schleyer and J. A. Pople, *Ab Initio Molecular Orbital Theory*, Wiley, New York, 1986.

2. D. B. Boyd and K. B. Lipkowitz, *J. Chem. Educ.*, **59**, 269 (1982).
3. U. Burkert and N. L. Allinger, *Molecular Mechanics*, ACS Monograph 177, Amer. Chem. Soc., Washington, 1982.
4. T. Clark, *A Handbook of Computational Chemistry*, Wiley, New York, 1985.
5. J. Sadlej, *Semi-Empirical Methods of Quantum Chemistry*, Ellis Horwood, Chichester, 1985.
6. For an account of quantum-organic chemistry in its very early days, see B. Pullman and A. Pullman, *Les Théories Electroniques de la Chimie Organique*, Masson, Paris, 1952.
7. J. E. Boggs, in an informal discussion, International School of Crystallography, 11th Course, Erice (Italy), May 1985.
8. H. Berthod, C. Giessner-Prettre and A. Pullman, *Theor. Chim. Acta*, **8**, 212 (1967).
9. L. Schäfer, J. D. Ewbank, V. J. Klimkowski and K. Siam, *J. Mol. Struct.*, **135**, 141 (1986).
10. K. Ohno and K. Morokuma (Eds.), *Quantum Chemistry Literature Data Base*, Bibliography of *ab initio* Calculations, Suppl. 5 for 1985, *J. Mol. Struct.*, **148**, No. 3/4 (1986).
11. M. B. Robin, *Higher Excited States of Polyatomic Molecules*, Vol. 3, Academic Press, Orlando, 1985.
12. H. Suzuki, *Electronic Absorption Spectra and Geometry of Organic Molecules*, Academic Press, New York, 1967.
13. T. Liljefors and N. L. Allinger, *J. Am. Chem. Soc.*, **98**, 2745 (1976).
14. L. A. Carreira, *J. Chem. Phys.*, **62**, 3851 (1975); J. F. Fisher and J. Michl, *J. Am. Chem. Soc.*, **109**, 1056 (1987).
15. Y. Morino, *J. Mol. Struct.*, **126**, 1 (1985): 'Mizushima preferred the French word, wishing to call attention to the existence of a well-defined isomer at an awkward position'.
16. W. Klyne and V. Prelog, *Experientia*, **16**, 521 (1960); V. Prelog, Curr. Contents, **30** (July 23), 12 (1984).
17. H. Eyring, G. H. Stewart and P. R. Smith, *Proc. Natl. Acad. Sci.* U.S.A., **44**, 259 (1958); G. H. Stewart and H. Eyring, *J. Chem. Educ.*, **35**, 550 (1958).
18. R. C. Bingham, *J. Am. Chem. Soc.*, **98**, 535 (1976).
19. A. C. P. Alves, J. Christoffersen and J. M. Hollas, *Mol. Phys.*, **20**, 625 (1971); erratum, *Mol. Phys.*, **21**, 384 (1971).
20. A. J. P. Devaquet, R. E. Townshend and W. J. Hehre, *J. Am. Chem. Soc.*, **98**, 4068 (1976).
21. A. Skancke and J. E. Boggs, *J. Am. Chem. Soc.*, **101**, 4063 (1979).
22. E. Switkes, *J. Chem. Phys.*, **67**, 3061 (1977).
23. R. Hoffmann, *Acc. Chem. Res.*, **4**, 1 (1971).
24. N. D. Epiotis, W. R. Cherry, S. Shaik, R. L. Yates and F. Bernardi, *Top. Curr. Chem.*, **70**, 1 (1977). For the application to acrolein, see pp. 102–109.
25. R. J. Loncharich, T. R. Schwartz and K. N. Houk, *J. Am. Chem. Soc.*, **109**, 14 (1987).
26. P. Masclet and G. Mouvier, *J. Electron Spectrosc. Relat. Phenom.*, **14**, 77 (1978).
27. H. Dodziuk, *J. Mol. Struct.*, **55**, 107 (1979).
28. R. Gleiter, G. Jahne, G. Muller, M. Nixdorf and H. Irngartiner, *Helv. Chim. Acta*, **69**, 71 (1986).
29. M. Rubio, A. Hernandez, J. P. Daudey, R. Cetina and A. Diaz. *J. Org. Chem.*, **45**, 150 (1980).
30. O. Kikuchi, *Bull. Chem. Soc. Jpn.*, **55**, 1669 (1982).
31. A. F. Cuthbertson and C. Thomson, *J. Mol. Graphics*, **5**, 92 (1987).
32. For the history of molecular mechanics, see M. Saunders and R. M. Jarret, *J. Comput. Chem.*, **7**, 578 (1986).
33. For an analysis of molecular mechanics, see J. C. A. Boeyens, *Structure and Bonding*, **63**, 65 (1985).
34. A. Y. Meyer, in *The Chemistry of Functional Groups*, Suppl. D (Eds. S. Patai and Z. Rappoport), Vol. 1, Chap. 1, Wiley, Chichester, 1983.
35. Molecular mechanics programs of the MM series devolve from Allinger's MM2 program. See N. L. Allinger, *J. Am. Chem. Soc.*, **99**, 8127 (1977).
36. T. Liljefors, J. C. Tai, S. Li and N. L. Allinger, *J. Comput. Chem.*, **8**, 1051 (1987).
37. J. Kao and N. L. Allinger, *J. Am. Chem. Soc.*, **99**, 975 (1977).
38. N. L. Allinger and J. C. Tai, *J. Am. Chem. Soc.*, **87**, 2081 (1965).
39. T. Liljefors and N. L. Allinger, *J. Am. Chem. Soc.*, **100**, 1068 (1978).
40. N. L. Allinger, Operating Instructions for MM2 and MMP2 Programs, updated as of August 1985. University of Georgia, Athens, Ga., U.S.A.
41. H. Dodziuk, *Bull. Acad. Pol. Sci.*, **21**, 627 (1973); *J. Mol. Struct.*, **20**, 363 (1974).
42. J. Kao, *J. Am. Chem. Soc.*, **109**, 3817 (1987). For an application to acrolein, see J. Kao, D. Leister and M. Sito, *Tetrahedron Lett.*, **26**, 2403 (1985).

43. D. A. Lightner, J. K. Gawroński, A. E. Hansen and T. D. Bouman, *J. Am. Chem. Soc.*, **103**, 4291 (1981).
44. P. Bowen and N. L. Allinger, *J. Org. Chem.*, **51**, 1513 (1986).
45. E. A. Cherniak and C. C. Costain, *J. Chem. Phys.*, **45**, 104 (1966).
46. C. E. Blom, G. Grassi and A. Bauder, *J. Am. Chem. Soc.*, **106**, 7427 (1984).
47. K. Kuchitsu, T. Fukuyama and Y. Morino, *J. Mol. Struct.*, **1**, 463 (1967–8) and **4**, 41 (1969). For definitive numbers, see *Landolt–Börnstein Zahlenwerte und Funktionen*, Neue Serie, Vol. 7, Springer, Berlin, 1976, p. 230.
48. M. Traetteberg, *Acta Chem. Scand.*, **24**, 373 (1973).
49. L. Carreira, personal communication cited in Reference 13.
50. G. R. De Maré, *J. Mol. Struct.*, **107**, 127 (1984).
51. A. Y. Meyer, *Chem. Soc. Rev.*, **15**, 449 (1986).
52. L. Carballeira, R. A. Mosquera and M. A. Rios, *J. Mol. Struct.*, **136**, 351 (1986).
53. P. N. Skancke, *J. Comput. Chem.*, **4**, 142 (1983).
54. U. Norinder, *J. Mol. Struct.*, **150**, 85 (1987).
55. P. G. Lykos, *Adv. Quantum Chem.*, **1**, 171 (1964).
56. A. Y. Meyer and J. Serre, *Theor. Chim. Acta*, **8**, 117 (1967).
57. S. Nagakura, *Mol. Phys.*, **3**, 105 (1960).
58. J. N. Murrell, *The Theory of the Electronic Spectra of Organic Molecules*, Methuen, London, 1963.
59. R. Hernandez, P. Masclet and G. Mouvier, *J. Electron Spectrosc. Relat. Phenom.*, **10**, 333 (1977).
60. P. Masclet, D. Grosjean, G. Mouvier and J. E. Dubois, *J. Electron Spectrosc. Relat. Phenom.*, **2**, 225 (1973).
61. S. D. Peyerimoff and R. J. Buenker, *Adv. Quantum Chem.*, **9**, 69 (1975): ethylene, pp. 88–91; formaldehyde, pp. 83–86.
62. C. Fridh and E. Lindholm, *Phys. Scr.*, **20**, 603 (1979).
63. T. G. Edwards and R. Grinter, *Theor. Chim. Acta*, **12**, 387 (1968).
64. W. Schäfer, A. Schweig, G. Maier, T. Sayrac and J. K. Crandall, *Tetrahedron Lett.*, 1213 (1974).
65. R. Gleiter, P. Schang and G. Seitz, *Chem. Phys. Lett.*, **55**, 144 (1978).
66. R. Gleiter, W. Dobler, E. Vogel, S. Böhm and J. Lex, *J. Am. Chem. Soc.*, **109**, 5156 (1987).
67. R. G. Parr, *The Quantum Theory of Molecular Electronic Structure*, Benjamin, New York, 1963.
68. I. Fischer-Hjalmars, *Adv. Quantum Chem.*, **2**, 25 (1965).
69. P. O. Löwdin, *Adv. Chem. Phys.*, **2**, 207 (1959), p. 259 et seq..
70. S. P. McGlynn, L. G. Vanquickenborne, M. Kinoshita and D. G. Carroll, *Introduction to Applied Quantum Chemistry*, Holt, Rinehart and Winston, New York, 1972, pp. 233–241.
71. C. J. M. Brugman, N. P. van Asselt, R. P. H. Rettschnick and G. J. Hoytink, *Theor. Chim. Acta*, **23**, 105 (1971).
72. H. C. Longuet-Higgins and J. N. Murrell, *Proc. Phys. Soc. (London)*, **A68**, 601 (1955).
73. K. Tabei and S. Nagakura, *Bull. Chem. Soc. Jpn.*, **38**, 965 (1965), and previous papers.
74. W. von Niessen, *Theor. Chim. Acta*, **31**, 111, 297 (1973), **32**, 13 (1973) and **33**, 7 (1974).
75. A. Y. Meyer, *Theor. Chim. Acta*, **9**, 401 (1968).
76. A. Y. Meyer and Y. Kesten, *Theor. Chim. Acta*, **20**, 352 (1971).
77. A. Gamba, G. F. Tantardini and M. Simonetta, *Theor. Chim. Acta*, **20**, 12 (1971).
78. G. Favini, A. Gamba and M. Simonetta, *Theor. Chim. Acta*, **13**, 175 (1969); A. Gamba, G. Tantardini and M. Simonetta, *Theor. Chim. Acta*, **23**, 336 (1972); G. Favini and G. Buemi, *Theor. Chim. Acta*, **24**, 61 (1972).
79. A. D. Walsh, *Trans. Faraday Soc.*, **41**, 498 (1945).
80. A. Moscovitz, A. E. Hansen, L. S. Forster and K. Rosenheck, *Biopolymers Symposia*, **1**, 75 (1964).
81. P. M. Vay, *J. Chim. Phys.*, **65**, 2043, 2050 (1968).
82. K. Nishimoto and N. Mataga, *Z. physik. Chem.*, **13**, 140 (1957).
83. R. B. Woodward, *J. Am. Chem. Soc.*, **63**, 1123 (1941).
84. E. S. Stern and C. J. Timmons, *Gillam and Stern's Introduction to Electronic Absorption Spectroscopy in Organic Chemistry*, 3rd edition, Arnold, London, 1970, pp. 78–88.
85. D. H. Williams and I. Fleming, *Spectroscopic Methods in Organic Chemistry*, 2nd edition, McGraw-Hill, London, 1973.
86. J. P. Flament and H. P. Gervais, *J. Mol. Struct.*, **90**, 351 (1982).
87. Spectrum recorded while preparing material for the report in Reference 88.

88. A. Y. Meyer, R. Pasternak, J. Sterling, N. Lander and R. Mechoulam, *Tetrahedron*, **32**, 2805 (1976).
89. R. N. Moore and G. S. Fisher, *J. Am. Chem. Soc.*, **78**, 4362 (1956).
90. J. J. Bloomfield and R. E. Moser, *J. Am. Chem. Soc.*, **90**, 5625 (1968). See also L. A. Paquette, J. C. Phillips and R. E. Wingard, *J. Am. Chem. Soc.*, **93**, 4516 (1971).
91. R. Hoffmann, E. Heilbronner and R. Gleiter, *J. Am. Chem. Soc.*, **92**, 706 (1970).
92. A. Y. Meyer and E. Zamir, unpublished calculation.
93. S. C. Neely, R. Fink, D. van der Helm and J. J. Bloomfield, *J. Am. Chem. Soc.*, **93**, 4903 (1971).
94. A. Y. Meyer and R. Pasternak, *Tetrahedron*, **33**, 3239 (1977).
95. A. Y. Meyer and R. Pasternak, *Theor. Chim. Acta*, **47**, 27 (1978).
96. D. P. Chong, *Theor. Chim. Acta*, **51**, 55 (1979).
97. L. Åsbrink, C. Fridh and E. Lindholm, *Chem. Phys. Lett.*, **52**, 63, 69, 72 (1977).
98. J. Del Bene and H. H. Jaffé, *J. Chem. Phys.*, **48**, 1807, 4050 (1968); **49**, 1221 (1968); **50**, 1126 (1969); R. L. Ellis, G. Kuehnlenz and H. H. Jaffé, *Theor. Chim. Acta*, **26**, 131 (1972).
99. R. Pariser and R. G. Parr, *J. Chem. Phys.*, **21**, 466, 767 (1953); R. G. Parr and R. Pariser, *J. Chem. Phys.*, **23**, 711 (1955); J. A. Pople, *Trans. Faraday Soc.*, **49**, 1375 (1953).
100. K. Ohno, *Adv. Quantum Chem.*, **3**, 240 (1967).
101. G. Höjer, S. Meza and M. E. Ruiz, *Acta Chem. Scand.*, **27**, 1860 (1973).
102. R. D. Brown and M. L. Heffernan, *Trans. Faraday Soc.*, **54**, 757 (1958); *Austr. J. Chem.*, **12**, 319, 330 (1959).
103. N. L. Allinger, J. C. Tai and T. W. Stuart, *J. Am. Chem. Soc.*, **90**, 2809 (1968).
104. A. Y. Meyer, unpublished work, referred to briefly in Reference 88.
105. A. Y. Meyer and R. Pasternak, *Theor. Chim. Acta*, **33**, 215 (1974).

The Chemistry of Enones
Edited by S. Patai and Z. Rappoport

CHAPTER **2**

Structural chemistry of enones

BERND SCHWEIZER

Institute of Organic Chemistry, ETH Zürich, CH-8092 Zürich, Switzerland

I. INTRODUCTION

This chapter deals with the structural characteristics of enone and enal groups in molecules. Because of the conjugated system, it can be expected that bond distances and bond angles vary considerably with the nature of the substituents and the geometrical constraints caused by ring systems or bulky substituents. The enone and enal fragments have therefore been split up into subgroups for this analysis.

The structural data were taken from three sources. Some studies of microwave spectra of molecules in the gas phase were available. This method is limited to small molecules and therefore only a small number of structures are known. Another small set of data has been taken from *ab initio* calculations, which for reliable results are also limited to molecules with few atoms. Most of the information is taken from X-ray and neutron diffraction analysis. Crystal structure analysis is certainly one of the most powerful methods presently available to obtain geometrical information about a molecule.

The crystal structure data for this study were taken from the Cambridge Structural Database (CSD)[1] version of July 1987 with about 62,000 bibliographic entries in the file. A search on the CSD retrieved 2158 structures containing the enone fragment and 104 structures with an enal group. Unfortunately about 20% of the entries are without atomic coordinates and are therefore useless for this analysis. On the CSD, beside the bibliography and the structural information, some remarks are given concerning experimental conditions and the accuracy of the structure determination. The supplied agreement factor R can be used as a crude criterion to judge the quality of the data. Quantity R is defined as the sum of the absolute differences between the observed and calculated structure factors, divided by the sum of the observed structure factors. Structure reports with $R > 0.085$ have been excluded for this analysis, and also structures containing numeric data errors or those where the authors mentioned disordered or partly disordered atomic positions. The positional parameters on the CSD are put into one of four classes (AS) which specify a range of the mean standard deviation σ of the interatomic distances. AS = 1 indicates $\sigma < 0.005$ Å, AS = 2 indicates $0.005 < \sigma < 0.010$ Å, AS = 3 indicates $0.010 < \sigma < 0.030$ Å and AS = 4 indicates $\sigma > 0.03$ Å. One has to be aware of the fact that the available data are averaged atomic positions obtained from crystals of very different quality, measured at different temperatures under very different experimental conditions. Even under the same experimental conditions, the applied weighting and the selection of the observations can lead to changes in the bond lengths of several standard deviations, as derived from the least-squares refinement procedure[2]. Interatomic distances from room temperature measurements tend to be short, owing to the effects of molecular vibrations in the crystal. Unfortunately, the number of precisely measured low-temperature structures was small and the variability within each subgroup large, so that the separate analysis of structures obtained at different temperatures was not practicable. For comparison of bond lengths, only entries with AS = 1 were used as far as possible, whereas the torsion angle analyses were carried out with all available data with $R < 0.085$.

The average value of a number of observations can be estimated in various ways. In principle, the observations should be weighted according to the precision of the measurement. However, because of the pre-screening of the data and the normally underestimated standard deviation of the diffraction experiments, the unweighted means is also acceptable for the calculation of average molecular dimensions[3]. The unweighted mean value is defined as $d = \sum d_i/n$, where d_i is the ith observation of the total n observations. The standard deviation σ of the mean values was calculated as $\sigma = [\sum(d_i - d)^2/(n-1)]^{1/2}$. The standard deviation in the diagrams is appended to the mean value in parentheses in units of the last significant figure.

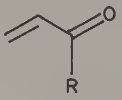
If the number of structures for a certain class of enones was big enough, a histogram of the C=O, C—C and C=C bond lengths of the enone group is given. The observations with the maximum and minimum values and single outliers were examined specially and removed for the calculation of the mean value if systematic errors were suspected.

The numbering of the atoms used to describe distances and angles starts at the carbonyl of the enone group with C(1), followed by the C atoms of the double bond [C(2), C(3)] and, in the case of the cyclic enones, continuing in the ring up to the number of the ring size.

II. ENONES

A. Acyclic Enones

The search on the CSD retrieved 773 molecules that contain an acyclic enone fragment. They were divided up into three groups depending on the type of C-substituent R on the carbonyl group, i.e. R = Csp^3, C aromatic, Csp^2 acyclic.



1. Aliphatic acyclic enones

For the class with an aliphatic C-atom attached to the carbonyl group, 121 entries in the CSD were found with the only condition that the agreement factor R is less than 0.085. Figure 1 shows a histogram of the C=C—C=O torsion angle of all acyclic enone fragments. As expected there is a preference for the enone group to be planar to allow a good delocalization of the π electrons. The dominant arrangement in the acyclic enone groups is apparently the s-*cis* conformation of the carbonyl and the double bond. It occurs about 2.5 times as often as the s-*trans* form. Some of the structures have an O—H or N—H substituent at C(3) that can form a hydrogen bond to the carbonyl oxygen, which possibly favors the s-*cis* arrangement. A selection was made of enone groups with a hydrogen atom at C(2) to eliminate the influence of the steric repulsion of bulky groups on the conformation. The structures which form hydrogen bonds have also been removed. This subset (shaded area in the histogram of Figure 1) shows an even more pronounced preference for the s-*cis* conformation. However, the cluster with torsion angle around 180° is not negligible, in contrast to the case of acyclic esters where no example of a *cis* (Z)-ester can be found[4]. There are a few examples with torsion angles between 45° and 120°. In all these enones there is another π substituent on C(2) that offers better delocalization for the electrons in the C=C bond, as in *E*-ethyl 3-oxo-2-((2-pyridyl)methylene)butanoate (**1**, Figure 2)[5] where steric repulsion forces the carbonyl group out of the plane of the C=C π system.

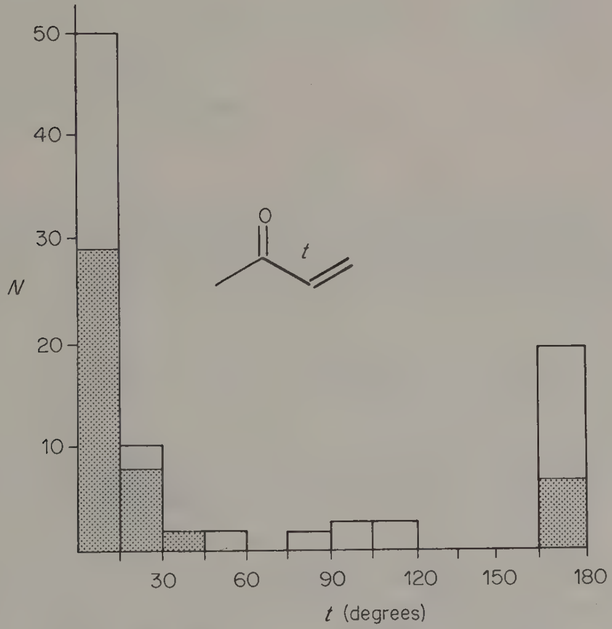
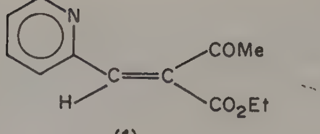
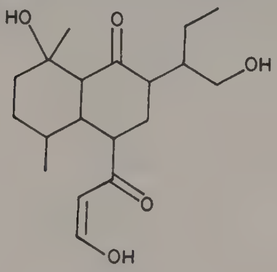


FIGURE 1. Histogram of the torsion angle C=C—C=O (deg, absolute value) in acyclic enones with aliphatic substituent at the carbonyl carbon. The shaded area shows enone fragments with a hydrogen atom on C(2)

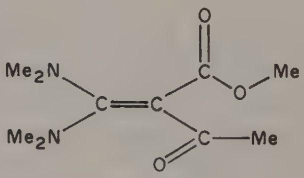


(1)

The histogram in Figure 3 shows that the bond length distribution of the 30 enone groups with AS = 1 is characterized by an enormous spread. The length of the C=O bond for these structures lies in the range of 1.203 Å to 1.268 Å. The longest value is observed in stemphyloxin (**2**)[6]. This is a typical example of a s-*cis* enone where the carbonyl oxygen forms an intramolecular hydrogen bond. From a single X-ray analysis it is not possible to decide whether this is an intermediate form with delocalized π bonds. This long carbonyl bond can also be explained by the fact that the β-hydroxyenone fragment can occur in two tautomeric forms; if both forms are present in the crystal, this would shorten the C—OH bond and elongate the C=O bond, as observed. Another example is methyl-2-(bis(dimethylamino)-methylene)-3-oxobutyrate (**3**)[7] where the C=C bond with a length of 1.461 Å and a torsion angle of about 60° has practically lost its double-bond character. The nominal C—C single bond is shortened to 1.413 Å. These types of structures contribute all the values in the histogram in Figure 3 for the C=O bonds longer than 1.22 Å, the C—C bonds shorter than 1.46 Å and the C=C bonds longer than 1.36 Å. To eliminate those effects on the analysis of the geometry, the molecules were selected where the enone group



(2)



(3)

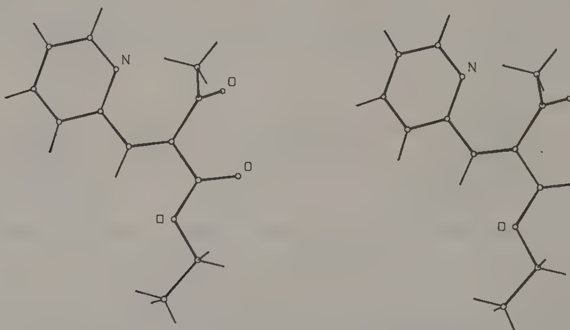


FIGURE 2. Stereoscopic drawing of the structure of **1**. Example of a nonplanar enone fragment

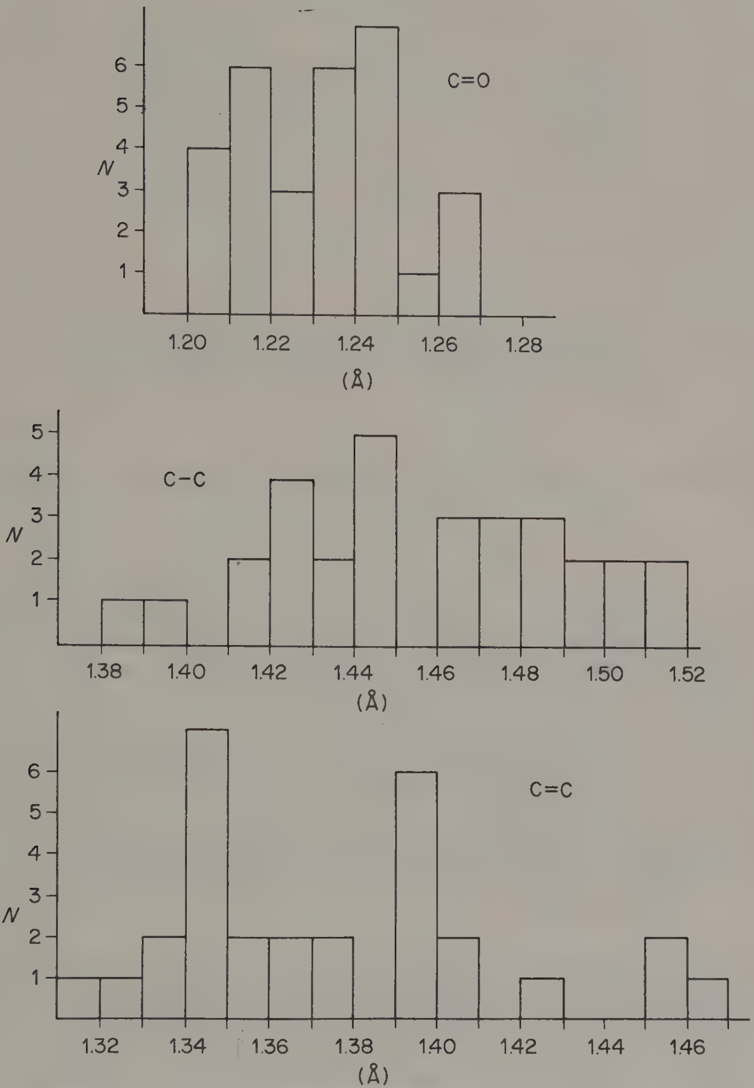


FIGURE 3. Histograms of bond lengths of the enone fragments of the acyclic enones with aliphatic substituent at the carbonyl group

was not involved in hydrogen bonding or tautomerism. The shortest value of 1.203 Å for the C═O bond of this subgroup is found in **1** (Figure 2). This molecule is one of the few examples where the π systems of the two double bonds are not coplanar. The angle of 91° inhibits the conjugation almost completely. Figure 4 shows the dependence of the two bond distances C═O and C—C in the enone fragment on the dihedral angle between the two π systems. The mean bond distance was taken of all molecules where the absolute value of the torsion angle O═C—C═C falls within the same 15° range. Because of the

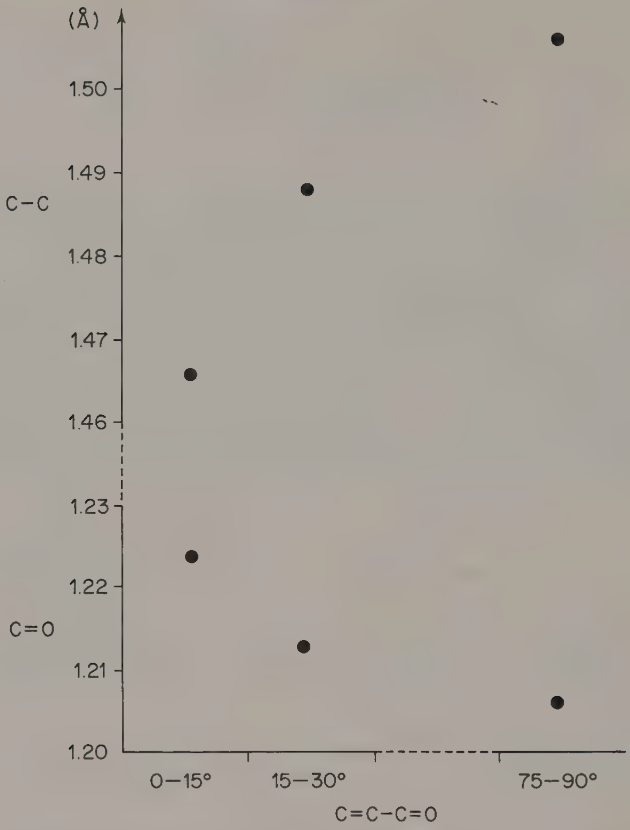
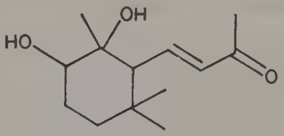


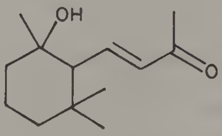
FIGURE 4. Mean value of the C—C and C=O bond lengths at different dihedral angles C=C—C=O of acyclic enones (for selection see text)

few entries (3 for the range 0–15° and 2 each for the ranges 15–30° and 75–90°) the plot has only qualitative significance, but at least it shows what one would expect: as the π systems of the two double bonds become coplanar the π delocalization of the electrons shortens the C—C single bond and lengthens the C=O double bond. The effect on the C=C double bond is not so clear, because the heterogeneity of the substituents overrides the influence of the conjugation.

From the selected structures alone two molecules have an enone group with only aliphatic substituents, 4-(2, 3-dihydroxy-2, 6, 6-trimethylcyclohexyl)but-3-en-2-one (**4**)[8] and 4-(2-hydroxy-2, 6, 6-trimethylcyclohexyl)but-3-en-2-one (**5**)[8]. They both belong to the



(**4**)



(**5**)

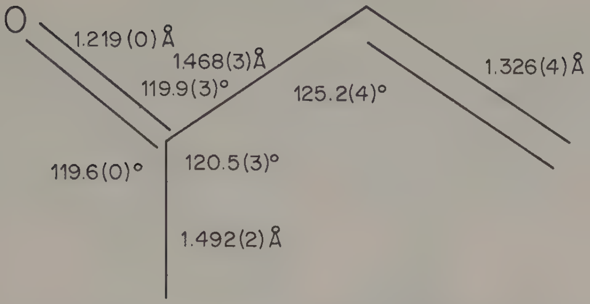


FIGURE 5. Averaged bond lengths (Å) and bond angles (deg) with standard deviations of the enone fragment of the acyclic enones (**4**) and (**5**) with aliphatic substituent at the carbonyl group

group with s-*trans* conformation. The averaged geometry of the two enone groups is given in Figure 5.

2. *Aromatic substituted acyclic enones*

The enone structures with an aromatic ring attached to the carbonyl group are so heterogeneous with respect to the substituents on the double bond that the values for the mean geometry of 19 structures in Figure 6 are characterized by large standard deviations. There is the same preference for the s-*cis* conformation as in the aliphatic enones with a nonnegligible number of s-*trans* forms. In spite of the conjugation, the bond distance to the aromatic ring is not shorter than in the structures with the saturated carbon substituents. An indication for the conjugation is the fact that the aromatic system tends to lie close to the plane of the carbonyl group, as can be seen in the histogram in Figure 7. All examples with a dihedral angle greater than 39° have aromatic rings with nonhydrogen atoms in the *ortho* position. The greatest deviations of the periplanar arrangement of structures with H substituents can be explained by steric effects as in 3-(3-benzoyl-4-(diethylamino)-5-methyl-1-pyrazolyl)-3-(diethylamino)-2-methyl-1-phenylprop-2-en-1-one (**6**)[9] where both

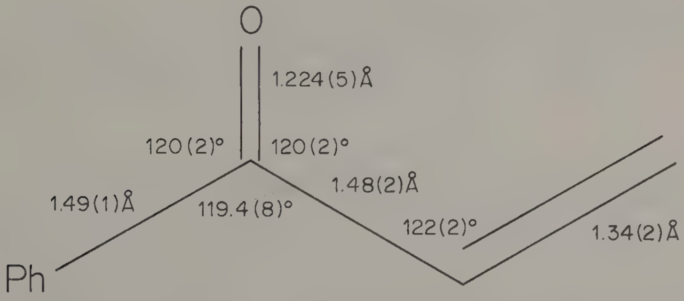


FIGURE 6. Averaged bond lengths (Å) and bond angles (deg) with standard deviations of the enone fragment of the acyclic enones with aromatic substituent at the carbonyl group

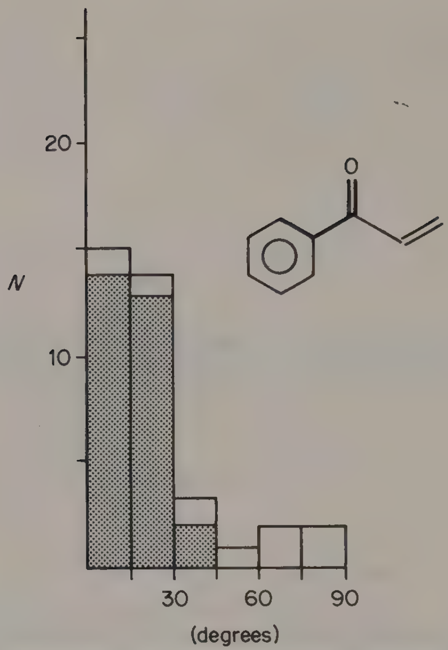
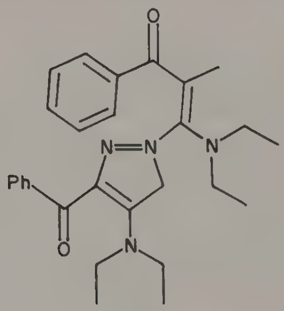


FIGURE 7. Histogram of the absolute value of the $O{=}C{-}C_{ar}{-}C_{ar}$ torsion angles (deg) in enones with aromatic substituent at the carbonyl group. Only the smaller of the two possible values is used. Shaded area includes only aromatic substituents with H atoms in *ortho* position

the phenyl ring (by 39°) and the C=C π system of the enone (by 42°) with the pyrazolyl ring as substituent are turned out of the plane of the carbonyl group.

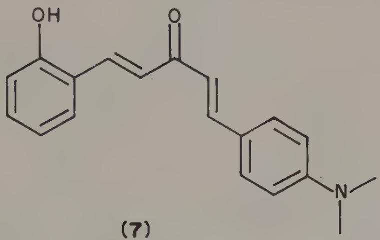


(6)

3. Acyclic dienones

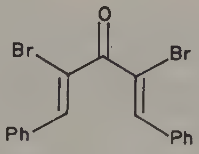
There are very few examples of known structures of acyclic dienones. In fact, there is only one structure with a reported accuracy of AS = 1, the *m*-dinitrobenzene clathrate of 1-

(*p*-dimethylaminophenyl)-5-(*o*-hydroxyphenyl)-penta-1,4-dien-3-one (**7**)[10] with two independent molecules in the crystal. The C=O distance (mean value 1.240 Å) is significantly longer and the mean distance between the carbonyl and the double-bond carbon is shorter (1.458 Å) than in the aliphatic and phenyl enones. This could be a delocalization effect, except that the short length of the C=C double bonds (1.324 Å) seems to contradict this explanation. The averaged values for the angles are 119.5° for O=C—C, 121.0° for C—CO—C and 124.2° for CO—C=C. They show no significant differences from the angles in the acyclic enone fragment.



(7)

Of the six dienone fragments, two have a *cis–cis*, two a *cis–trans* (**7**) and two a *trans–trans* conformation of the O=C—C=C groups. Whereas the *cis–cis* and *cis–trans* dienones are planar within the precision of the experiment, the *trans–trans* form is quite distorted. The deviation by 22–39° from the planar arrangement in the two symmetrically independent molecules of (*Z*,*Z*)-2,4-dibromo-1,5-diphenylpenta-1,4-dien-3-one (**8**)[11] is obviously caused by steric repulsion.



(8)

B. Cyclic Enones

In 1005 of the 2158 retrieved enone structures of the CSD, the enone group is part of a ring fragment. Whereas in the small cyclic systems the constraints caused by the ring system dominate, in the seven- or higher-membered rings the difference from the geometry of the acyclic enones becomes negligible. The following describes the geometry of the three- to six-membered rings containing an enone fragment.

1. Cyclopropenones

Only two structures of substituted cyclopropenone rings were found: 2,3-bis(*p*-chlorophenyl)cyclopropenone (**9**)[12] and 2,3-diphenylcyclopropenone (**10**)[13]. Both structures belong to the AS class 1. As can be expected from the similarity of the two molecules, the geometry of their cyclopropenone rings does not differ substantially. The average bond lengths and angles of the three fragments (**10** contains two crystallographically independent molecules) are given in Figure 8. The most pronounced difference from the acyclic and other cyclic enones is the short C—C bond of 1.412 Å in the ring. This is in good agreement with a microwave study of cyclopropenone[14] where a C—C distance of 1.412 Å is reported. Because the carbonyl oxygen withdraws electrons from the ring, a change in the

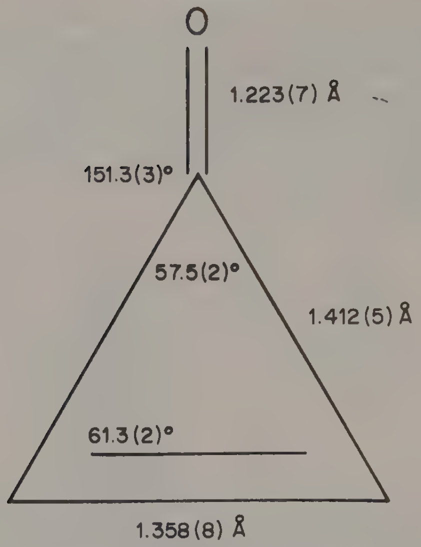
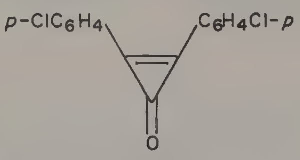
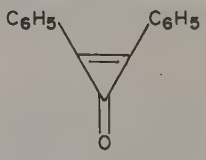


FIGURE 8. Averaged bond lengths (Å) and bond angles (deg) with standard deviations of the cyclopropenone fragment

bond lengths towards a delocalized cyclopropenyl cation with uniform C—C distances can be expected. The increase in the length of the C═O bond, compared with the value of 1.212 Å in cyclopropenone, is also in acceptable agreement with this assumption, taking into account that the oxygens of **9** are involved in hydrogen bonding in the crystal. A greater discrepancy is observed for the length of the C═C bond. In the microwave experiment this distance was determined as 1.302 Å, in contradiction to the expected elongation towards the structure of the cyclopropenyl cation. An *ab initio* molecular orbital study[15] for cyclopropenone predicts a distance of 1.33 Å. The significantly longer value of 1.358 Å from the X-ray structures is probably also an effect of the phenyl substituents which are almost coplanar with the three-membered ring plane (maximum dihedral angle 10°) and thus allow a further delocalization of the electrons of the double bond and also cause a steric strain on the bond. The carbonyl oxygen in both molecules of **9** lie within the standard deviation in the plane of the cyclopropene ring (the oxygen in **10** is forced to lie in the plane by crystallographic symmetry).



(9)



(10)

2. *Cyclobutenones*

As with the cyclopropenones, the number of structures containing cyclobutenone fragments is very small. Only seven entries were found in the CSD, and two of them (3-

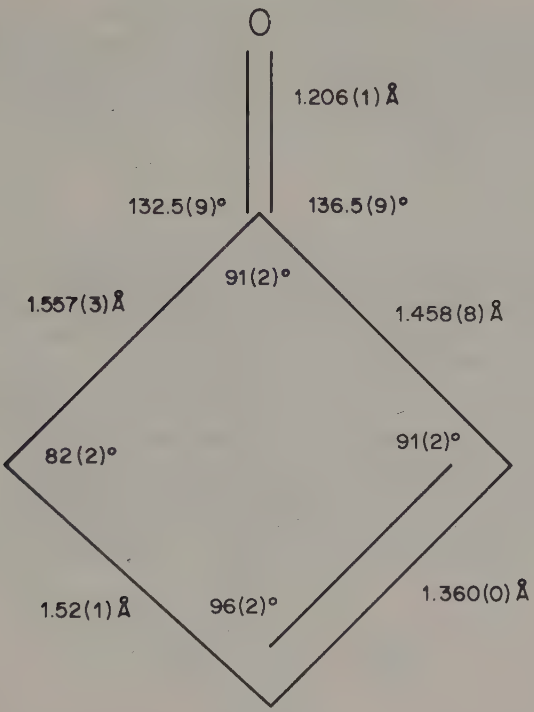
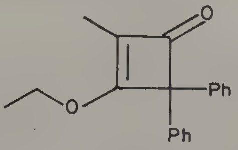
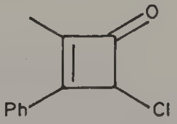


FIGURE 9. Averaged bond lengths (Å) and bond angles (deg) with standard deviations of the cyclobutenone fragment

ethoxy-2-methyl-4, 4-diphenylcyclobut-2-en-1-one (**11**)[16] and 4-chloro-2-methyl-3-phenylcyclobut-2-en-1-one (**12**)[17]] with reported accuracy of the C—C bonds better than 0.01 Å (AS = 2) have been used to calculate the mean values for the geometric parameters given in Figure 9. Due to geometrical constraints the bond angles in the ring differ appreciably from the ideal values. It is interesting that both the sp^2 (mean value of the three angles, 93°) and the sp^3-type angles show about the same deviation from the standard values. This pattern is also seen in the less precise structures with cyclobutenone rings that were excluded from the evaluation of the geometrical parameters listed in Figure 9. The value for the C=O bond length is the shortest compared with the other ring systems and the acyclic enones. However, the low precision and the small sample of the structures does not allow the difference to be regarded as significant.



(11)



(12)

In contrast to the puckered cyclobutane, four-membered rings containing a double bond are expected to be planar. This is the case within the experimental error for **11**, whereas the ring in **12** shows (according to the published standard deviation) a probable significant distortion from planarity (as can be seen by the torsion angle C—CO—C=C of 3.1°). In the paper describing the structure this is explained by intermolecular steric effects.

3. Cyclopentenones

For the search of the cyclopenten-2-one fragments on the CSD, only molecules were selected with saturated carbon atoms in the 4- and 5-position. The average geometry in the five-membered ring of 26 fragments is shown in Figure 10. Histograms for the three bonds C=O, C—C and C=C in the enone fragment are given in Figure 11. Of all the bond lengths, the C=O distance shows the least variation, with the exception of a lonely entry with a value of 1.183 Å in the structure of 4-norestr-3(5)-ene-2, 17-dione (**13**)[18]. Inspection of the structure shows that this is clearly associated with the large atomic displacement parameter of the oxygen due to disorder or high thermal motion in the crystal. A similar outlier can be observed in the histogram of the C—C bond of 1.422 Å. This is found in the structure of d-homo-norestr-3(5)-ene-2, 17-dione (**14**)[19]. In contrast, the cyclopentenone ring fused to a six-membered ring, as in **13** and other compounds with a steroid ring pattern, do not show similar short distances. The atoms involved in the short bond of **14**

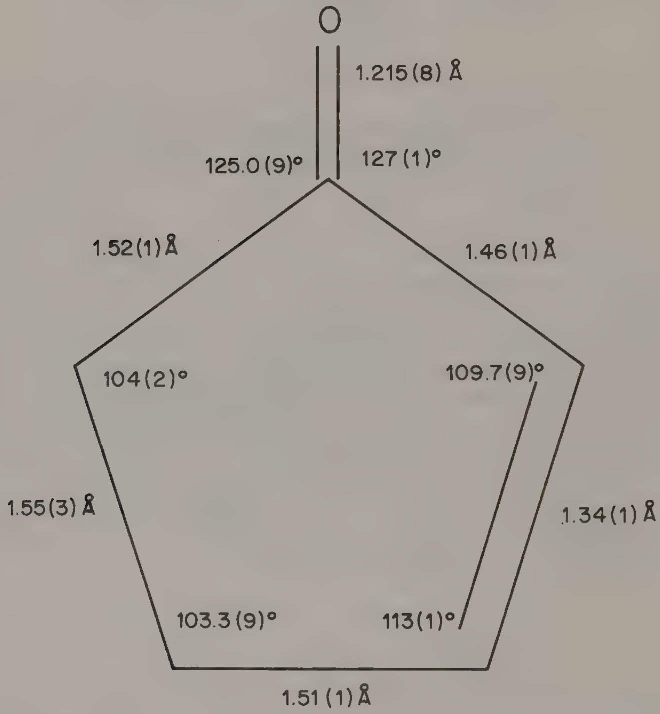


FIGURE 10. Averaged bond lengths (Å) and bond angles (deg) with standard deviations of the cyclopenten-2-one fragment

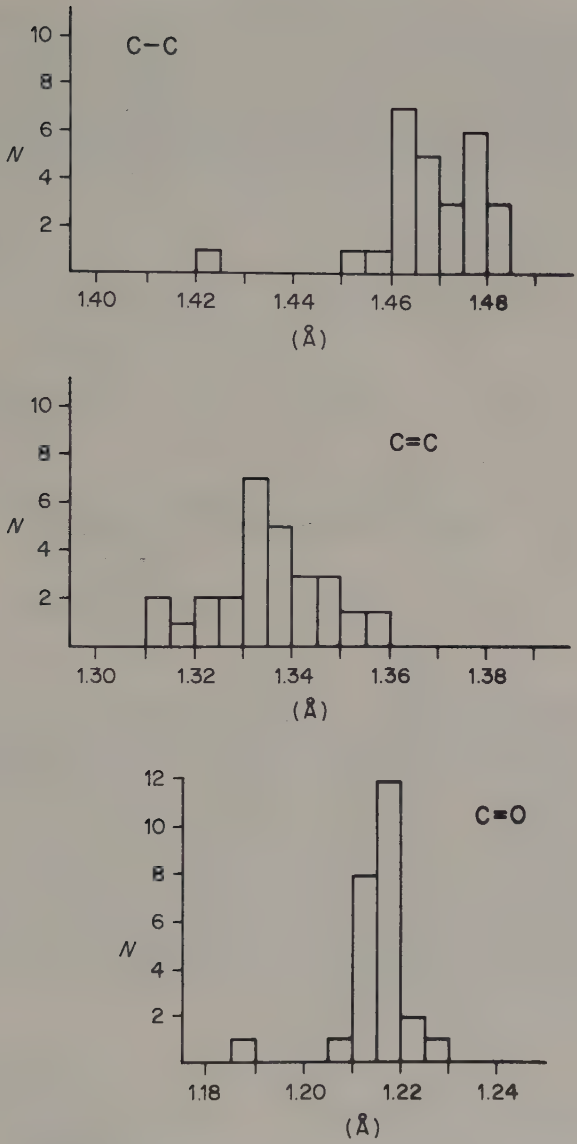
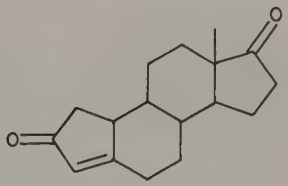
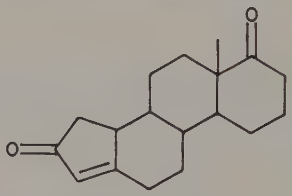


FIGURE 11. Histograms of the bond lengths (Å) of the enone fragments in cyclopent-2-en-1-ones

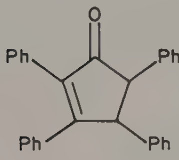
have also high atomic displacement parameters, suggesting that the short bond has more an experimental than a chemical origin. Apart from this structure, the variation of the C—C single bond is smaller than that of the C=C double bond. Many of the cyclopentenone rings are fused at the C=C bond to other rings of different sizes, resulting in more or less strain on the double bond. The longest values for the C=C bond are found in tetra-phenyl substituted enones like *trans*-2, 3, 4, 5-tetraphenylcyclopent-2-en-1-one (**15**)[20] (1.351 Å) or *trans*-4-cyano-2, 3, 4, 5-tetraphenylcyclopent-2-en-1-one (**16**)[21] (1.358 Å). The two phenyl groups attached to the double bond are turned out of the plane of the enone fragment by 40° and 45° in **15** and by 35° and 44° in **16**. This still allows some delocalization of the electrons of the double bond into the π system of the phenyl rings, which may be a factor, beside the steric strain caused by the phenyl groups, in the elongation of the C=C bond.



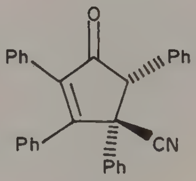
(13)



(14)

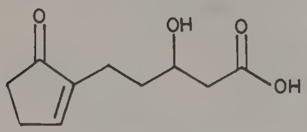


(15)

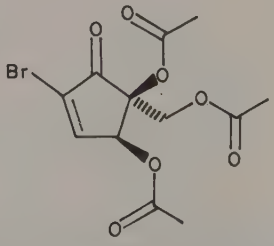


(16)

In a five-membered ring of carbon atoms a planar arrangement of the atoms would give minimum bond-angle strain. The resulting eclipsed conformation of the substituents, however, is energetically unfavorable. This leads to a puckered ring conformation in molecules like cyclopentanones and cyclopentenes. In contrast, the ring skeleton of cyclopent-2-en-1-one and 3-methylcyclopent-2-en-1-one is planar, as was shown by microwave studies[22,23]. To compare those results with X-ray structures, a selection of molecules was made where the cyclopentenone ring has no cyclic substituent. Planar rings are found in those structures where the substituents can avoid close nonbonding contacts without deforming the ring skeleton like 2-(4′-carboxy-3′-hydroxybutyl)-cyclopent-2-en-1-one (**17**)[24] and monobromopentenomycin triacetate (**18**)[25]. Most of the known structures contain bulky phenyl groups as ring substituents, as in **16**. They normally show an appreciable deformation of the ring.



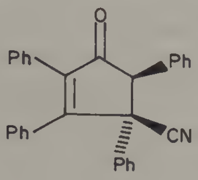
(17)



(18)

The conformation of a five-membered ring can be described by two parameters[26,27] obtained from the five torsion angles in the ring. The puckering amplitude ω (deg) expresses the distortion of the ring from planarity and the phase angle θ (deg) gives the position of a conformation along the path between the twisted form ($\theta = 0°, 36°, 72°, \ldots$) and the envelope form ($\theta = 18°, 54°, 90°, \ldots$).

The greatest puckering amplitude is observed for the ring in *cis*-4-cyano-2, 3, 4, 5-tetraphenylcyclopent-2-en-1-one (**19**)[21] with $\omega = 25°$ (typical values for cyclopentanes are around 40°) and a phase angle θ of 68°, which is close to a perfect twist conformation. An interesting phenomenon can be observed in the structure of **19**, which contains two independent molecules. One shows a significant ring puckering ($\omega = 17°$), but the ring in the second molecule is rather flat ($\omega = 7°$) despite the four phenyl substituents.



(19)

Figure 12 shows a diagram of the out-of-plane deformation ω vs. the conformation phase angle θ of 52 cyclopentenone rings from X-ray structures with reported accuracy in

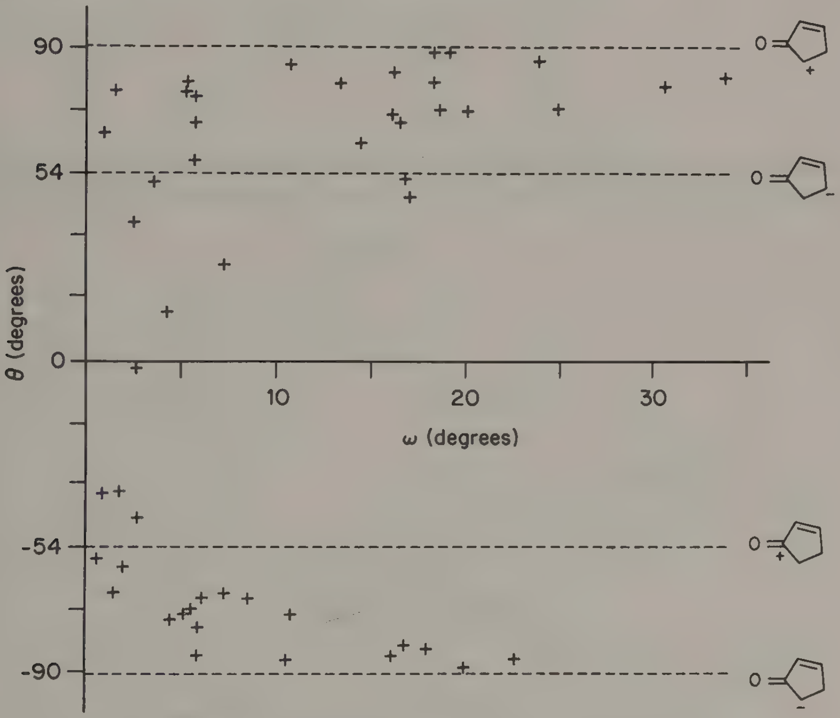
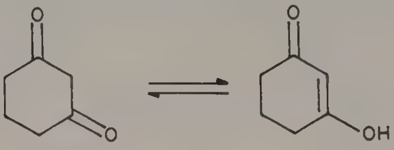


FIGURE 12. Scattergram of the plane deformation ω (deg) vs. conformation phase angles θ (deg) in cyclopent-2-en-1-one rings. The dashed lines indicate phase angles of envelope forms with the marked ring atom as the out-of-plane atom

the C—C bond lengths <0.01 Å (AS = 1, 2). Neglecting the broad scatter of the ring conformation for the approximately planar cyclopentenones with $\omega < 10°$, it is obvious that the more puckered rings show no appreciable torsion about the double bond. There is no highly puckered structure in the range between $\theta = -54°$ to $54°$, the region for a maximal torsion angle about the C=C bond in the ring. Most conformations are close to the twist form with C(4) and C(5) sticking out of the best plane through the ring ($\omega = \pm 72°$) or the envelope ($\omega = \pm 90°$) with C(5) as the out-of-plane atom.

4. *Cyclohexenones*

The average geometry of the cyclohex-2-en-1-one fragments is shown in Figure 13. It includes values of 115 rings with saturated carbon atoms in the 4-, 5- and 6-position from X-ray structures with AS = 1 and $R < 0.085$. The histograms of the C=O, C—C and C=C bond of the enone fragment are given in Figure 14. The spread of the bond lengths in the enone group seems to be much greater than in the five-membered rings. Close inspection of the structures shows that the values of 1.23–1.25 Å, 1.40–1.44 Å and 1.35–1.36 Å for the C=O, C—C and C=C bond, respectively, belong to enone–enol type structures like 1,3-cyclohexanedione (**20**)^{28} (1.25, 1.41 and 1.35 Å). If those structures are excluded, there is the same tendency as in the acyclic enones that the twisted enone groups tend more towards the values for isolated bonds. Structures with planar enone groups (which offer a better



(20)

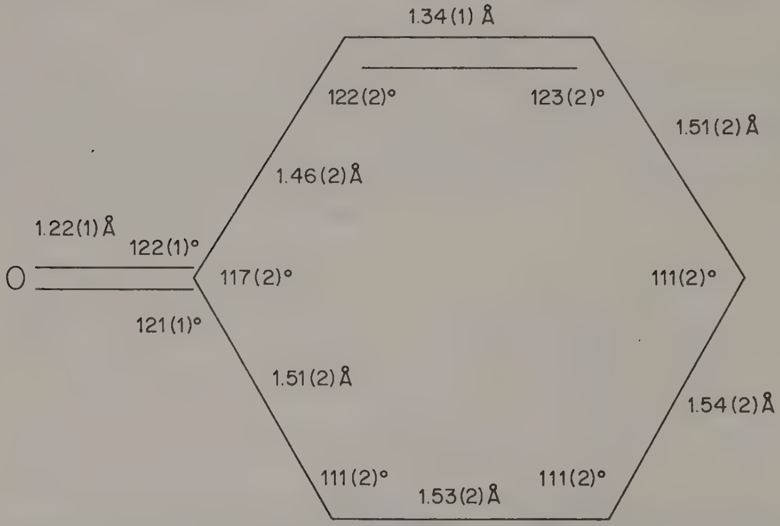


FIGURE 13. Averaged bond lengths (Å) and bond angles (deg) with standard deviations of the cyclohex-2-en-1-one fragment

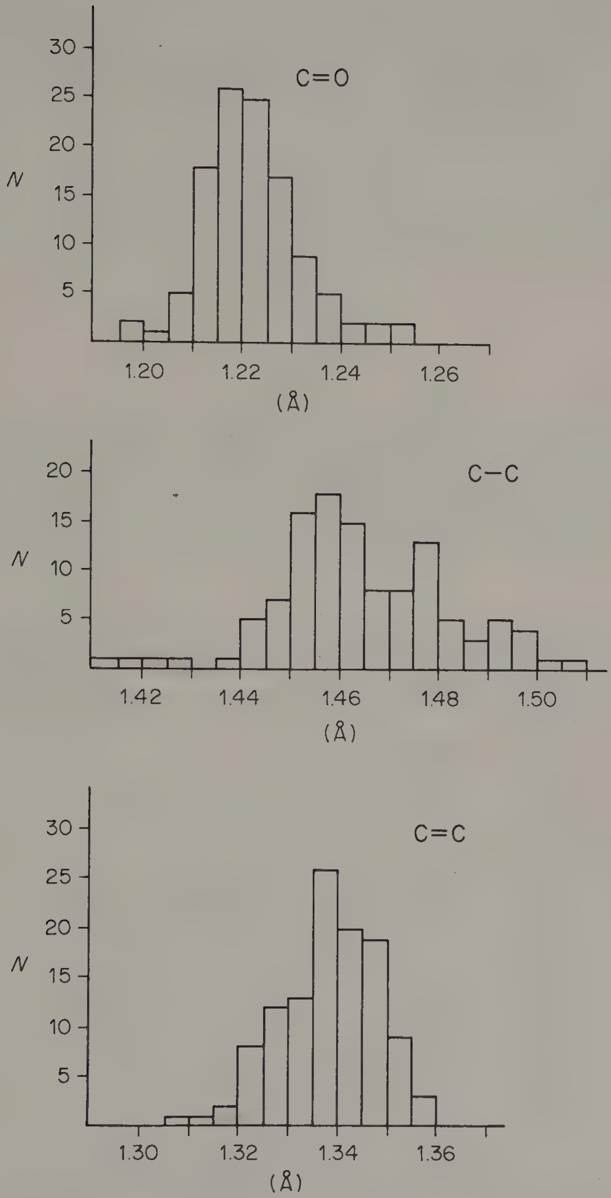
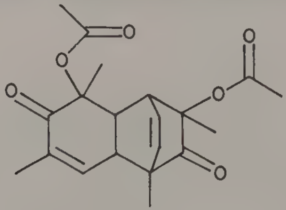


FIGURE 14. Histograms of the bond lengths (Å) of the enone fragments in cyclohexenones

delocalization for the electrons and therefore have elongated C=O bonds) show less puckering of the six-membered ring. This results in an increase in the sum of the bond angles in the ring. This is a possible explanation for the widening of the C(2)—CO—C(6) angle with increase in the C=O bond length. The greatest torsion of the two planes of the π systems, i.e., the carbonyl group and the double bond with 36°, is observed in 1, 4-etheno-2, 8-diacetoxy-2, 4, 6, 8-tetramethyloctahydronaphthal-5-ene-3, 7-dione (**21**)[29]. This structure shows the following bond lengths: C(1)=O (1.21 Å), C(1)—C(2) (1.48 Å) and C(2)=C(3) (1.33 Å). The C—CO—C angle of 113.6° is significantly smaller than the value given for the mean geometry in Figure 13 (the largest value of the torsion angle of the structures used for this figure is 8°). A scatterplot of the angles C(2)—C(1)—C(6) and O=C(1)—C(6) for those enone fragments with no substituents on C(2) and C(6) is shown in Figure 15. The variation of the two angles is obviously not independent (correlation coefficient, 0.71),



(**21**)

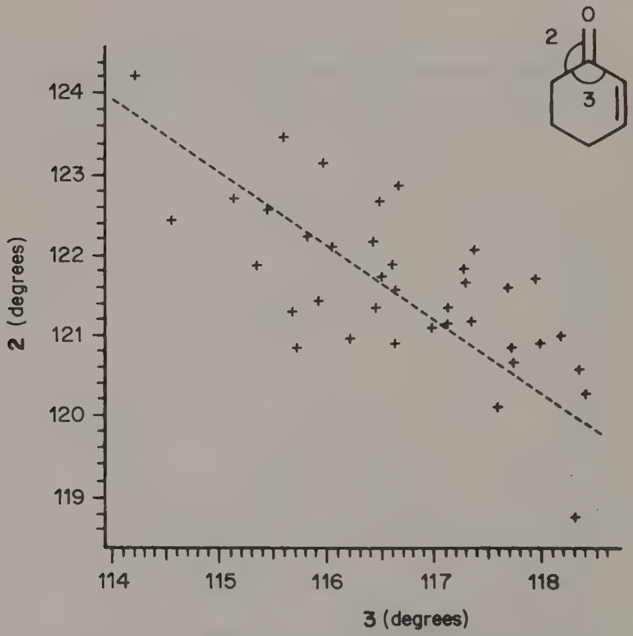
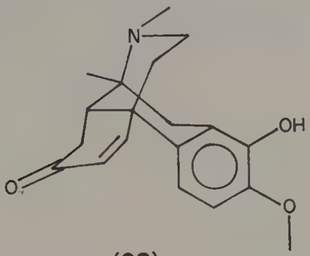


FIGURE 15. Scattergram of the bond angles O=C—C(6) (2) and C(2)—C(1)—C(6) (3) in cyclohexenone rings. The slope of the linear regression line is −0.94, the correlation coefficient is 0.71

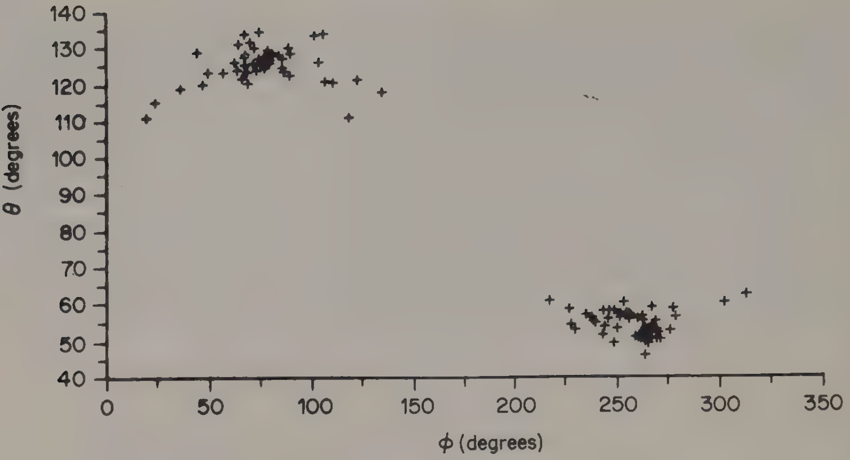
whereas the correlations of these angles with the third angle on the carbonyl group [O═C(1)—C(2)] are not significant (correlation coefficients, 0.42 and 0.33). Because the carbonyl group in all those examples does not deviate appreciably from a planar arrangement, a change of one bond angle cannot be completely independent of the other two. Thus the angle O═C(1)—C(2) seems to be more or less fixed by the enone group. The bond to the sp^3 carbon C(6) then adapts the other two bond angles to the ring geometry. An interesting example is the structure of 4-hydroxy-7-oxo-3-methoxy-17-methyl-5,6-dehydromorphinan (**22**)[30]. It has two independent molecules in the unit cell. The different surrounding of the molecules leads to changes in the enone-ring conformation and to a drastic difference in the two correlated bond angles of the carbonyl group. The values for the angles O═C(1)—C(6) (120.1°, 124.2°) and C(2)—C(1)—C(6) (117.6°, 114.2°) cover practically the whole range of the scatterplot in Figure 15, whereas the angle O═C(1)—C(2) shows a much smaller difference (122.3°, 121.3°).



(22)

A description of the conformation of a six-membered ring needs three parameters[27]. These can be chosen as a parameter Q (Å) for the total puckering amplitude, and two phase angles θ and ϕ (deg) describing the type of conformation. A chair conformation is given by $\theta = 0$ or 180° with arbitrary ϕ, a boat conformation by $\theta = 90°$ and $\phi = 0, 60, 120°, \ldots$ and a twist-boat conformation by $\theta = 90°$ and $\phi = 30, 90, 150°, \cdots$. If the enone group is kept planar, the ring can adopt only a half-boat conformation with C(5) sticking out of the plane. This corresponds to ϕ, θ values of 60°, 125° or 240°, 55° depending on whether C(5) sticks up or down from the least-squares plane through the other ring atoms (which is arbitrary for all structures where the absolute conformation was not determined).

The diagrams in Figure 16 list θ vs. ϕ and θ vs Q for cyclohexenone rings with AS = 1 or 2. It shows two clusters of points in the θ, ϕ diagram of about equal weight, representing these two arbitrary forms of the same puckering as described above. Most of the points lie in the ϕ range of 60–90° and 230–270°, respectively, which represent all conformations between the half chair ($\phi, \theta = 90°, 125°; 270°, 55°$) with C(5) and C(6) bending out of the least-squares plane on opposite sides and a half boat with C(5) sticking out of the plane. The half-chair form forces the carbonyl group out of the plane of the π system of the C═C double bond. This is not correlated with a deviation of the bond around the carbonyl $C(sp^2)$ atom from coplanarity. The maximum deviation of the carbonyl carbon from the plane through its substituents is 0.05 Å and is found in 2, 3, 4, 5, 6-pentamethyl 4, c-5, c-6-trinitrocyclohex-2-en-1-one (**23**)[31] (Figure 17, middle) with a typical half-chair form ring. The θ, Q diagram shows that there is no correlation between the different forms of conformation and the puckering amplitude. To see the influence of the steric effects of the substituents, a subgroup of structures was selected with only hydrogen atoms attached to C(2) and C(6). These structures show much less deviation from planarity of the enone group; the torsion angle O═C—C═C deviates less than 8° from 180° for most of the structures, a few examples having values up to 15°. No difference could be observed in the distribution of the ring conformations.



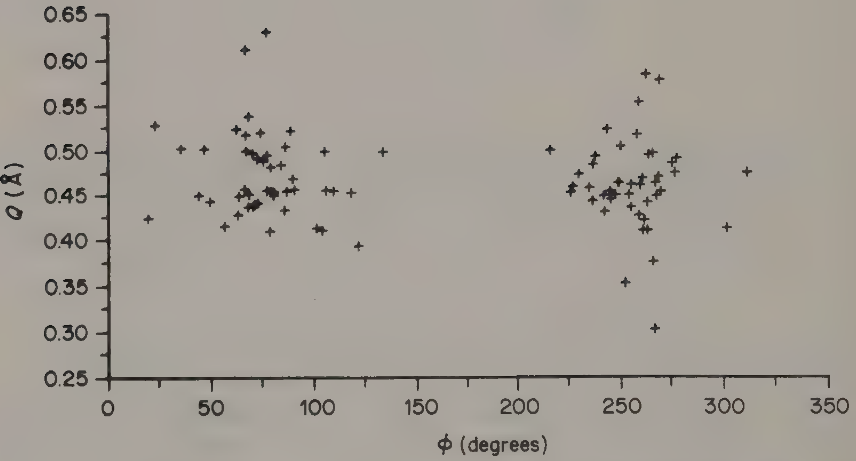


FIGURE 16. Scattergrams of the puckering parameters of cyclohexenone rings. Top: diagram of the two phase angles θ (deg) and ϕ (deg). Bottom: diagram of the total puckering amplitude Q (Å) with the phase angle ϕ is given

It is possible that in fused ring systems certain conformations could be enforced by the ring constraints. However, a selection of structures with no rings fused to the cyclohexenone ring (14 compounds with AS < 3) shows the same variation in the conformation. The typical ring conformations are shown in Figure 17. The top drawing shows the structure of 4, 5-bis(methoxycarbonyl)-6-(*N*′-formyl-*N*, *N*′-dimethylhydrazino)-2-methyl-1-phenylcyclohex-1-en-3-one (**24**)[32] as an example of a half boat, and in the middle, the enone ring of **23** has been chosen as a representative for the half-chair form.

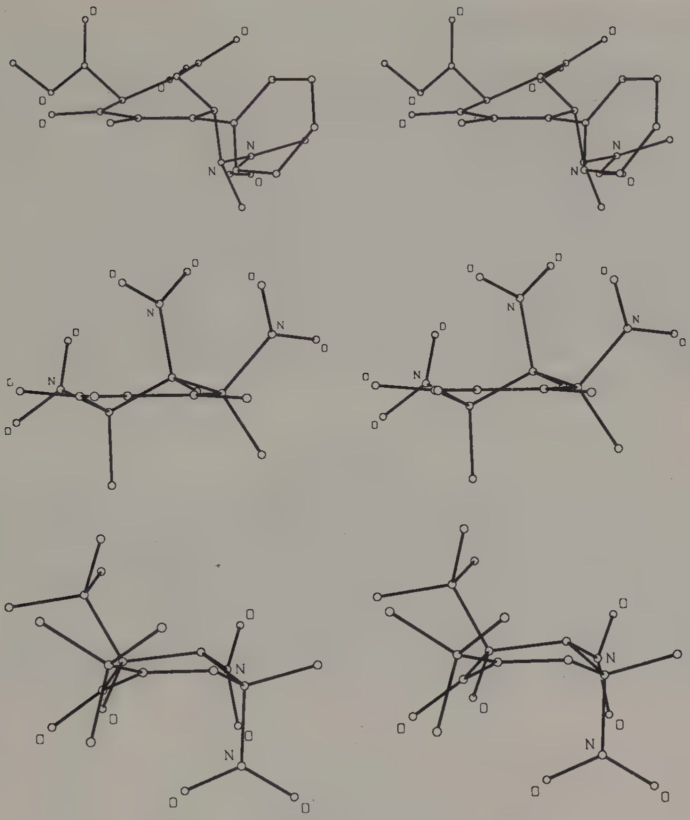
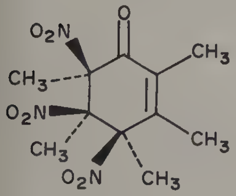
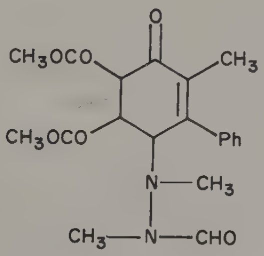


FIGURE 17. Stereoscopic drawings of typical ring conformations in cyclohexenones: half boat in the structure of **24** (top), half-chair form of the ring in **23** (middle) and boat form of the ring in **25** (bottom)

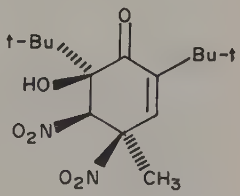
The bottom of Figure 17 shows the structure of 2, 6-di-*t*-butyl-c-6-hydroxy-4-methyl-4, c-5-dinitrocyclohex-2-en-1-one (**25**)[33], which is the only example of a boat form.



(23)



(24)



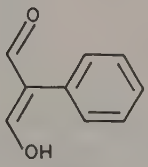
(25)

C. Hydrogen Bonding in Enones

In their analysis of hydrogen bonding to sp^2- and sp^3-hybridized oxygen atoms, Murray-Rust and Glusker[34] show that the highest concentration of hydrogen bonds to carboxyl oxygen occurs along the direction of the conventionally drawn sp^2-type lone-pair orbitals, in the plane of the carbonyl group with its substituents. Both the keto and the enone group show a striking well-resolved concentration of hydrogen bonds along these directions. However, whereas the distribution in the ketones is symmetric, in the enones the concentration of points is almost twice as high on the saturated side. The authors argue that the dipole (or induced dipole) of the enone fragment is asymmetric with a negative charge on the oxygen and a positive charge on C(3), and that the alignment with the dipole of the group forming the hydrogen bond is close to 180° when occupying the lone pair on the saturated side. A hydrogen bond on the other side would form an angle of the two dipoles equal to about 90°. This could be an explanation for the more favored position of the hydrogen bond.

III. ENALS

A total of 116 structures with an enal group were found on the CSD. Figure 18 shows the histogram of the C=O, C—C and C=C bond lengths from 33 enal fragments of structures with $R < 0.08$ and AS = 1. The C=O bond length is somewhat shorter than in the enones, with the exception of the four-membered cyclic enones. The single entry with the long value of 1.238 Å is found in phenylmalondialdehyde (**26**)[35], an enal–enol structure. This molecule shows also the shortest C—C bond (1.431 Å) and one of the longest C=C bonds (1.373 Å). The strong intermolecular hydrogen bond between the two oxygens in the crystal (O···O distance 2.5 Å) obviously favors the delocalization of the π bonds.



(26)

As in the enones there is a tendency of increasing C=O distance with decreasing C—C length (correlation coefficient, 0.64). The longest C—C bond of 1.484 Å is found in *E*-*β*-chloro-*α*-(methoxycarbonyl)-*p*-nitrocinnamaldehyde (**27**)[36] with a corresponding short C=O bond of 1.198 Å. The histogram in Figure 18 for the C=C bond shows two main regions of points. The values around 1.33 Å are observed in enals where the C=C bond is not involved in further delocalization, either because of the lack of unsaturated substituents or because the π systems of such groups are turned out of the enal plane considerably. An example is compound **27**, where both the phenyl and the ester substituent are almost perpendicular to the enal plane. The cluster with values around 1.39 Å belongs to structures with twisted π systems of the C=C bond or to enals with extended delocalized systems. An example of the first group is α-(7-chloro-3, 4-dihydro-4-methyl-3-oxo-1(2*H*)-quinoxazolinyl-benzylidene)malonaldehydic acid ethyl ester (**28**)[37]. The two planes defined by the substituents and the corresponding methylene carbon atom show an angle of about 30° (C=C distance 1.409 Å). The second group can be represented by pyrrole-2, 5-dicarboxaldehyde (**29**)[38] with bond lengths of 1.363–1.398 Å in the four independent molecules in the crystal.

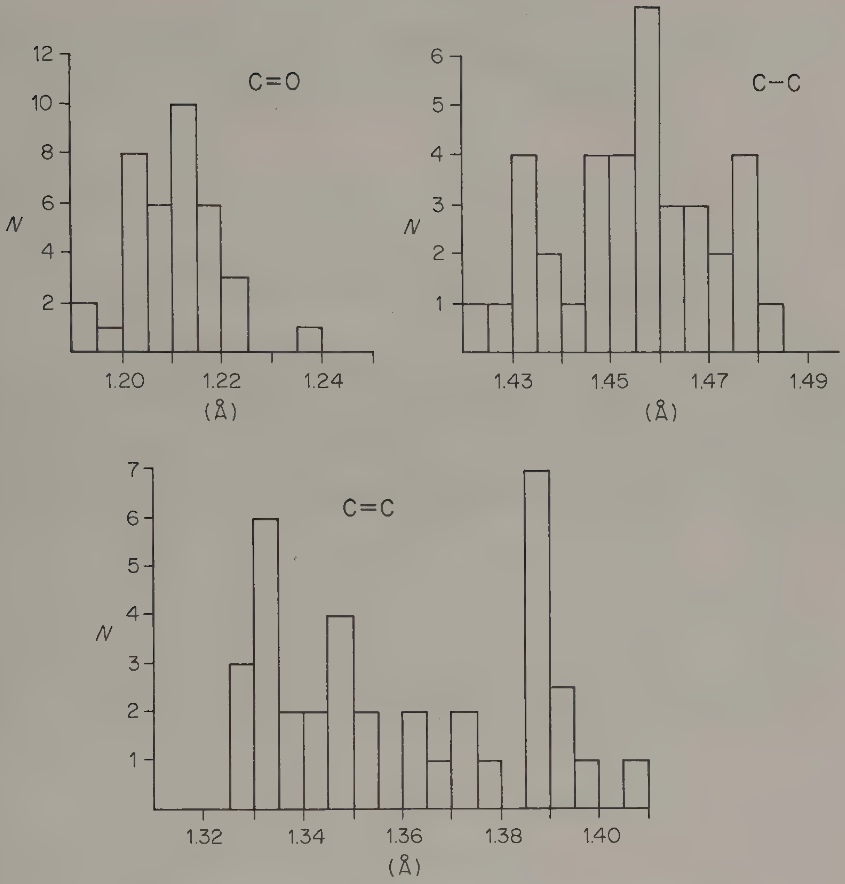
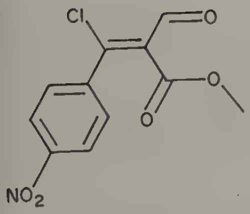
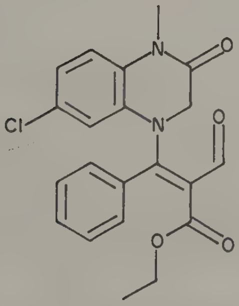


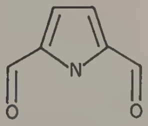
FIGURE 18. Histograms of the bond lengths (Å) in enal fragments



(27)



(28)



(29)

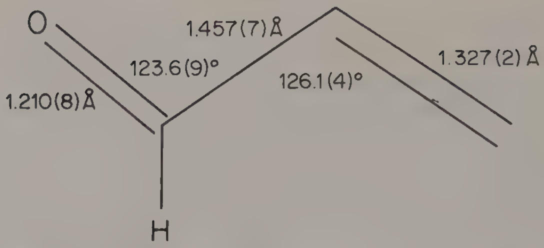


FIGURE 19. Averaged bond lengths (Å) and bond angles (deg) with standard deviations of the enal fragment

In Figure 19 the averaged geometry is given only for the two structures with 'isolated' enal groups, i.e. no additional conjugation and no strain by cyclic substitution. The two molecules are 3-(adamant-1-yl)-3-chloropropenal (**30**)[39] and (5,8-epoxy-5,8-dihydroionylidene)-acetaldehyde (**31**)[40]. A pronounced difference from the enones is seen in the O=C—C angle, which opens in the enals to 124° compared with 120° in the acyclic enones. This is clearly an effect of the carbon substituent in the enones. An extreme value of

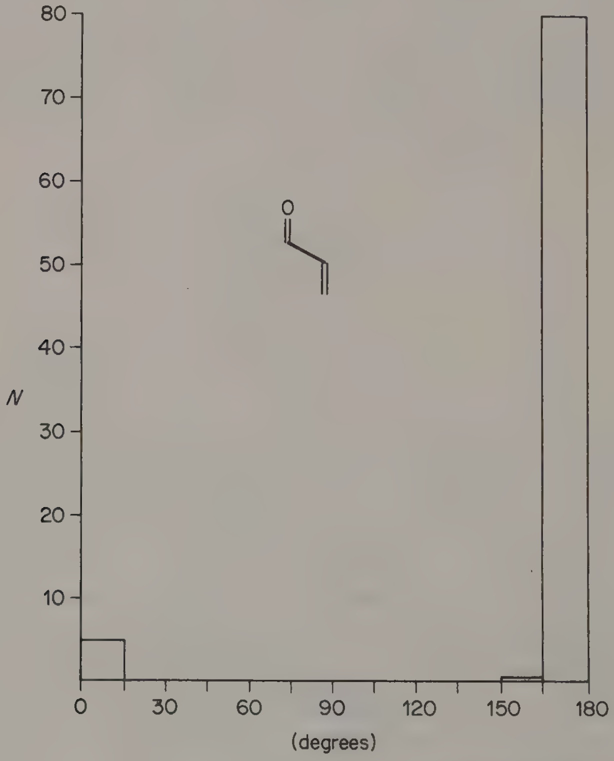
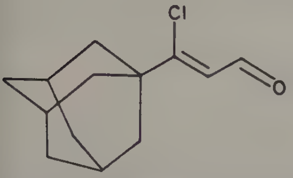
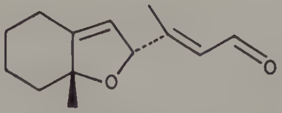


FIGURE 20. Histogram of the C=C—C=O torsion angle (deg, absolute value) in the enal fragments

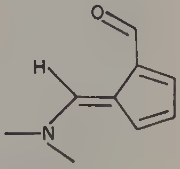
128° can be found in two independent molecules of 2-formyl-6-(*N,N*-dimethylamino)pentafulvene (**32**)^{41}, where the widening can be attributed to steric repulsion between the carbonyl oxygen and the C(6) hydrogen.



(30)

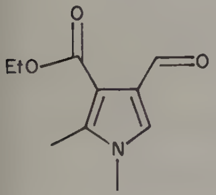


(31)

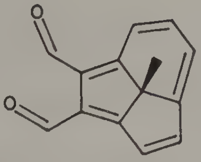


(32)

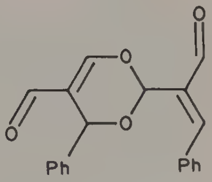
In contrast to the enones, the dominant conformation of the enals is the s-*trans* form as shown by the histogram in Figure 20. In fact there are only four examples of s-*cis* enals. Two of them are in the previously discussed molecules **27** and **28**. The latter is a structure with four independent molecules in the cell and shows two enal groups in the *cis* and six in the *trans* conformation. This mixture of conformations may well be due to hydrogen bonding between the hydrogen atom on the nitrogen and the aldehyde oxygens. The third example is another pyrrole derivative, 3-ethoxycarbonyl-1,2-dimethyl-4-pyrrolecarboxaldehyde (**33**)^{42}. The fourth example is found in 7-methyl-7*H*-cyclopent(*cd*)indene-1,2-dicarboxaldehyde (**34**)^{43}, where one of the two enals has the s-*cis* form. The s-*cis* conformation in the last two mentioned compounds is clearly enforced by steric reasons. It can be seen from the histogram in Figure 20 that there are, unlike the enones, no enal groups that deviate drastically from a planar arrangement. The greatest torsion angle of 18° around the C—C bond is found in 2-(benzylideneacetaldehyde-c)-5-formyl-4-phenyl-4*H*-1,3-dioxin (**35**)^{44} in the phenyl-substituted enal fragment. This is clearly due to the less bulkier aldehyde group of the enal compared with the keto group in the enones.



(33)



(34)



(35)

IV. REFERENCES

1. F. H. Allen, S. A. Bellard, M. D. Brice, B. A. Cartwright, A. Doubleday, H. Higgs, T. Hummelink, B. G. Hummelink-Peters, O. Kennard, W. D. S. Motherwell, J. R. Rodgers and D. G. Watson, *Acta Crystallogr., Sect. B*, **35**, 2331 (1979).
2. P. Seiler, W. B. Schweizer and J. D. Dunitz, *Acta Crystallogr., Sect. B*, **40**, 319 (1984).
3. R. Taylor and O. Kennard, *Acta Crystallogr., Sect. B*, **39**, 517 (1983).
4. W. B. Schweizer and J. D. Dunitz, *Helv. Chim. Acta*, **65**, 1547 (1982).
5. V. Nevalainen, T. A. Pakkanen, T. T. Pakkanen, E. Pohjala and A. Nieminen, *Finn. Chem. Lett.*, 134 (1984).
6. I. Barash, S. Manulis, Y. Kashman, J. P. Springer, M. H. M. Chen, J. Clardy and G. A. Strobel, *Science*, **220**, 1065 (1983).

7. N. V. Kamath and K. Venkatesan, *Acta Crystallogr., Sect. C*, **40**, 559 (1984).
8. P. Uebelhart, A. Baumeler, A. Haag, R. Prewo, J. H. Bieri and C. H. Eugster, *Helv. Chim. Acta*, **69**, 816 (1986).
9. A. Gieren and V. Lamm, *Acta Crystallogr., Sect. C*, **38**, 844 (1982).
10. F. H. Herbstein, M. Kapon, G. M. Reisner and M. B. Rubin, *J. Inclusion Phenomena*, **1**, 233 (1984).
11. N. W. Alcock and J. F. Sawyer, *Acta Crystallogr., Sect. B*, **32**, 285 (1976).
12. K. Peters and H. G. von Schnering, *Chem. Ber.*, **118**, 2147 (1985).
13. H. L. Ammon, *J. Am. Chem. Soc.*, **95**, 7093 (1973).
14. R. C. Benson, W. H. Flygare, M. Oda and R. Breslow, *J. Am. Chem. Soc.*, **95**, 2772 (1973).
15. A. Komornicki, C. E. Dykstra, M. A. Vincent and L. Radom, *J. Am. Chem. Soc.*, **103**, 1652 (1981).
16. L. S. Trifonov, A. S. Orahovats, R. Prewo, J. H. Bieri and H. Heimgartner, *J. Chem. Soc., Chem. Comm.*, 708 (1986).
17. S. M. Krüger, J. A. Kapecki, J. E. Baldwin and I. C. Paul, *J. Chem. Soc.* (*B*), 796 (1969).
18. B. Massim, E. O. Schlemper and P. Crabbé, *J. Chem. Soc., Perkin Trans. 1*, 2337 (1983).
19. E. O. Schlemper, B. Massim and P. Crabbé, *Acta Crystallogr., Sect. C*, **40**, 1455 (1984).
20. R. L. Harlow and S. H. Simonsen, *Cryst. Struct. Commun.*, **6**, 695 (1977).
21. R. L. Eagan, M. A. Ogliaruso, B. H. Arison and J. P. Springer, *J. Org. Chem.*, **49**, 4248 (1984).
22. D. Chadwick, A. C. Legon and D. J. Millen, *J. Chem. Soc., Chem. Commun.*, 302 (1978).
23. Y.-S. Li, *J. Mol. Struct.*, **125**, 117 (1984).
24. A. F. Mishnev, Ya. Ya. Bleidelis, I. A. Milman and Ya. F. Freimanis, *Zh. Strukt. Khim.*, **25**, 161 (1984).
25. T. Date, K. Aoe, K. Kotera and K. Umino, *Chem. Pharm. Bull.*, **22**, 1963 (1974).
26. J. D. Dunitz, *X-ray Analysis and the Structure of Organic Molecules*, Cornell University Press, Ithaca, NY, 1979.
27. D. Cremer and J. A. Pople, *J. Am. Chem. Soc.*, **97**, 1354 (1975).
28. M. C. Etter, Z. Urbanczyk-Lipkowska, D. A. Jahn and J. S. Frye, *J. Am. Chem. Soc.*, **108**, 5871 (1986).
29. B Karlsson, A. M. Pilotti and A. C. Wiehager, *Acta Chem. Scand., Ser. B*, **29**, 1059 (1975).
30. J. I. Minamikawa, K. C. Rice, A. E. Jacobson, A. Brossi, T. H. Williams and J. V. Silverton, *J. Org. Chem.*, **45**, 1901 (1980).
31. M. P. Hartshorn, W. T. Robinson, J. Vaughan, J. M. White and A. R. Whyte, *Aust. J. Chem.*, **38**, 161 (1985).
32. J. A. Moore, O. S. Rothenberger, W. C. Fultz and A. L. Rheingold, *J. Org. Chem.*, **49**, 1261 (1984).
33. M. P. Hartshorn, K. H. Sutton and J. Vaughan, *Aust. J. Chem.*, **36**, 2339 (1983).
34. P. Murray-Rust and J. P. Glusker, *J. Am. Chem. Soc.*, **106**, 1018 (1984).
35. D. Semmingsen, *Acta Chem. Scand., Ser. B*, **31**, 114 (1977).
36. Z. Rappoport and A. Gazit, *J. Org. Chem.*, **51**, 4112 (1986).
37. J. P. Freeman, D. J. Duchamp, C. G. Chidester, G. Slomp, J. Szmuszkovicz and M. Raban, *J. Am. Chem. Soc.*, **104**, 1380 (1982).
38. H. Adams, N. A. Bailey, D. E. Fenton, S. Moss, C. O. Rodriguez de Barbarin and G. Jones, *J. Chem. Soc., Dalton Trans*, **21**, 862 (1985).
39. V. P. Litvinov, V. S. Dermugin, V. I. Shvedov, V. E. Shklover and Yu. T. Struchkov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1858 (1985).
40. M. Acemoglu, R. Prewo, J. H. Bieri and C. H. Eugster, *Helv. Chim. Acta*, **67**, 175 (1984).
41. H. L. Ammon, *Acta Crystallogr., Sect. B*, **30**, 1731 (1974).
42. A. Conde, A. Lopez Castro, R. Marquez, J. P. Declercq and G. Germain, *Acta Crystallogr., Sect. B*, **35**, 2228 (1979).
43. R. Mccague, C. J. Moody, C. W. Rees and D. J. Williams, *J. Chem. Soc., Perkin Trans. 1*, 909 (1984).
44. C. Reichardt and K.-Y. Yun, *Tetrahedron Lett.*, **23**, 3163 (1982).

The Chemistry of Enones
Edited by S. Patai and Z. Rappoport

CHAPTER 3

Conformations, chiroptical and related spectral properties of enones

JACEK GAWRONSKI
Faculty of Chemistry, Adam Mickiewicz University, 60780 Poznan, Poland

I. INTRODUCTION

Enone conformation is best evaluated by the torsional angle ω between the conjugated C=O and C=C bonds (Figure 1). Two conformations with $\omega = 0$ and $\omega = 180°$ are referred to as *planar s-cis* and *planar s-trans*, respectively, and the intermediate conformations are nonplanar.

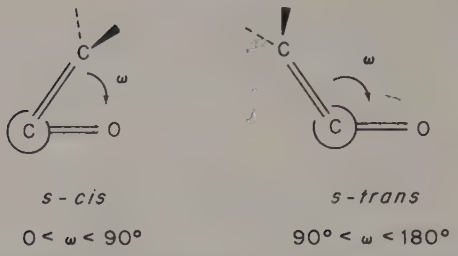
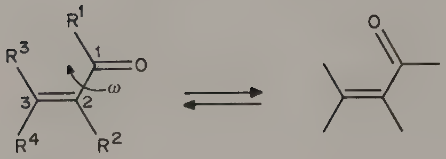
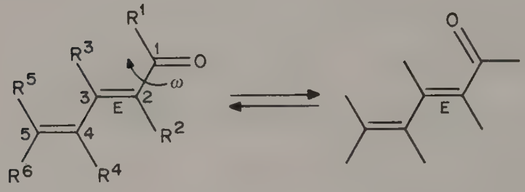


FIGURE 1. Conformation of an enone group with positive helicity ($\omega > 0$)



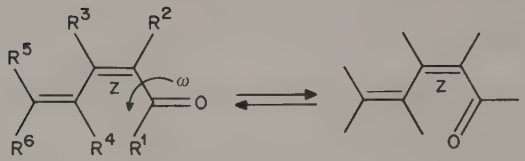
It

Ic



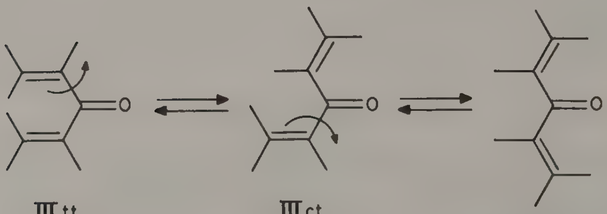
IIEt

IIEc



IIZt

IIZc



IIItt

IIIct

IIIcc

The term 'nearly planar enone group' certainly lacks precision but its frequent appearance can be justified by the observation that conjugation of the C═O and C═C groups and spectral properties determined by it do not change significantly if the torsion angle ω is small. On the other hand, subtle conformational changes can exert significant effect on enone biological activity in steroidal 4-en-3-ones.

Except for highly strained enones in which the C═C bond can be deformed by twisting and/or pyramidalization, the C═C bond is essentially planar. Thus the conformation of the enone group, defined by the angle ω, determines its spectroscopic and chemical properties. Consequently IR, NMR, UV and CD spectroscopic methods can be used for determining the preferred conformation of enones in solution. In addition, solid-state enone conformation is directly provided, when applicable, by X-ray crystallography and conformational data of reasonable accuracy for isolated molecules can be obtained by molecular mechanics calculations.

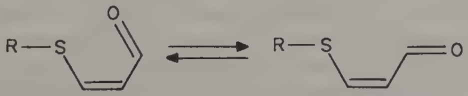
The scope of this chapter includes discussion of conformation of enones (**I**, R^1 = alkyl) and enals (**I**, R^1 = H), linearly conjugated dienones (**II**, R^1 = alkyl) and dienals (**II**, R^1 = H), as well as cross-conjugated dienones (**III**). The substituents R can constitute a part of a ring structure or, with the exception of R^1, they can be heteroatoms (N, O, S, halogen). Occasional reference will be given to compounds with more than two C═C bonds conjugated with the C═O group (polyenones, polyenals).

II. CONFORMATIONS

A. *Ab Initio* and Molecular Mechanics Calculations

Conformational equilibria of enones can be determined by *ab initio* calculations. The accuracy of this approach is exemplified by the results of Houk and coworkers[1] who optimized *s-cis* and *s-trans* conformations of 2-propenal (**1a**) with *ab initio* gradient optimizations using the split-valence 6-31G* basis set. At the 3-21G level calculations erroneously predict the same energy for **1a** in *s-cis* and *s-trans* conformations. However, at the 6-31G* level, the planar *s-trans* conformation is preferred by 1.7 kcal mol^{-1} over the planar *s-cis* conformation, in excellent agreement with experiment and other *ab initio* studies[2]. The calculated geometries are in reasonable agreement with microwave spectral studies in the vapor phase[3]. The rotational barrier of **1a** on going from the *s-trans* to *s-cis* conformation was found to be 8.9 kcal mol^{-1} at the 6-31G*//3-21G level[1]. This is higher than a barrier of 4.0 kcal mol^{-1} in going from the *s-trans* to a nonplanar conformation and a barrier of 6.6 kcal mol^{-1} from the *gauche* to the *s-cis* conformation, as found by a microwave study in the gas phase[4].

Ab initio conformational study of (*Z*)-3-fluorothio-2-propenal (R = F) demonstrated that *s-cis* conformation is favored over *s-trans* conformation by 1.2, 3.8 and 6.5 kcal mol^{-1} at STO-3G, STO-3G* and 6-31G* levels, respectively. This conformational preference is due to 1,5-type attractive forces between sulfur and oxygen, that qualitatively can be rationalized by electrostatic effects of dipolar character between F—S and C═O bonds[15a]. Understandably, the attractive forces between sulfur and oxygen are much weaker in (*Z*)-3-methylthio-2-propenal (R = Me) and the *s-trans* conformer is more stable by 1.2 kcal mol^{-1} [15b].



Despite their importance *ab initio* methods require prohibitive amounts of computer time to calculate structures and energies of even the simplest molecules; hence the molecular mechanics calculations are becoming increasingly popular.

TABLE 1. Calculated *s-cis* (ω_1) and *s-trans* (ω_2) conformations and energies for enals and enones **I**[a]

Compound	R^1	R^2	R^3	R^4	ω_1	ω_2	$\Delta E(\omega_1 - \omega_2)$ (kcal mol^{-1})
1a	H	H	H	H	0.0	180.0	1.64
1b	H	Me	H	H	0.0	180.0	3.06
1c	H	H	Me	H	13.4	180.0	1.34
1d	H	H	H	Me	0.0	180.0	1.82
1e	H	Me	Me	H	18.1	180.0	2.65
1f	H	Me	H	Me	2.8	178.6	3.26
1g	H	H	Me	Me	14.9	180.0	1.41
1h	H	Me	Me	Me	22.2	172.9	3.06
2a	Me	H	H	H	0.0	180.0	0.56
2b	Me	Me	H	H	0.0	180.0	1.57
2c	Me	H	Me	H	12.9	155.1	– 1.74
2d	Me	H	H	Me	0.0	180.0	0.71
2e	Me	Me	Me	H	34.8	142.0	– 1.47
2f	Me	Me	H	Me	6.9	177.6	1.70
2g	Me	H	Me	Me	18.8	151.2	– 1.74
2h	Me	Me	Me	Me	48.9	139.7	– 0.60

[a] Reprinted with permission from T. Liljefors and N. L. Allinger, *J. Am. Chem. Soc.*, **98**, 2745 (1976). Copyright (1976) American Chemical Society.

Conformations and energies of acrolein (**1a**), 3-buten-2-one (**2a**) and their methyl derivatives, calculated by Liljefors and Allinger[5] by the use of the force field for delocalized systems, are shown in Table 1. The aldehydes (**1a–1h**) are all predicted to exist in a planar or close to planar *s-trans* conformation to the extent of 90% or more at room temperature in the vapor phase. The higher energy *s-cis* conformations of acrolein (**1a**), methacrolein (**1b**) and crotonaldehyde (**1d**) are also predicted to be planar. In other aldehydes a nonplanar ($\omega > 0$) rather than the planar *s-cis* conformation is more stable, largest deviations from planarity being due to a methyl group as R^3 substituent. However, the energy difference between the nonplanar and planar *s-cis* conformation is small (0.5 kcal or less).

Conformational equilibrium in enones appears more sensitive to substitution pattern than is the case for the corresponding enals. As in the case of enals, the geometry of the most stable enone conformation is mainly determined by the substituent R^3. When R^1 and R^3 are methyl groups, their repulsive interaction is relieved by twisting around the $C_{(1)}$—$C_{(2)}$ partial double bond. Thus, for $R^3 = H$ a planar *s-trans* conformation is calculated to be most stable (**2a**, **2b**, **2d**, **2f**), while in the remaining cases ($R^3 = Me$) it is the nonplanar *s-cis* conformation predicted to dominate the conformational equilibrium.

The calculated barriers to rotation, $\Delta E(90° - \omega_2)$, around the partial double bond $C_{(1)}$—$C_{(2)}$ are in the oder 5–7.2 kcal mol^{-1} for enals. Again, repulsion between $R^3 = Me$ and the aldehyde hydrogen increases the energy of the planar *s-trans* conformation and lowers the barrier to rotation by about 1.5 kcal mol^{-1}. In the case of enones the barrier between the lowest energy conformation and the other stable conformation is generally less than 5.5 kcal mol^{-1}. Figure 2 shows calculated potential curves for enones **2c**, **2e**, **2g** and **2h**. The barrier to rotation is at approximately $\omega = 110°$ and it is less than 2 kcal mol^{-1} for enones **2e** and **2h**, which have methyl substituents for both R^2 and R^3. For the fully methylated enone **2h** the more important barriers appear at $\omega = 0$ and $\omega = 180°$.

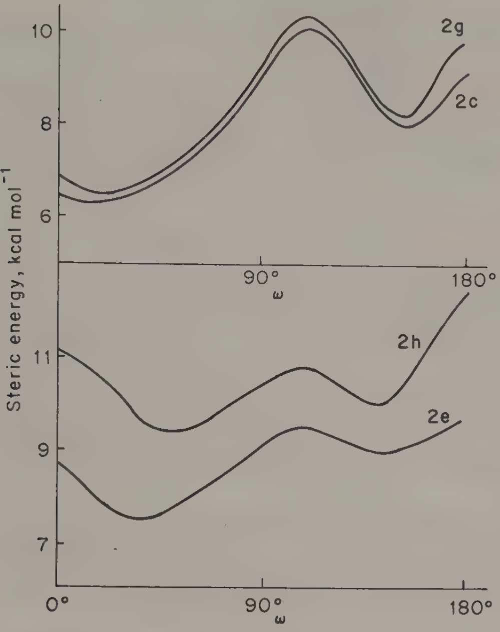
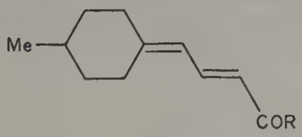


FIGURE 2. Calculated potential curves for enones **2c**, **2e**, **2g** and **2h**. Reprinted with permission from T. Liljefors and N. L. Allinger, *J. Am. Chem. Soc.*, **98**, 2745 (1976). Copyright (1976) American Chemical Society

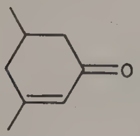
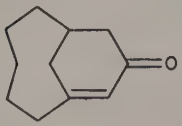
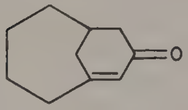
As expected, the calculated steric energy differences between planar *s-cis* and *s-trans* conformations of *E* and *Z* dienals and dienones **3–6** follow the trend already discussed for structurally equivalent enals **1c**, **1d** and enones **2c**, **2d**[6].



	R	ΔE(*s-cis–s-trans*) kcal mol^{-1}
(3)	H	1.64
(4)	Me	0.54
(5)	H	2.19
(6)	Me	−1.82

In bicyclic bridgehead enones of the [*m.n.*1] type ($m = 5,4,3$; $n = 3,2$) inherent strain is released in another way. Molecular mechanics calculations show that while the C=O and C=C bonds remain nearly coplanar, the C=C bond is increasingly deformed upon shortening the methylene bridges (m, n)[7]. Table 2 shows the calculated twisting and pyramidal deformations of the C=C bond with the increasing inherent strain of the bicyclic enones **8–11**. It is seen that in monocyclic and large bicyclic enones there is little or no strain and so there is little twisting deformation (i.e. twisting the planes at each end of the C=C bond) as well as pyramidal deformation (i.e. the deformation of each end of the

TABLE 2. Calculated C=C bond deformations[a]

Compound	Average twisting deformation (deg)	Pyramidal deformation (deg)	C=C deformation (kcal mol^{-1})	Inherent deformation (kcal mol^{-1})
(**7**) 	2.5	2 and 4	0.2	3.4
(**8**) 	4	1 and 9	0.5	16.9
(**9**) 	14	14 and 21	4.7	17.7
(**10**) 	21	19 and 37	11.3	21.3
(**11**) 	36	29 and 60	30.5	32.3

[a] Taken from H. O. House, in *Stereochemistry and Reactivity of Systems Containing π Electrons* (Ed. W. H. Watson), Verlag Chemie Int., Deerfield Beach, 1983, p. 287 and reproduced by permission of Verlag Chemie, GmbH, Weinheim

C=C bond from a planar structure toward the pyramidal structure). Significant strain (above 10 kcal mol^{-1}) localized in the C=C bond begins with the [3.3.1] system (**10**) and a very large amount of strain is predicted for the [3.2.1] system (**11**).

B. Infrared Spectroscopy

Measurement of the C=O and C=C stretching bands in the 1750–1500 cm^{-1} region is conveniently used for establishing enone conformation. The assessment of enone conformation is based on the analysis of the following parameters: (i) the position of the $\nu_{C=O}$ and $\nu_{C=C}$ bands; (ii) the separation of the C=O and C=C stretching frequencies: $\Delta\nu = \nu_{C=O} - \nu_{C=C}$; and (iii) the ratio of integrated band intensities: $r_i = A_{C=O}/A_{C=C}$.

It has been found by Braude and Timmons[8] and Timmons and coworkers[9] that the carbonyl group in *s-cis* conformation absorbs invariably at higher frequencies than does that in *s-trans* conformation, the typical difference being 20–25 cm^{-1}. Since the C=O bond order is reduced in the *s-trans* conformation **B** due to the effect of conjugation, $\nu_{C=O}$ values are lower. Polar solvents and substituents stabilize form **B** and shift $\nu_{C=O}$ to lower wave numbers in both conformations. The conformational and substitution effect is illustrated by the data for cyclic enones **12** and **13** of unambiguous *s-trans* and *s-cis* conformation (Table 3).

(A) (B)

Due to greater coupling between the two vibrations in *s-cis* conformation the separation of the C=O and C=C frequencies ($\Delta\nu$) is greater in *s-cis* conformation[9,10]:

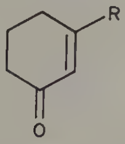
s-cis	$\Delta\nu > 60\text{–}70\ \mathrm{cm}^{-1}$
s-trans	$\Delta\nu < 60\text{–}70\ \mathrm{cm}^{-1}$

Table 4 contains the IR data for some representative acyclic enals and enones. The higher frequency $\nu_{C=O}$ band is assigned to the **Ic** conformer, the opposite assignment is made for the $\nu_{C=C}$ bands. This is in agreement with the calculated vibrational spectra for **Ic** and **It** conformers of 3-buten-2-one (**2a**)[11].

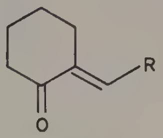
As can be seen enals ($R^1 = H$) prefer *s-trans* conformation, in agreement with the calculated vibrational spectra for this conformation[11]. As shown by the IR spectra, the amount of *s-cis* acrolein (**1a**), normally about 5%, could be enriched to about 28% by trapping from thermal molecular beams with temperatures between 284 and 890 K into an argon matrix[24].

Enone (R^1 = alkyl, aryl) *s-trans* conformation is stabilized for R^2 = alkyl and $R^3 = H$ (**2b, 2f**), while *s-cis* conformation is favored for $R^2 = H$ and R^3 = alkyl[25] (**2c, 2g, 14c, 14e**). Bulky R^1 substituents (Ph, Bu^t) tend to shift conformational equilibrium to a nonplanar *s-cis* (**14a**) or planar *s-cis* (**14d, 17**), even in the absence of an R^3

TABLE 3. IR data for cyclic *s-trans* and *s-cis* enones (in CCl_4)



(**12**)



(**13**)

(**a**) R = H
(**b**) R = Me
(**c**) R = Ph
(**d**) R = Cl
(**e**) $R = NMe_2$

Compound	$\nu_{C=O}$ (cm^{-1})	$\nu_{C=C}$ (cm^{-1})	$\Delta\nu$ (cm^{-1})	r_i	Reference
12a	1691 1674[a]	1621	53–70	110	12
13a	1697	1618	79	2.5	13
12b[b]	1680 1672[a]	1635	37–45	6.6	14
13b[b]	1693	1622	71	1.1	14
12c	1668	1613	55	6.0	
13c	1691	1601	90	0.8	13
12d	1688 1655[a]	1612	43–76	4.7	12
13d	1698	1580	108	0.9	16
12e[b]	1639	1571	68	0.5	17
13e[b]	1656	1555	101	0.4	17

[a] Splitting due to Fermi resonance with the first overtone of the out-of-plane bending vibration of the $H_{(2)}$ atom.
[b] Solvent C_2Cl_4.

TABLE 4. IR data for acyclic enals and enones **I** (in CCl_4)

Compound	R^1	R^2	R^3	R^4	$\nu_{C=O}$ (cm^{-1})	$\nu_{C=C}$ (cm^{-1})	$\Delta\nu$ (cm^{-1})	r_i	Reference
1a	H	H	H	H	1704	1618	86	33	18
1b	H	Me	H	H	1702	1638	64	9.5	19
1d	H	H	H	Me	1700	1644	56	6.1	19
1g	H	H	Me	Me	1686	1638	48	5.4	19
1h	H	Me	Me	Me	1681	1643	38	3.0	20
2a	Me	H	H	H	1706 1685	1618	88 67	7.0	18
2b	Me	Me	H	H	1684	1631	53	15	9
2c^a	Me	H	Me	H	1699	1618	81	1.6	21
2d^a	Me	H	H	Me	1705 1684	1634 1645	71 39	0.8 26	21
2e	Me	Me	Me	H	1696	1626	70	2.6	19
2f	Me	Me	H	Me	1674	1647	27	5.8	9
2g	Me	H	Me	Me	1693	1621	72	0.7	9
2h	Me	Me	Me	Me	1690	1622	68	1.9	9
14a	Bu^t	H	H	H	1696	1609	87	2.8	18
14b■	Bu^t	Me	H	H	1692 1676	1624	68 52	8.0 7.4	22
14c^a	Bu^t	H	Me	H	1692	1620	72	1.6	21
14d^a	Bu^t	H	H	Me	1697	1632	65	0.8	21
14e	Bu^t	H	Me	Me	1678	1617	61	1.0	13
14f	Bu^t	Me	Me	Me	1689	1621	67	7.5	9
15	H	H	H	Ph	1687	1629	58	7.3	23
16	Me	H	H	Ph	1697 1674	1612 1628	85 46	0.7 10.2	23
17	Ph	H	H	Ph	1670 1648	1610 1620	70 28	0.6 5.5	23

[a] In hexane.

alkyl substituent. Nonplanar *s-cis* conformations are dominant for R^2, R^3 substituted enones **2e**, **2h** and **14f**. In a number of cases both conformers (**Ic**, **It**) are present in solution, as evidenced by double enone $\nu_{C=O}$ and $\nu_{C=C}$ absorption bands. This is the case of enones having $R^1 = Me$ and $R^2 = R^3 = H$ (**2a**, **2d**, **16**). From the analysis of band intensities of 3-buten-2-one (**2a**) at temperatures between 163 K and 473 K it was found that ΔH (*s-cis–s-trans*) is 0.565 ± 0.052 kcal mol^{-1} in the vapor phase[26]. In one case (**14b**) the two carbonyl bands were attributed to *s-trans* nonplanar ($\omega = 120°$) and *s-trans* planar conformations[22].

Effect of substitution of the enone group on the $\nu_{C=O}$ and $\nu_{C=C}$ positions is summarized in Table 5.

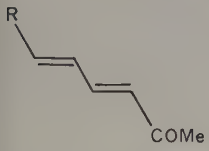
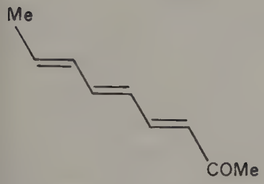
IR data for acyclic dienones and trienones (Table 6) are consistent with those for the corresponding enones[27]. The $\nu_{C=O}$ frequency is ca 10 cm^{-1} lower in dienones compared to enones, yet the difference of $\nu_{C=O}$ between the **IIc** and **IIt** conformers (20 ± 3 cm^{-1}) is nearly the same as in enones. The assignment of $\nu_{C=C}$ in dienones and trienones (and hence $\Delta\nu$) is frequently met with ambiguity. In the case of *E*-dienones **18** and **19** and *E*-trienone **20** in which R^3 and R^4 are hydrogen atoms, bands of both **IIEt** and **IIEc** conformers are seen in the IR spectra. The *Z*-isomers **21** and **22** exhibit a single carbonyl band, in agreement with the expectation for a single **IIZc** conformer. The dienals **3** and **5** exist in a single *s-trans* conformation regardless of the *E* or *Z* configuration, according to the IR data.

TABLE 5. IR absorption data (in chloroform) for enones in *s-cis* and *s-trans* conformation[a]

Substituents in positions	$\nu_{C=O}$ (cm^{-1}) Ic	$\nu_{C=O}$ (cm^{-1}) It	$\nu_{C=C}$ (cm^{-1}) Ic	$\nu_{C=C}$ (cm^{-1}) It	$\Delta\nu$ (cm^{-1}) Ic	$\Delta\nu$ (cm^{-1}) It
—	1702 ± 6	1684 ± 5	1615 ± 5	1615 ± 5	87	69
2	1699 ± 5	1678 ± 6	1618 ± 5	1625 ± 7	81	53
3	1696 ± 6	1676 ± 9	1626 ± 8	1632 ± 14	70	44
2,3	1692 ± 4	1670 ± 5	1622 ± 5	1638 ± 10	70	32
3,3	1690 ± 4	1675 ± 5	1620 ± 7	1635 ± 2	70	40
2,3,3	1685 ± 7	1669 ± 4	1622 ± 5	1635 ± 4	63	34

[a] Reproduced by permission of Pergamon Press from R. Barlet, M. Montagne and P. Arnaud, *Spectrochim. Acta*, **25A**, 1081 (1969).

TABLE 6. IR data for dienones and trienones[6,27]

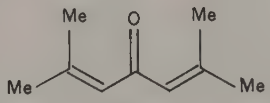
Compound		R	$\nu_{C=O}$	$\nu_{C=C}$	Solvent
	**3**		1680	1630 1570	neat
	5		1665	1630 1570	neat
	18	Me	1690 1670	1643 1596	CCl_4
	19	Ph	1693 1676 1657	1626 1615 1601 1592	CCl_4
	**20**		1681 1663	1640 1611 1580	neat
	**21**	Me	1690	1634 1580	CCl_4
	22	Ph	1685	1615 1581 1568	CCl_4

It has been found that the intensities of the $\nu_{C=O}$ and $\nu_{C=C}$ bands vary with enone conformation, the former being higher in *s-trans* enones, the latter being higher in *s-cis* enones. As it is rather inconvenient to compare absolute band intensities of different compounds, Erskine and Waight have introduced the ratio of integrated band intensities, $r_i = (\varepsilon_{C=O}/\varepsilon_{C=C})$, as another measure of enone conformation[13]. The r_i values, with corrections of Cottee and coworkers[9], are as follows: *s-cis*, $0.6 < r_i < 3.5$; *s-trans*, $r_i > 5.2$. Schrader and coworkers found the following ratios of intensity in the IR and Raman spectra, based on model calculations[28]:

	s-trans *s-cis*
IR	$2.6 < r_i < 2.6$
Raman	$0.5 < r_i < 0.5$

Table 3 contains r_i data for enones of well-defined conformation, while Table 4 gives examples of r_i values for acyclic enones. As can be seen, both $\Delta\nu$ and r_i values give consistent indication of enone conformation.

One of the reasons for small r_i values for enones of *s-cis* conformation is the presence of vibrational coupling in these species, as demonstrated by isotope substitution studies[29]. Low r_i value allows one to assign *s-cis* conformation to the cross-conjugated dienone, phorone (**23**)[12].



(**23**)

$\nu_{C=O}$ 1678 cm^{-1}
$\nu_{C=C}$ 1637, 1619 cm^{-1}
r_i 0.15 (in CCl_4)

Enones of nonplanar conformation (e.g. **14f**, Table 4) give high r_i values, on account of reduced vibrational coupling. However the r_i parameter does not allow one to distinguish *s-cis* and *s-trans* conformations of 3-dialkylamino-substituted enones[17]. This can be done with the help of the $\Delta\nu$ value, as shown by the IR data for selected heterosubstituted enones (Table 7).

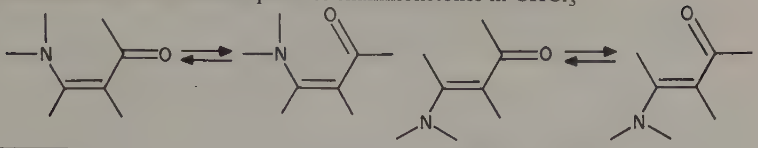
The conformations of $C_{(3)}$-heterosubstituted enones are comparable to those of the corresponding methyl analogs (cf. Table 4). Due to lowering of the $\nu_{C=C}$ frequencies the $\Delta\nu$ values for $C_{(3)}$-heterosubstituted enones are higher than those of alkyl-substituted enones. Thus, $\Delta\nu$ values for the chloroenone **24** and for 3-penten-2-one (**2d**), both in *s-trans*

TABLE 7. IR data for heterosubstituted acyclic enones **I** (in CCl_4 or C_2Cl_4)

Compound	R^1	R^2	R^3	R^4	$\nu_{C=O}$ (cm^{-1})	$\nu_{C=C}$ (cm^{-1})	$\Delta\nu$ (cm^{-1})	Reference
24	Me	H	H	Cl	1697 1686	— 1583	— 103	30
25[a]	Me	H	H	OMe	1697 1662	1601 1626	96 36	31
26	Me	H	H	NMe_2	1673 1623	1586	87 37	32
27	Me	H	H	NMe_3^+	1686	1645	41	33
28	Me	Me	H	Cl	1685	1610	75	16
29[a]	Me	Me	H	OMe	1693 1667	1604 1646	89 21	31
30	Me	Me	H	NMe_2	1670 1609	1576 1565	94 44	34
31	Me	H	Me	Cl	1705 1675	 1610	95 65	16
32	Me	H	Me	OMe	1689	1590	99	23
33	Me	H	OMe	Me	1685 1660	1599 1632	86 28	23
34	Me	H	Me	NMe_2	1653	1553	100	17
35	Me	Me	Me	Cl	1700	1612	88	16
36	Bu^t	H	H	Cl	1696	1595	101	30
37	Bu^t	H	H	OMe	1689	1596	93	31
38	Bu^t	H	H	NMe_2	1665	1584	81	32
39	Bu^t	H	H	NMe_3^+	1704	1642	62	33

[a] $\nu_{C=O}$ and $\nu_{C=C}$ bands are further split due to the presence of the —OMe rotamers.

TABLE 8. Predictions for the IR absorption of enaminoketones in $CHCl_3$[a]



$\nu_{C=O}$ (cm^{-1})	1615	1640	1595	1620
$\nu_{C=C}$ (cm^{-1}	1585	1565	1550	1530
$\Delta\nu$ (cm^{-1})	30	75	45	90

[a] Reproduced by permission of Pergamon Press from D. Smith and P. J. Taylor, *Spectrochim. Acta*, **32A**, 1477 (1976).

conformation, are correspondingly 103 cm^{-1} and 39 cm^{-1}. This does not apply to trimethylammonium-substituted enones **27** and **39**, which show IR frequencies close to the methyl analogs **2d** and **14d**. Conformation of enones **32** and **33** is worth mentioning. Enone **32** exists in solution in a single *s-cis* conformation, according to the IR data, while enone **33** is mostly in *s-trans* conformation. The difference is due to the diminished steric interaction between $R^1 = Me$ and $R^3 = OMe$ in *s-trans* **33**, as opposed to the more severe $R^1 = Me$ and $R^3 = Me$ interaction in **32**.

The combined effect of $C_{(3)}$-amino group configuration and enone conformation on the position of IR bands in enaminoketones is shown in Table 8[35].

C. Ultraviolet Spectroscopy

1. Transitions

Acrolein (**1a**) is the prototype for conjugated carbonyl molecules and its electronic states have been studied both experimentally and theoretically[36]. The importance of the *s-cis* conformer of **1a** stems from the much debated *s-cis–s-trans* photoisomerization process and the reversible ring closure of acrolein to an oxetane intermediate. As the molecule exists almost exclusively in *s-trans* conformation, its electronic states in *s-cis* conformation can most straightforwardly be tested through *ab initio* and semiempirical calculations.

Although calculated energy differences for ground and excited states frequently differ significantly from those obtained experimentally, correct order of the states is provided by numerous calculations. *Ab initio* SCF calculations by Dykstra[37], later challenged by Davidson and Nitzsche[38], gave planar ground and lowest excited singlet and triplet states for *s-trans* and *s-cis* conformations of acrolein. The π–π^* states were calculated very close energetically to the n–π^* states and the manifold of the excited states showed only minor differences between the *s-cis* and *s-trans* forms. The recent semiempirical calculation of Boerth[36], with the use of the INDOUV valence-shell method developed by Van-Catledge, gave good reproduction of the ordering of excitations to the non-Rydberg states and statisfactory agreement between calculated and experimental energies of the π–π^* states was obtained. In addition to acrolein (**1a**), *trans*-crotonaldehyde (**1d**), 3-buten-2-one (**2a**) and 3-penten-2-one (**2d**) singlet excitation energies were calculated for the planar conformations shown in Table 9. The n–π^* transition is the lowest in energy, in acrolein experimentally found at 3.0–3.9 eV. The 0—0 bands for both singlet and triplet are the most intense bands in the n–π^* system in acrolein, the singlet identified experimentally at 3.21 eV and the triplet at 3.01 eV[39]. Alkyl substitution produces in carbonyl systems a blue shift in the n–π^* bands[40] and this is well reproduced by the results of INDOUV

TABLE 9. INDOUV vertical excitation energies and oscillator strengths[a] for simple enals and enones

State symmetry (excitation type)	**1a**, *s-trans*		**1d**, *s-trans*		**2a**, *s-cis*		**2d**, *s-cis*	
	ΔE	f	ΔE	f	ΔE	f	ΔE	f
A'' (n$-\pi_1^*$)	2.59 (2.10)	6×10^{-5}	2.63 (2.14)	2×10^{-5}	2.61 (2.17)	4×10^{-7}	2.66 (2.23)	3×10^{-6}
A'' (n$\sigma-\pi_1^*$)	4.46 (3.75)	0.002	4.48 (3.79)	0.003	4.48 (3.84)	0.001	4.53 (3.92)	0.001
A'' (n$-\pi_2^*$)	6.19 (5.95)	0.002	5.90 (5.63)	4×10^{-4}	5.83 (5.61)	0.002	5.64 (5.40)	7×10^{-5}
A' ($\pi_2-\pi_1^*$)	6.39 (3.19)	0.763	6.16 (3.09)	0.862	6.15 (3.27)	0.337	5.90 (3.29)	0.444
A'' ($\sigma_{\mathrm{CC,CH}}-\pi_1^*$)	7.36 (7.04)	5×10^{-4}	7.24 (6.95)	9×10^{-6}	7.25 (6.98)	1×10^{-4}	7.04 (6.85)	0.002
A' ($\pi_2-\pi_1^*$)	7.98 (4.75)	0.011	7.81 (4.66)	0.008	8.15 (4.71)	0.260	7.91 (4.88)	0.220

[a] Energies (ΔE, in eV) and oscillator strengths (f) are for transitions from the ground state to the excited single states. Transition energies to the excited triplet states are given in parentheses.

Reprinted with permission from Boerth, *J. Org. Chem.*, **47**, 4085 (1982). Copyright (1982) American Chemical Society.

calculations (Table 9), the relative order of transition energies, **1a** < **2a** < **1d** < **2d**, matching that found experimentally. As the n–π^* excitation reduces the charge on an oxygen atom, hydrogen bonding interactions of the solvent and the carbonyl group also result in a blue shift of the n–π^* bands[41,42].

Of other calculated transitions (Table 9) the π_2–π_1^* transition is well-documented experimentally. The singlet π–π^* band system in acrolein is centered at 5.96 eV, as compared to the calculated value 6.39 eV. This band undergoes red shift in polar media and is also red shifted by alkyl substitution (Woodward rules[43], *vide infra*). The calculation delivers the transition energies in the expected order, i.e. decreasing with substitution. Interestingly, the $^3A'$ (π_2–π_1^*) state is calculated to lie in the proximity of the $^3A''$ (n–π_1^*) state. Experimentally, a low-lying triplet at 3.05 eV has been assigned to the $^3A'$ (π–π^*) state[44].

The π–π^* band, dominating the UV region spectra of enones and enals, has received much attention. Because of its intensity (ε_{exp} *ca* 10^4) and accessibility (experimentally found in the range 200–250 nm, i.e. 6.2–5.0 eV) it is conveniently used for analytical purposes. The accumulated evidence, particularly that from the CD spectroscopy (*vide infra*), point to the composite nature of the experimental π–π^* enone (enal) band.

Liljefors and Allinger have addressed this problem in their VESCF–CI calculation of electronic absorption spectra of enals and enones[5]. Inclusion in the configuration interaction of all singly and doubly excited configurations yielded two transitions to occur in the vicinity of the experimental absorption maximum. Summation of Gaussian curves representing the two calculated bands resulted in most cases in a new single broad band with a maximum comparing favorably with the experimental one (Figure 3). Table 10 shows the calculated and experimental π–π^* bands for simple enals and enones, using the conformer geometries and populations calculated earlier by molecular mechanics[5]. The experimental and calculated values agree within 0.14 eV, with the exception of **2g** (0.22 eV). The VESCF–CI calculations correctly reproduce the progressive alkyl substitution effect on the position of the π–π^* band maximum. For highly alkylated enones **2g** and **2h** two separate π–π^* bands are predicted by calculation; the short-wavelength maximum (*ca* 190 nm) has not yet been observed in practice. A further point of interest is the difference in

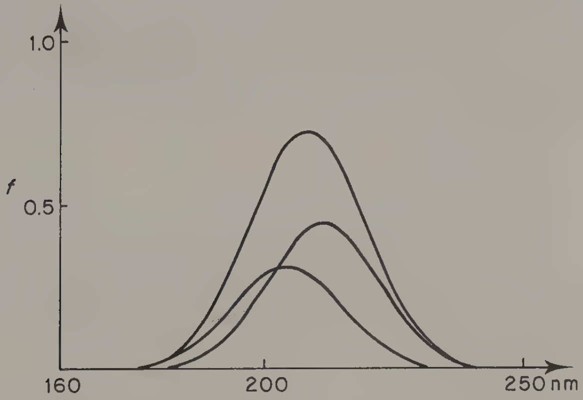


FIGURE 3. Summation of Gaussian curves for acrolein (**1a**)[5]. Reprinted with permission from T. Liljefors and N. L. Allinger, *J. Am. Chem. Soc.*, **98**, 2745 (1976). Copyright (1976) American Chemical Society

TABLE 10. Calculated and experimental spectra[a]

Compd	Conformation[b]	Calcd, nm (ev)[c]	f	Sum of Gaussian curves (nm)[d]	Exptl, nm (eV)	ε in ethanol	Ref.
1a	*s-trans*	210.5 (5.89) 203.5 (6.09)	0.45 0.32	208	207 (5.99)	11,200	45
1b	*s-trans*	226.2 (5.48) 201.6 (6.15)	0.38 0.37	214	216 (5.74)	11,000	45
1c	*s-trans*	219.0 (5.66) 207.6 (5.97)	0.57 0.19	218			
1d	*s-trans*	217.9 (5.69) 208.0 (5.96)	0.59 0.16	217	218 (5.69)	17,900	45
1e	*s-trans*	235.7 (5.26) 208.0 (5.96)	0.42 0.31	234 210 (sh)[e]			
1f	$\omega_2 = 178.6°$	234.3 (5.29) 208.7 (5.94)	0.43 0.30	233 210 (sh)[e]	226 (5.48)	16,100	45
1g	*s-trans*	226.2 (5.48) 211.5 (5.86)	0.62 0.12	226	235.5 (5.26)	11,900	45
1h	$\omega_2 = 172.9°$	246.4 (5.03) 215.6 (5.75)	0.44 0.25	246 216	245 (5.06)	13,000	
2a	*s-trans*	208.7 (5.94) 200.6 (6.18)	0.51 0.25	208	208.5 (5.95)	8,200[f]	19
2a	*s-cis*	223.4 (5.55) 202.5 (6.12)	0.32 0.05				
2b	*s-trans*	214.5 (5.78) 204.9 (6.05)	0.49 0.25	214	217.8 (5.69)	10,200	9

2b	*s-cis*	230.0 (5.39)	0.34				
		209.4 (5.92)	0.01				
2c	$\omega_1 = 12.9°$	226.6 (5.47)	0.39	227	226[g] (5.48)	8,500	21
		204.9 (6.05)	0.03				
2d	*s-trans*	214.5 (5.78)	0.67	215	220 (5.63)	11,600[f]	19
		205.2 (6.04)	0.08				
2d	*s-cis*	230.8 (5.37)	0.34				
		205.9 (6.02)	0.04				
2e	$\omega_1 = 34.8°$	233.0 (5.32)	0.30	233	235.5 (5.26)	4,570	46
		199.6 (6.21)	0.08	200			
2f	$\omega_2 = 177.6°$	223.0 (5.56)	0.55	222	227.9 (5.44)	12,600	9
		210.1 (5.90)	0.18				
2g	$\omega_1 = 18.8°$	232.6 (5.33)	0.40	233	237 (5.23)	12,700	9
		206.6 (6.00)	0.02				
2h	$\omega_1 = 48.9°$	243.1 (5.10)	0.21	243	244.5 (5.07)	5,300	9
		191.3 (6.48)	0.18	191			
2h	$\omega_2 = 139.7°$	239.8 (5.17)	0.26				
		190.4 (6.51)	0.26				

---

[a] Reprinted with permission from T. Liljefers and N. L. Allinger, *J. Am. Chem. Soc.*, **98**, 2745 (1976). Copyright (1976) American Chemical Society.

[b] If one conformation predominates by more than 90%, only this conformation was considered.

[c] The calculated values were corrected for ethanol solvent by −0.4 eV for all transitions. This is the mean difference between absorption maxima in vapor phase and in ethanol solution for a number of α, β-unsaturated aldehydes and ketones.

[d] The band width at half-height was estimated to be 6000 cm^{-1} from the spectrum of mesityl oxide (**2g**). The value was used for all transitions. (See also Ref. 21) For **2a**, **2b**, **2d**, **2h** the sum is taken over a weighted combination of four bands, corresponding to the conformer populations at 25 °C, calculated from Table 1.

[e] sh = shoulder.

[f] In cyclohexane.

[g] Estimated from spectrum in hexane [$\lambda_{\max}$ 221 nm (5.62 eV)] by subtracting 0.14 eV. This is the difference of the transition energies in hexane and ethanol for the related compound **2g**[9].

the calculated UV spectra of *s-cis* and *s-trans* enones. In general there is a decrease in the absorption intensity for an *s-cis* conformation compared to an *s-trans* conformation. Especially low are the f values for the short-wavelength π–π^* band in a planar *s-cis* conformation. Comparison of *s-cis* and *s-trans* conformations of **2a**, **2b**, **2d** and **2h** reveals the trend for lower π–π^* excitation energy for an enone in *s-cis* conformation, compared to that in *s-trans* conformation. This point is further discussed below.

The relative position of the singlet n–π^* and the lowest singlet π–π^* transition in polyenals and polyenones is still the subject of discussion[47]. In general, the energy gap between the two transitions diminishes with increasing conjugation. Knowledge of the nature of the lowest transition becomes important for molecules such as retinals and their analogues. It is postulated that the n–π^* transition, although directly not observable, remains the lowest energy singlet transition in retinals in non-hydrogen bonded solvents[48].

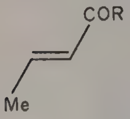
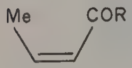
2. π–π^* Band: substitution and conformational effects

The position of the enone (enal) π–π^* band maximum varies with substitution and conformation. The early empirical correlations of Woodward[43] and Fieser[49] are shown in Table 11 (*A*). Despite widespread use, particularly in the field of polycyclic enones (terpenoids), these rules show the drawback of not taking into account any difference in the electronic absorption spectra between *s-cis* and *s-trans* conformations of the conjugated system. Such a difference is predicted by calculations on the basis of the difference in the 1,4-two-electron repulsion integral, which is larger in *s-cis*, compared to *s-trans* conformation. Thus, enones listed in Table 12 should all absorb at the same wavelength,

TABLE 11. Woodward–Fieser increments (*A*) and revised Liljefors–Allinger values (*B*) for calculation of $\lambda_{max}^{ethanol}$ in enones and enals **I** (in nm)

		A	*B*
Parent value	$R^1 = H$		207 (**It**)
	$R^1 =$ alkyl	215	209 (**It**)
			215 (**Ic**)
$R^2 =$ alkyl		+10	+10
R^3 or $R^4 =$ alkyl		+12	+12
Exocyclic C=C		+5	—
Endocyclic C=C (in six-membered ring)		—	+7

TABLE 12. UV data for enones, in hexane[21]

Enone	R	λ_{max} (nm)	ε ($l\,mol^{-1}\,cm^{-1}$)
	Me (**2d**)	214	11,800
	Bu^t (**14d**)	222	11,100
	CMe$_2$Bu^t	226	11,500
	Me (**2c**)	221.5	8,500
	Bu^t (**14c**)	222	8,600
	CMe$_2$Bu^t	226	10,300

according to Woodward–Fieser rules. It is known from the IR measurements that all enones in Table 12, with the exception of **2d**, are in *s-cis* conformation with varying degree of nonplanarity and this conformational effect is clearly reflected in their $\lambda_{\max}$ values.

The empirical Woodward–Fieser rules were put on a theoretically sounder basis by Liljefors and Allinger[50]. Their comprehensive evaluation of the conformational effect, based on VESCF calculations, increased the general applicability of the rules and has shown that the Woodward–Fieser rules work successfully because of some fortuitous cancellations.

For planar or nearly planar *s-cis* or *s-trans* enones the revised values (Table 11, *B*) for calculation of the $\lambda_{\max}$ include a 6 nm difference between the parent values of nonplanar *s-cis* and planar *s-trans* conformers, removal of the increment due to the exocyclic double bond and addition of a 7 nm increment for a double bond in a six-membered ring. The 'ring closure effect' is not the result of calculations on the π system alone but most probably it originates from the changes which occur in the σ system upon cyclization of an enone.

For enones which are seriously nonplanar additive increments cannot be used to predict $\lambda_{\max}$[50]. The effect of the alkyl group is to donate electrons to the p orbital of the atom to which it is attached. The resulting rise in the ground state energy of the molecule leads to a red shift of transitions originating from the π orbital. The amount of the red shift is a function of the dihedral angle ω: at $\omega = 90°$ alkyl substitution affects only the two atomic orbitals of the double bond. Thus increments would have to be functions of ω. This difficulty is solved if the results of calculations of $\lambda_{\max}$ for the two longest wavelength π–π^* transitions as a function of ω are applied. Figure 4 displays the results for a series of enones, with the oscillator strengths of each of the transitions shown at 0, 90° and 180°. The prediction of $\lambda_{\max}$ for a given substitution pattern (Figure 4) requires knowledge of ω; on the other hand knowledge of $\lambda_{\max}$ enables one to estimate the enone torsional angle ω.

Several regularities in the calculated $\lambda_{\max}/\omega$ plots are apparent:

(i) The absorption for the first transition occurs at a longer wavelength in *s-cis* compared to *s-trans* conformation, the calculated difference being almost invariably 15 nm between $\omega = 0$ and $\omega = 180°$.

(ii) The slope of the curve for the first transition is smaller on the *s-trans* side compared to the *s-cis* side. Thus $\lambda_{\max}$ shifts are more sensitive to deviation from planarity of enones in *s-cis* conformation, compared to *s-trans* enones.

(iii) Nonplanar enones absorb at shorter wavelengths than their planar counterparts, but the curve for the first transition becomes more shallow with increasing alkyl substitution. Thus $\lambda_{\max}$ of highly alkylated enones is nearly insensitive to changes of the angle ω.

For conformational analysis of enones the oscillator strength of the longer-wavelength π–π^* transition can be used, providing that the two π–π^* transitions are sufficiently separated. Calculations show that for the longer-wavelength transition the oscillator strength is higher in *s-trans* compared to *s-cis* conformation and it is zero at $\omega = 90°$. For the second transition the oscillator strength is small for planar conformations and large at $\omega = 90°$[50]. This is in line with the experimental findings of Braude and Timmons on the decrease in the intensity of the π–π^* band due to enone nonplanarity[51a].

Braude and Sondheimer[51b] introduced the relation between the torsional angle ω and the oscillator strength f_ω (or ε_ω), given in equation 1:

$$\cos^2 \omega = \frac{f_\omega}{f_{\text{planar}}} = \frac{\varepsilon_\omega}{\varepsilon_{\text{planar}}} \tag{1}$$

where f_{planar} and $\varepsilon_{\text{planar}}$ are respectively the oscillator strength and molar absorption

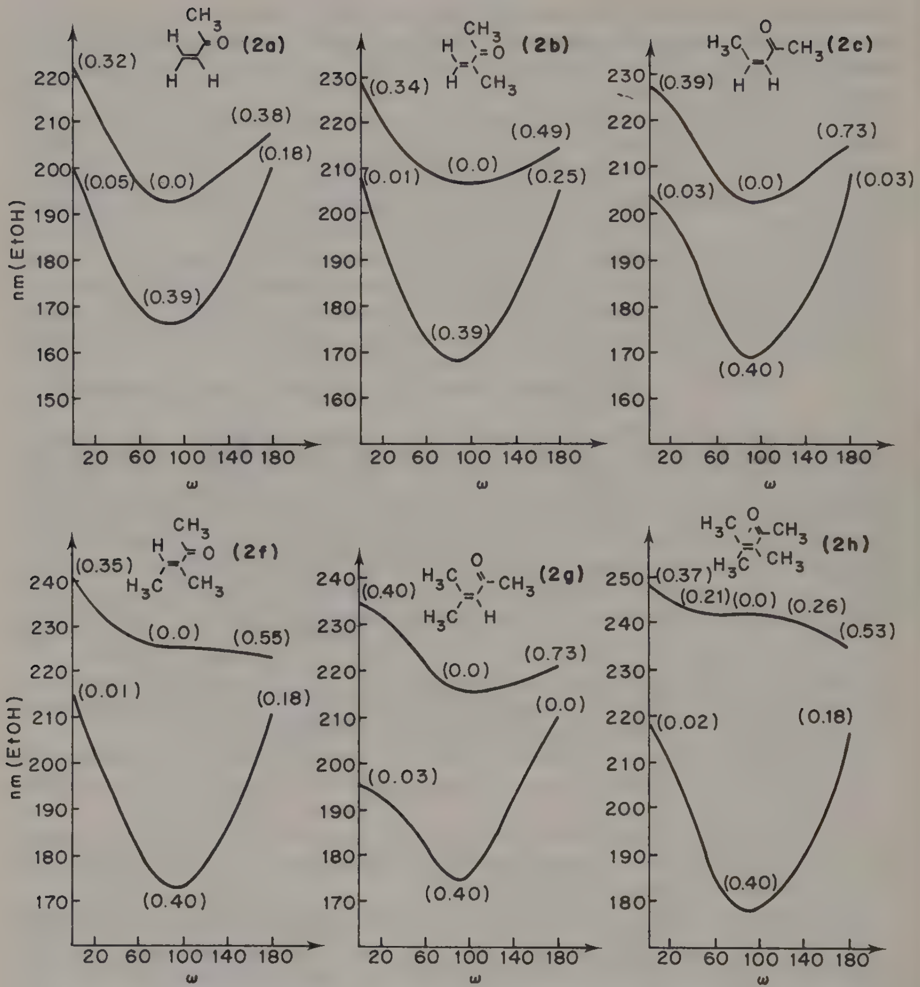
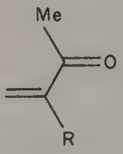


FIGURE 4. The two π–π^* transitions of lowest energy calculated for various substitution patterns of enones. Reprinted with permission from T. Liljefors and N. L. Allinger, *J. Am. Chem. Soc.*, **100**, 1068 (1978). Copyright (1978) American Chemical Society

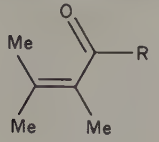
coefficient for the planar conformation. UV data for the two enones, **2b** and **14b**, show the difference in their conformation. Enone **2b** is *s-trans* planar, while **14b** is nonplanar, with $\omega = 135°$ according to equation 1[22]:



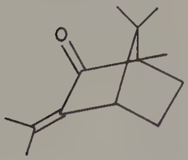
(**2b**) $R = Me\ \varepsilon_{214}^{\text{hexane}} = 10{,}500$

(**14b**) $R = Bu^t\ \varepsilon_{217.5}^{\text{hexane}} = 5{,}250$

Accordingly, enones **2h** and **14f** are both *s-cis* nonplanar, their nonplanarity increasing with the bulkiness of the R group, as calculated using the data for planar enone **40**:

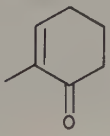


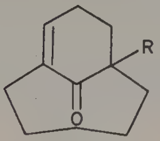
		ω
(**2h**)	R = Me $\varepsilon_{244.5}^{\mathrm{EtOH}} = 5{,}300^{9}$	48°
(**14f**)	R = Bu^{t} $\varepsilon_{240}^{\mathrm{EtOH}} = 2{,}490^{9}$	63°

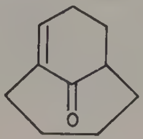


(**40**) $\varepsilon_{241}^{\mathrm{methylcyclohexane}} = 12{,}000^{52}$ 0°

The relative sensitivity of $\lambda_{\max}$ and ε toward strain is illustrated by the data for the substituted 2-cyclohexenones **41–43** and **7–9** (see Table 2). Enones **41–43** absorb at similar wavelengths but their ε values drop significantly with the increase of nonplanarity and decrease of delocalization (the ω value for the analogue of **42**, R = *p*-$\mathrm{ClC_6H_4NHCO}$, is 148°, according to X-ray diffraction analysis[53]). On the other hand, enones **7–9** are nearly planar, according to molecular mechanics (page 7). The red shift of $\lambda_{\max}$ in **8** and **9** compared to **7** is due to the C=C bond distortion from planarity[7,54].

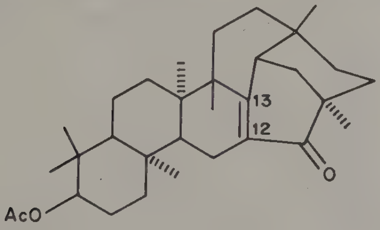




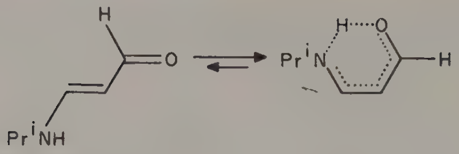


	(**41**)	(**42**) R = H	(**43**)
$\lambda_{\max}^{\mathrm{EtOH}}$ (nm)	235	238	238
ε	10,000	5,630	3,000
	(**7**)	(**8**)	(**9**)
$\lambda_{\max}^{\mathrm{MeCN}}$ (nm)	232	240	250
ε	13,800	14,800	5,070

A similar effect of strain is seen in the UV data for enone **44**, a derivative of katonic acid[55]. In addition to slight pyramidalization at C-12, the most severe deformation is the twist of the C=C bond by an average of 26°, as found by X-ray analysis. With the C=C and C=O bonds nearly coplanar, the 35 nm red shift of $\lambda_{\max}$ calculated from the Woodward–Fieser rules must originate from the C=C bond deformation.



(**44**) $\lambda_{\max}^{\mathrm{EtOH}}$ 273 nm
ε 8,900



	E, s-trans	*Z, s-cis*
$\lambda_{max}^{cyclohexane}$ (nm)	264	306
ε	28,000	14,100
λ_{max}^{MeOH} (nm)	281	
ε	35,600	

SCHEME 1

Although enals almost invariably prefer the *s-trans* conformation[45], the *s-cis* conformation can be stabilized by intramolecular hydrogen bonding. Thus enaminoaldehydes and enaminoketones (**It**, R = NH_2 or NHR) in nonpolar solvents undergo $E \rightarrow Z$ isomerization, the *Z, s-cis* structure being stabilized by hydrogen bonding between the amino and carbonyl groups. An example of such a process, which can be monitored by UV spectroscopy, is provided in Scheme 1[56].

The observed large difference of λ_{max} (42 nm) is due to configurational ($E \rightarrow Z$) and conformational (*s-trans* → *s-cis*) change, as well as to the intramolecular hydrogen bond, all of them contributing to the formation of the resonance-stabilized *Z, s-cis* isomer. Supporting evidence for the stability of the *Z, s-cis* structure in enaminoaldehydes in nonpolar solvents at low temperatures comes from the NMR studies[57]. UV spectra show similar preference of 3-hydroxyenones for intramolecularly hydrogen-bonded *Z, s-cis* structures[58].

The effect of the R^4 substituent on the enone λ_{max} is seen in the data of Table 13. The

TABLE 13. Effect of R^4 substituent on λ_{max} of enones **I** (in alcohol)

Compound	R^4	λ_{max} (nm)	$\Delta\lambda$ (nm)[a]	Reference
2d	Me	220	—	13
24	Cl	229	+9	33
25	OMe	246	+26	58
26	NMe_2	300	+80	56
27	NMe_3^+	206.5	−13.5	33
2f	Me	228	—	9
28	Cl	231	+3	16
30	NMe_2	304	+76	34
2g	Me	237	—	9
31	Cl	238	+1	16
32	OMe	257	+20	58
34	NMe_2	310	+73	56
14d	Me	227	—	21
36	Cl	232.5	+5.5	33
37	OMe	255	+28	58
38	NMe_2	311	+84	56
39	NMe_3^+	207.5	−19.5	33

[a] $\Delta\lambda$ is the shift of λ_{max} by comparison with the R^4 = Me substituted enone.

TABLE 14. UV data (in ethanol) for rigid *s-trans* (**12**) and *s-cis* (**13**) enones

R	Enone	λ_{max} (nm)	Ref.	Enone	λ_{max} (nm)	Ref.	$\Delta\lambda_{max}^{(13-12)}$ (nm)
H	**12a**	225	12	**13a**	230	13	+5
Me	**12b**	231		**13b**	244		+13
Cl	**12d**	231.5	12	**13d**	245	16	+13.5
OMe	**12f**	251		**13f**	276	59	+25
NMe_2	**12e**	298	56	**13e**	334	56	+36

batochromic shift of λ_{max} falls in the order:

$$NMe_2 > OMe > Cl \approx Me > NMe_3^+$$

in both *s-trans* (upper two sections of Table 13) and *s-cis* (lower two sections of Table 13) conformations. Furthermore, by comparing the λ_{max} values of the two series of enones of rigid conformation and neglecting small differences in the enone alkyl substitution pattern, one can arrive at the shift of λ_{max} due to *s-trans* → *s-cis* conformational change in R^4-substituted enones (Table 14).

The conformational and configurational effects appear to affect the UV spectra of dienones and dienals (Table 15). Both *E* and *Z* dienals **3** and **5** have *s-trans* conformation, according to molecular mechanics[6], thus the $E \rightarrow Z$ configurational change is estimated to produce a 9 nm red shift and a drop in the ε value. Neglecting the effect of the R^1 substituent, a 9–10 nm red shift and a drop in the ε value is found for the *s-trans* → *s-cis* conformational change, by comparison of the data for **4** and **6**, and **3** and **45**. The combination of configurational and conformational effects is seen in the UV data for the pairs of *E*/*Z* dienones **18**, **21**; **47**, **48**; and **50**, **51** (Table 16).

TABLE 15. UV data for the π–π^* transition in **II***E* and **II***Z* dienals and dienones (in cyclohexane)[6]

R^1	**II***E*	λ_{max} (nm)	ε	**II***Z*	λ_{max} (nm)	ε
H	**3**	278	34,700	**5**	287	22,000
Me	**4**	281	30,500	**6**	291	19,700
Bu^t	**45**	287	26,100			

TABLE 16. UV data for the π–π^* transition in dienones **II***E* and **II***Z*, $R^1 = R^6 = Me$ (in cyclohexane)[27]

Compound	R^2	R^3	R^4	R^5	λ_{max} (nm)	ε ($l\,mol^{-1}\,cm^{-1}$)
18 (*E*)	H	H	H	H	265	28,950
21 (*Z*)	H	H	H	H	273	13,960
46 (*E*)	Me	H	H	H	269	28,200
47 (*E*)	H	Me	H	H	272.5	22,800
48 (*Z*)	H	Me	H	H	279	7,360
49 (*E*)	H	H	Me	H	267.5	28,300
50 (*E*)	H	H	H	Me	278	27,000
51 (*Z*)	H	H	H	Me	286	22,700
52 (*E*)	H	Me	H	Me	276	10,000

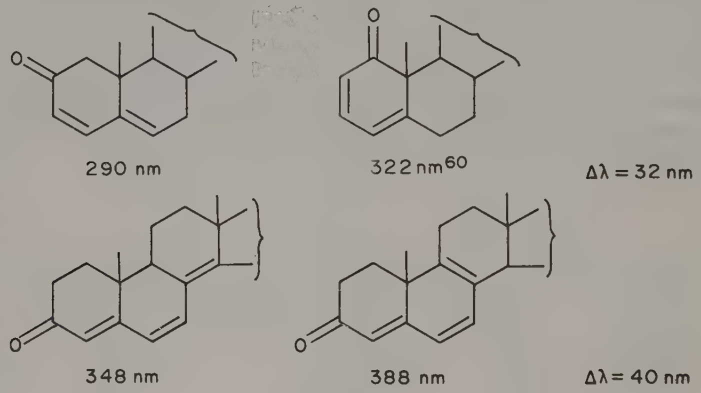
TABLE 17. Woodward–Fieser increments for calculation of $\lambda_{max}^{ethanol}$ of alkyl substituted dienones **II** (in nm)

Parent value (R^1 = alkyl)	245
R^2 = alkyl	+ 10
R^3 = alkyl	+ 12
R^4 or R^5 or R^6 = alkyl	+ 18
Exocyclic C=C	+ 5
Homoannular diene component	+ 39

A set of increments for calculating λ_{max} of dienones, supplementing those for enones, has been empirically found by Woodward[43] and Fieser[49] (Table 17). Despite the fact that no provision for conformational effects has been included, it works satisfactorily with planar or nearly planar chromophores, e.g. *E*-dienones **18**, **46**, **47** and **50**.

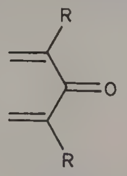
Dienones **47** and **52** both have *s-cis* conformation but, unlike **47**, **52** has a nonplanar diene portion of the chromophore, due to the 1,3-repulsion of the two substituents R^3 and R^5. Consequently, the ε value of the latter is much lower than that of the former.

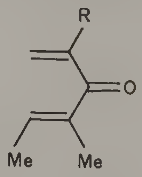
The + 39 nm increment for a homoannular diene component of the dienone chromophore (Table 17) can be traced to the conformational effect due to the diene *s-trans* → *s-cis* change. The examples in Scheme 2 from the steroid series illustrate this point, using rigid cyclic structures (solvent ethanol).



SCHEME 2

As expected, the position of λ_{max} of cross-conjugated dienones of the type **III** is also sensitive to conformational changes[61]. Despite the presence of additional methyl substituents in dienones **54** and **56**, their λ_{max} is blue-shifted compared to **53** and **55**,





(λ_{max} in ethanol)

(**53**) R = H 230 nm

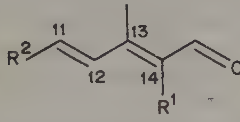
(**54**) R = Me 225 nm

(**55**) R = H 252 nm

(**56**) R = Me 234 nm

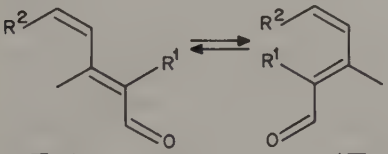
respectively. Apparently, when the carbonyl group in the divinyl ketone (**53**) is flanked by the two additional α, α′-substituents, the dienone chromophore is forced to nonplanarity.

The conformational dependence of the π–π^* transition in polyenals and polyenones with participation of the *s-cis*–*s-trans* equilibria of the diene subunits is of a more complicated nature. An example is provided by *all-trans*-retinal (**57**) and 11-*cis*-retinal (**59**)—the chromophore of visual pigments, and their 14-methyl derivatives **58** and **60**[62]. The positions of λ_{max} and ε values of *all-trans* retinals **57** and **58** are very similar, as they have planar chromophores (**IItt** conformer of the dienal portion). 11-*cis*-Retinal (**59**) is known from the X-ray studies to have a significantly nonplanar conformation in the solid state, i.e. **IItc** with the angle $\omega_{12,13} = 39°$[63]. According to calculations[64] the solution spectral data of **59** are determined by the contributions of both **IItc** and **IItt** conformers. Owing to the nonplanarity of the *s-cis* diene unit in the **IItc** conformer the position of λ_{max} of **59** is only slightly blue-shifted, compared to **57**. On the other hand, the 11-*cis*-14-methyl derivative **60** can take up a planar **IItt** conformation and a nonplanar **IItt** conformation, with $\omega_{12,13}$ around 100°. This results in a 35 nm blue shift of λ_{max} and a large drop of the ε value for **60**, compared to **58**.



(IItt)

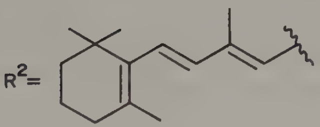
	R^1	λ_{max}(nm)	ε
(57)	H	368	47,500
(58)	Me	373	46,000



(IItt) (IItc)

	R^1	λ_{max}(nm)	ε
(59)	H	363	26,200
(60)	Me	338	18,000

(in hexane)



D. Nuclear Magnetic Resonance

1. *Proton magnetic resonance*

Due to the effect of the electric dipole moment and the anisotropic magnetic susceptibility of the carbonyl group, the *s-trans* → *s-cis* conformational change will result in a downfield shift of the R^3 (H or alkyl) resonance and an upfield shift of the R^4 resonance. Thus the increase of the **Ic** conformer population causes greater separation of resonances of protons at $C_{(3)}$. By comparing chemical shifts of the vinyl protons at $C_{(3)}$ in a series of structurally related vinyl ketones $R^1C(O)CH{=}CH_2$ it can be demonstrated that the increase of the **Ic** population follows the increase in the bulkiness of the R^1 group (Table 18). For calculation of the percentage content of **Ic** conformer in alkyl vinyl ketones equation (2) was used[65]:

$$\%\ \mathrm{Ic} = 180[(\delta_{R^3} - \delta_{R^4}) - 0.15] \qquad (2)$$

TABLE 18. NMR data for vinyl protons R^3 and R^4 in enones and enals (solvent CCl_4)[22,65]

Compound	R^1	R^2	$\delta(R^3)$	$\delta(R^4)$	$\delta(R^3) - \delta(R^4)$	%**Ic**
1a	H	H	6.23	6.07	0.16	2
2a	Me	H	6.11	5.82	0.29	25
61	Pr^i	H	6.16	5.66	0.50	63
14a	Bu^t	H	6.26	5.60	0.66	92
2b	Me	Me	5.90	5.73	0.17	4
62	Pr^i	Me	5.87	5.70	0.17	4
14b	Bu^t	Me	5.35	5.35	0	[a]

[a] Nonplanar conformation.

The NMR data for *E*- and *Z*-3-penten-2-one (**2c** and **2d**), having *s-trans* and *s-cis* conformation respectively, were the basis for the assignment of methyl resonances in mesityl oxide (**2g**)[66]. The increased bulkiness of the R^2 substituent in the 3,3-dimethylenone **2h** results in a nonplanar *s-cis* enone conformation, with subsequent reduction of the deshielding effect of R^3 by the carbonyl group. This is seen as a substantial reduction of the separation of signals of R^3 and R^4 methyl groups in **2h**, compared to the data for the planar *s-cis* enone **40** (Table 19).

It is known that ketones form a 1:1 solvate with aromatic solvents, such as benzene and toluene. Timmons[68,69] and Williams[70] have correlated the aromatic solvent induced shift (ASIS) of resonances of vinyl and allyl protons:

$$\Delta = \delta(CCl_4) - \delta(\text{benzene})$$

with the conformation of the enone molecule. Large positive shift of the R^4 resonance, relatively large R^3 shift and small positive or negative R^2 shift are characteristic of *s-trans* conformation (upper part of Table 20). Positive shifts ($\Delta > 0$) were observed for substituents R^2 and R^4 in enone *s-cis* conformation, R^3 displaying small or negative shift (lower part of Table 20). The formation of the aromatic solvent shell around the enone group is influenced by steric hindrance and by the nonplanarity of the enone group, as well as by dipole–dipole interactions. Thus different shifts are seen for the two *s-cis* enones **2g** and **2h** with varying degree of nonplanarity, and for *Z*/*E* stereoisomeric 3-chloroenones **66**/**35** and **67**/**68**. This discrepancy, apparently due to the presence of the C=O and C—Cl dipoles in the molecule, has led to the proposal of the benzene solvation model. According to this model, the 3-alkyl group in 3-chloro-2,3-dialkylenones undergoes either a large solvent shift (enones **66**, **67** of *Z*-configuration) or a small solvent shift (enones **35**, **68** of *E*-configuration)[16]. The empirical solvent shift–structure correlations discussed above were extended to the variable-temperature measurements of Δ[72].

TABLE 19. NMR data for vinyl and methyl protons R^3 and R^4 in enones (solvent CCl_4)

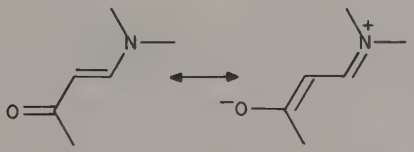
Compound	$\delta(R^3)$	$\delta(R^4)$	$\delta(R^3) - \delta(R^4)$	Reference
2c	2.12	6.09	—	66
2d	6.71	1.90	—	66
2g	2.11	1.86	0.25	66
2h	1.82	1.76	0.06	67
40	2.10	1.76	0.34	52

TABLE 20. Solvent shifts Δ of vinyl and allyl protons in enones and enals **I**

Compound	R^1	R^2	R^3	R^4	$\Delta = \delta(CCl_4) - \delta(\text{benzene})$			Ref.
					R^2	R^3	R^4	
63	H	H	Ph	H	0.27	—	0.73	71
15	H	H	H	Ph	0.25	0.66	—	71
64	H	Me	Cl	Me	0.20	—	0.40	16
65	H	Me	Me	Cl	0.05	0.44	—	16
2a	Me	H	H	H	0.18	0.50	0.58	69
2b	Me	Me	H	H	0.04	0.32	0.19	68
2d	Me	H	H	Me	0.12	0.41	0.54	69
2f	Me	Me	H	Me	0.00	0.38	0.35	68
28	Me	Me	H	Cl	0.15	0.65	—	16
2g	Me	H	Me	Me	0.26	0.01	0.39	69
2h	Me	Me	Me	Me	0.40	0.02	0.19	16
66	Me	Me	Cl	Me	0.66	—	0.66	16
35	Me	Me	Me	Cl	0.28	0.15	—	16
67	Ph	H	Cl	Me	0.40	—	0.47	16
68	Ph	H	Me	Cl	0.15	0.15	—	16

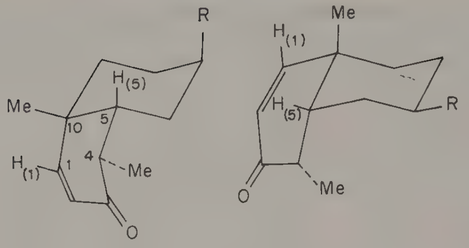
The analysis of the lanthanide induced shifts (LIS) allowed one to estimate the population of conformers in enals and enones, the former being predominantly in *s-trans* conformation (% *s-trans*: 100 in **1b**, 91 in **1d** and 86 in **15**), the latter being in both *s-trans* and *s-cis* conformations (% *s-cis*: 27 in **2a**, 12 in **2b**, 72 in **2g**, 63 in **16** and 83 in **17**)[73]. Paramagnetic shift reagents were also used in the conformational analysis of dienones **II** ($R^1 = R^5 = Me$, $R^2 = R^3 = R^4 = H$, $R^6 = \text{alkyl}$)[74]. The results of a detailed analysis were compatible with the presence of both **IIEt** and **IIEc** conformers of *E*-dienone and a nonplanar **IIZc** conformer of *Z*-dienone.

Information about the individual conformers in the equilibrium can be provided by the NMR spectra, if the barrier to *s-trans–s-cis* interconversion is higher than 5–6 kcal mol^{-1}. In enaminoketones the rotational barrier around the $C_{(1)}$—$C_{(2)}$ formal single bond is higher than in other enones, due to the stabilization of the polar resonance form by the amino substituent:



This enabled studying the conformational equilibrium of enaminoketones RCOCH$=$CHNMe$_2$, based on the analysis of coupling constants in various fragments of the molecule. It has been established that the percentage of the *s-trans* conformation decreased with the increase in bulk of R and it was higher in polar solvents than in nonpolar ones[75].

Long-range coupling can provide indirectly information on the conformation of derivatives of *cis*-1-octalen-3-one (Figure 5)[76]. Coupling of the order 1–2 Hz through four bonds between $H_{(1)}$ and $H_{(5)}$ was found in several derivatives having a 4α-methyl group. Such coupling requires planar (W-type) arrangement of the $H_{(1)}$—$C_{(1)}$—$C_{(10)}$—$C_{(5)}$—$H_{(5)}$ bonds, which is seen in the nonsteroidal conformation (**A**). The nonsteroidal conformation, with negative ω angle, is favored over the steroid-like one (**B**), apparently



(A) (B)

FIGURE 5. Nonsteroidal (**A**) and steroidal (**B**) conformation of *cis*-1-octalen-3-one derivatives

owing to the removal of the strain caused by the 4α-methyl substituent, which occupies the axial position in the steroidal conformation.

2. Carbon-13 magnetic resonance

By slowing down dynamic *s-cis–s-trans* interconversion of enones, low-temperature carbon-13 magnetic resonance measurements allow one to characterize separately enone conformers. The temperature at which signals split is related to enone structure; sufficiently high free enthalpy of activation ΔG^* for the *s-trans* → *s-cis* conversion is found for dienones (Table 21)[77] and for enaminoketones (Table 22). For **26** $\Delta G^*_{255^\circ}$ is $12.2 \pm 0.2\,\text{kcal mol}^{-1}$. It should be noted that even at low temperature *s-cis* conformation of enal **69** could be detected by the carbon-13 NMR technique, as a minor constituent of the equilibrium mixture. However, no *s-trans–s-cis* conformational equilibrium could be detected in the diene fragment of the dienones **18**, **46** and **47**. Dienones **46** and **47** and enaminoketone **70** exist as single conformers, according to the NMR data.

It can be seen in the data for **18** and **26** that resonance signals of $C_{(1)}$–$C_{(3)}$ appear in a lower field in *s-trans* conformation, i.e. $\delta_{s\text{-}trans} - \delta_{s\text{-}cis} > 0$. A similar trend, resulting from changes in electron density distribution on enone carbon atoms due to the *s-trans–s-cis* interconversion, was noted for 3-alkoxyenones[79]. In nonplanar enones, for which the effect of conjugation is less pronounced, the $C_{(1)}$ signal appears at a higher field compared to planar systems[80].

For enones having $R^1 = \text{Me}$ and $R^2 = \text{H}$ it has been found from the carbon-13 magnetic resonance data that the resonance signal of R^1 occurs at a lower field in the *s-cis*, compared to the *s-trans* conformation (the 'γ-effect'). In addition $^3J_{(\text{COMe},H)}$ is zero in the *s-cis*

TABLE 21. Low-temperature (117 K) carbon-13 magnetic resonance data for *E*-dienones (in vinyl chloride)[77]

Compound	Conformer	$C_{(1)}$	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	R^1
18	**IIt**	199.17	128.67	145.14	129.57	140.33	25.18
	IIc	197.17	*a*	141.20			30.61
46	**IIt**	199.33	133.01	140.00	127.23	138.72	25.40
47	**IIc**	199.05	124.13	149.79	134.34	134.24	32.12

[a] Covered by solvent signals.

TABLE 22. Low-temperature carbon-13 magnetic resonance data for *E*-enaminoketones $RCOCH{=}CHNMe_2$[78]

Compound	Conformer	$C_{(1)}$	$C_{(2)}$	$C_{(3)}$	$\frac{\mathrm{Ic}}{\mathrm{It}}$	Solvent	*T*(K)
	It			160			
69 (R = H)		205.5	98.7		0.05	acetone	193
	Ic			161			
	It	198.3	97.5	151			
26 (R = Me)					1.5	$CDCl_3$	219
	Ic	197.7	92.8	148			
70 (R = Ph)	Ic	187	90.3	153	100	$CDCl_3$	223

conformation, while weak coupling (1.4–3.1 Hz), characteristic of a planar W-type bond arrangement, is found in the *s-trans* conformation[81].

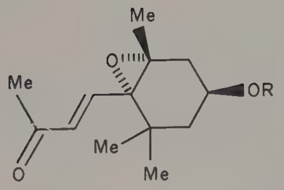
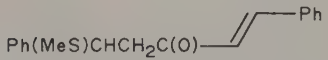
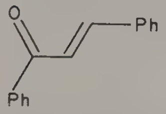
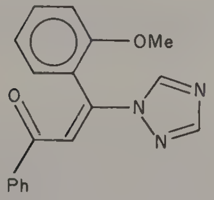
E. X-Ray Crystallography

Despite the wealth of X-ray data on enones accumulated in the literature, conclusions concerning conformations should be drawn with care. As will be shown in the following discussion, structurally related enones can have different solid state conformations. In a number of cases two conformers of the same enone exist in the solid state, including the cases of two independent conformers in the crystal cell. The underlying reason for the presence of different conformers in the solid state is the rather shallow potential for the change of the angle ω around the position corresponding to the energy minimum. The free-energy difference between the conformation in the crystal and another preferred conformation in solution is frequently small and fully compensated by crystal packing effects[82].

In the absence of severe steric effects the enone group tends to take up a planar or nearly planar conformation. Any distortion from planarity is usually more pronounced in the *s-cis* conformation than in the *s-trans* conformation. As was the case for solution conformation, increasing the size of R^1 and R^3 substituents in the enone molecule brings about the shift of conformational equilibrium toward the *s-cis* conformation (see examples in Scheme 3). In order to minimize steric interactions, aromatic (heteroaromatic) substituents R^3 and R^4 are not coplanar with the C=C bond, with a large deviation from coplanarity being found in the case of the *o*-methoxyphenyl substituent R^3 (dihedral angle 59.1°) in **73**[86]. Molecules of **72** can exist in the crystal in the *s-trans* or *s-cis* conformation, depending on the temperature at which crystals are grown[84]. In addition, two isomeric ring-substituted derivatives of 2′-nitrochalcone, **74** and **75**, were found to have different conformations in the solid state[87]. The 4-bromo derivative **74** has a nonplanar *s-cis* conformation, as does chalcone (**17**), while the 3-bromo derivative **75** is in a nonplanar *s-trans* conformation. These results clearly demonstrate the importance of crystal packing forces in determining the preferred conformation in the crystal.

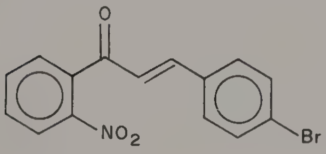
Nonplanar enone *s-cis* conformations are found in the X-ray-determined structures of several cyclic chalcone analogs **76–79** (Table 23).

Cyclic *s-trans* enones show a tendency for an increase in nonplanarity with an increase in ring size. Thus 2-cyclopentenones can either take-up a planar or envelope E(5) conformation (Figure 6), with the ω values (from the X-ray data) close to 180° for the planar conformation (Table 24). In 2-cyclohexenones $C_{(5)}$ and/or $C_{(6)}$ are out of the plane

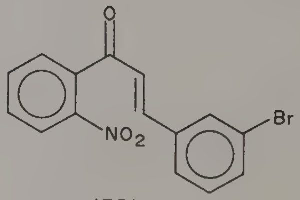
		ω (deg)	Reference
71		– 172.3	83
72		178.8[a] – 11.0[b]	84 84
17		16.9	85
73		23.4	86

SCHEME 3

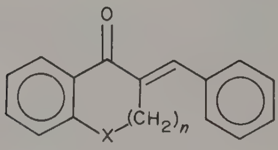
[a] Crystals grown from ethanol at temperatures higher than 55 °C.
[b] Crystals grown from ethanol at temperatures 20–45 °C.



(74)



(75)



76 –79

TABLE 23. Enone torsional angle ω in cyclic analogs of chalcone

Compound	X	*n*	ω (deg)	Reference
76	CH_2	0	6.5	88
77	CH_2	1	11.3	89
78	O	1	21.8	90
79	O	2	8.5	91

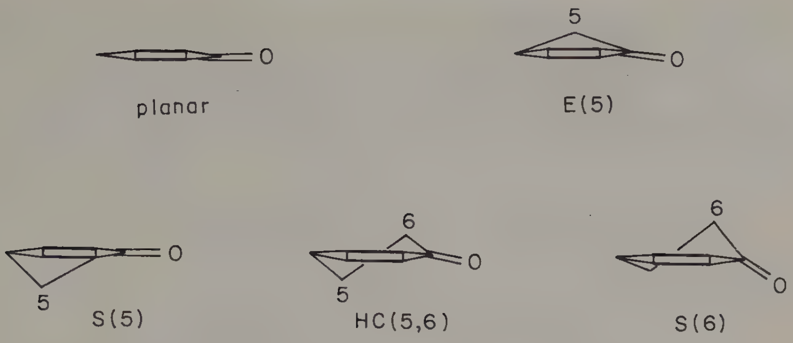
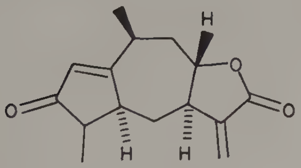
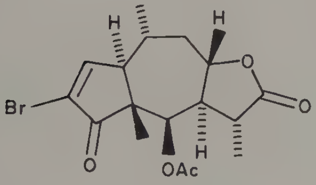
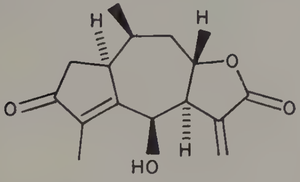
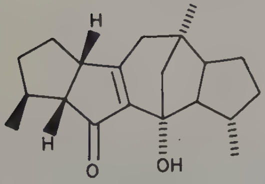
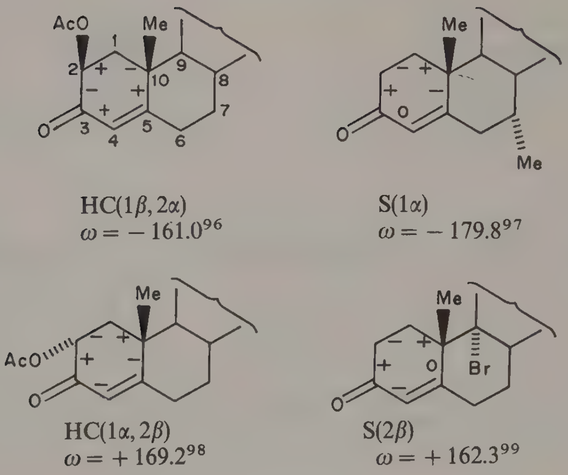


FIGURE 6. Typical conformations of 2-cyclopentenones (top) and 2-cyclohexenones (bottom). Only one enantiomer of each conformer is shown

TABLE 24. Conformations of polycyclic 2-cyclopentenones

Compound	2-cyclopentenone ring	ω (deg)	Reference
	*E*(5α)	172.5	92
	*E*(5β)	– 168.4; – 174.4[a]	93
	planar	178	94
	planar	– 179.1	95

[a] Two independent molecules.



HC(1β, 2α)
$\omega = -161.0$[96]

S(1α)
$\omega = -179.8$[97]

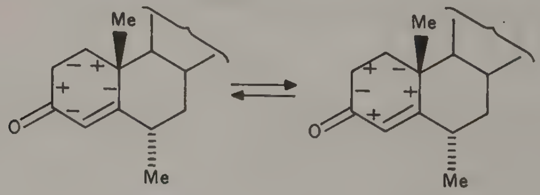
HC(1α, 2β)
$\omega = +169.2$[98]

S(2β)
$\omega = +162.3$[99]

SCHEME 4

defined by $C_{(1)}$—$C_{(4)}$ to give a sofa (S) or half-chair (HC) conformer (Figure 6). The enone group is nearly planar in the S(5) conformer and the nonplanarity increases on going from the HC(5, 6) to the S(6) conformer. Typical examples are provided by ring A conformations of steroidal 4-en-3-ones (Scheme 4). The 'inverted' HC(1β, 2α) and the S(2β) conformers are apparently of lower energy compared to the 'normal' S(1α) and HC(1α, 2β) conformers if these are destabilized by the 1, 3-diaxial repulsive interactions, e.g. 2β-OAc–10β-Me or 1α-H–9α-Br.

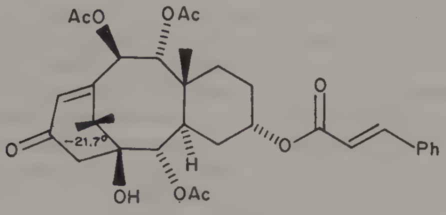
The relation of the geometry of steroidal hormone molecules to their biological activity has been discussed in detail by Duax and coworkers[100] as well as by Romers and coworkers[101]. An interesting outcome of the X-ray studies of steroidal 4-en-3-ones is the discovery of ring A flexibility. Thus ring A in the cortisol–methanol (1:1) solvate assumes S(1α) conformation[102] and in the cortisol–pyridine (1:1) solvate it has HC(1α, 2β) conformation[103]. In two different crystalline forms of 19-nortestosterone ring A can have either HC(1α, 2β) conformation with two independent molecules in the asymmetric unit[104] or it can have both HC(1α, 2β) (70%) and HC(1β, 2α) (30%) conformations[105]. In addition, the same steroid molecule can have distinctly different conformations in the solid state and in solution. An example is 17α-acetoxy-6α-methylprogesterone in which the enone ring is an 'inverted' HC(1β, 2α) in the solid state[106] but extensive NMR and CD studies of Kirk and coworkers[82] show 'normal' HC(1α, 2β) conformation in solution:



HC(1α, 2β) HC(1β, 2α)

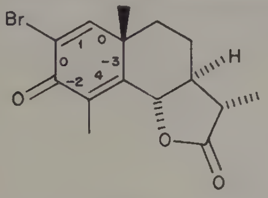
The small energy difference between 4-en-3-one conformers causes flexibility of ring A in steroids and this in turn may show its importance in binding the hormone molecule in the receptor active site.

The less-common conformations of 2-cyclohexenone ring are found in strained molecules. One type of these comprises enones with an anti-Bredt type C=C bond. In the taxicin derivative **80** the 2-cyclohexenone ring assumes a boat conformation, flattened at the carbonyl end. In addition, the C=C bond is long (1.361 Å) and twisted (dihedral angle − 15.5°)[107].

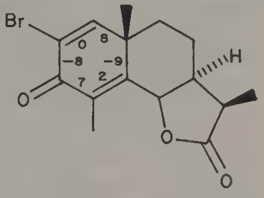


(80)

In general, introduction of additional sp^2-hybridized carbon atoms enhances the tendency of the enone ring toward flattening. Thus, the cyclopentene-1,2,3-trione ring is planar[108] and so is the 1,4-cyclohexadien-3-one ring in numerous polycyclic natural compounds, especially steroids[101]. However, deviations from planarity due to the strain are observed in structurally related molecules, e.g. 2-bromosantonins **81**[109] and **82**[110].

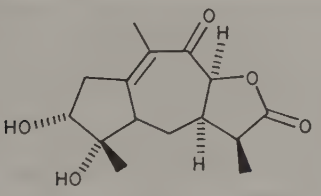


(81)

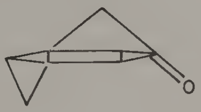


(82)

X-ray data for 2-cycloheptenones and higher homologues are less abundant. The 2-cycloheptenone ring in carolenalone (**83**) takes up a twist-chair (TC) conformation, with a distinctly nonplanar enone group ($\omega = -157°$). The C=C bond is also nonplanar, with torsional angle 11°, indicating strain present in the fused 2-cycloheptenone ring[111].



(83)



TC

III. CHIROPTICAL PROPERTIES

A. Linear Dichroism

Linear dichroism (LD) spectra, a product of anisotropic absorption of light, are obtained for molecules having nonrandom organization. In such systems the absorption of plane-polarized light varies with the direction, the dichroic ratio, R_D, being defined as the ratio of absorption of linearly polarized light with the electric vector parallel to the principal optical direction ($A_{\parallel}$) to that with the electric vector perpendicular to the principal optical direction ($A_{\perp}$):

$$R_D = A_{\parallel}/A_{\perp} \tag{3}$$

Although LD measurements provide a multitude of spectroscopic and structural information[112,113], no application of linear dichroism measurements to conformational analysis of enones has been reported. However, the direction of the transition moment of the chromophore can be obtained from the LD measurements, providing that the orientation of the molecules is known. This information is important in chiroptical studies, including exciton interactions between chromophores (Section III.B.6).

The direction of the electric transition moment of polycyclic enones has been determined by Yogev and coworkers[114], using LD measurements of enones partially oriented in stretched polyethylene films. The dichroic ratio R_D is related to the angle α between the orientation axis of the molecule and the transition moment vector of the

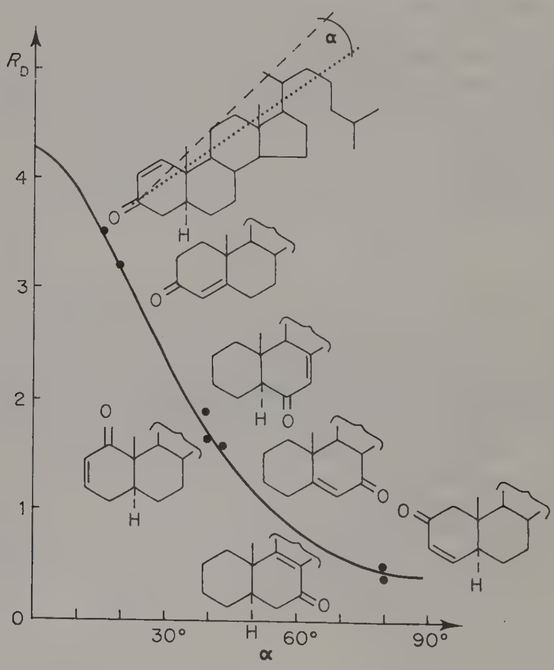


FIGURE 7. Plot of the dichroic ratio R_D *vs.* α according to equation 4 for the distribution factor $f = 0.5$. The circles are measured R_D values of cholestenones plotted against α values calculated from a geometrical model, line ------ is the π–π* transition moment vector and ······ is the orientation axis. Reproduced with permission from A. Yogev, J. Riboid, J. Marero and Y. Mazur, *J. Am. Chem. Soc.*, 91, 4559 (1969). Copyright (1969) American Chemical Society

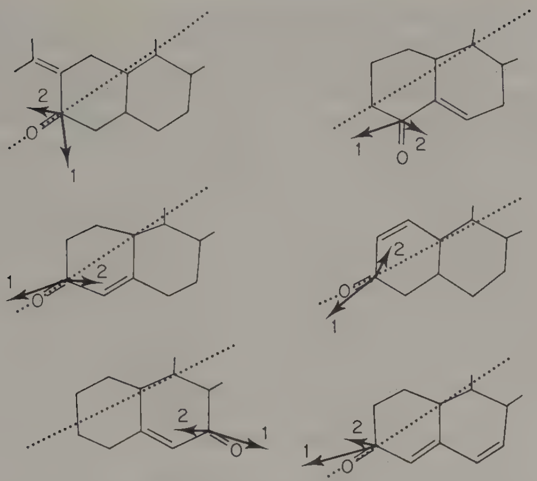


FIGURE 8. Calculated transition moment vectors (twice the calculated length, per unit charge) for the two π–π^* transitions above 200 nm (the longest wavelengths are denoted 1). The geometries of the compounds are shown as calculated by molecular mechanics. The dotted lines represent the assumed directions of the orientation axes. Reprinted with permission from J. Gawronski, T. Liljefors and B. Norden, *J. Am. Chem. Soc.*, **101**, 5515 (1979). Copyright (1979) American Chemical Society

chromophore (equation 4):

$$R_D = \frac{f\cos^2\alpha + \frac{1}{3}(1-f)}{\frac{1}{2}\sin^2\alpha + \frac{1}{3}(1-f)} \qquad (4)$$

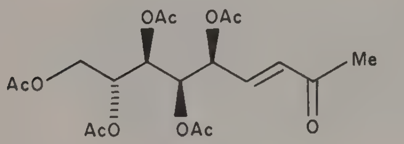
where f is the distribution factor of the molecules in the oriented film. Steroidal enones having a cholestane skeleton give different R_D values and hence different values of α, depending on the location of the enone group in the skeleton (Figure 7). The orientation axis of the molecules having a cholestane skeleton was chosen as the longitudinal principal axis. Subsequent LD measurements of Norden and coworkers have shown that the transition moment of the long-wavelength π–π^* band is directed approximately along the line connecting the end atoms of the enone chromophore, in agreement with calculations by the VESCF–CI method, including all singly and doubly excited configurations. The direction of the transition moment of the second π–π^* transition was also calculated, but due to its complicated and varying nature no generalization could be made[115]. The calculated transition moment vectors for the two π–π^* transitions in some enones are shown in Figure 8. As in the case of UV measurements, low intensity and its overlap with the strong long-wavelength π–π^* band have made it difficult to obtain an experimentally well-resolved short-wavelength π–π^* band from the LD spectra.

B. Circular Dichroism

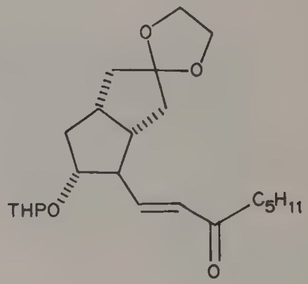
1. General

Unlike techniques discussed in the preceding parts of this chapter, circular dichroism measurements provide information on a variety of aspects of molecular chirality and are capable of delivering information on the absolute sense (i.e. sign) of the enone torsional angle ω (Figure 1). In fact, much of the research effort on chiroptical properties of enones over the past 25 years has been directed toward establishing and refining the relation between ω and the sign/magnitude of the Cotton effects for the individual enone transitions (for accounts of the subject see References 116–121). As is the case with other chromophores, e.g. dienes, conformational effects are frequently overriden by the effects due to the substitution in the vicinity of the chromophore.

Owing to the high sensitivity of chiroptical techniques to conformational and configurational effects, empirical comparisons are still the easiest and reliable method for establishing the stereostructure of chiral molecules. Caution is advised regarding attempts to draw conclusions from chiroptical data for compounds with considerable conformational freedom. Acyclic enones, such as **84** and **85**, exist in both *s-cis* and *s-trans* conformations, in addition to any number of conformations due to the rotation of the C—C bond, connecting the chromophore to the closest chiral center. Unless low-temperature CD measurements are used, Cotton effects are small, due to the contributions of many conformers. Not surprisingly, the majority of the published CD data refer to enones with restricted rotational freedom.



(**84**)



(**85**)

n–π*,	Δε	+ 0.11 (313 nm)	in MeCN	+ 0.03 (327 nm)	in MeOH
π–π*,	Δε	ca. 0 (215 nm)		+ 1.4 (236 nm)	

It is worth adding that CD measurements are capable of uncovering bands ordinarily not seen in the isotropic absorption spectra. The vibronic structure of the n–π* (R band, 400–280 nm) transition is much better resolved in the CD spectra than in the UV spectra and, in addition to the π–π* (K band, 260–230 nm) Cotton effect, two more Cotton effects can be observed in the short-wavelength (220–185 nm) region (*vide infra*).

Early ORD studies of steroidal cyclohexenones by Djerassi and coworkers[122] and Whalley[123] have established the relation between the helicity of the *s-trans* enone chromophore and the sign of the n–π* and π–π* Cotton effects:

$90° < \omega < 180°$	n–π* (R band)	Cotton effect < 0
	π–π* (K band)	Cotton effect > 0

(opposite Cotton effects for $-90° > \omega > -180°$).

For *s-cis* enones the relation between helicity and chiroptical properties appears more complex. The recent orbital helicity rule of Kirk[121] combines chiroptical properties of both *s-trans* and *s-cis* enones by considering the helicity defined by the relative directions of the p orbitals at $C_{(2)}$ and $C_{(1)}$ (Figure 9). Positive orbital helicity, as defined in Figure 9, gives rise to a positive n–π* Cotton effect and a negative π–π* Cotton effect (note that the

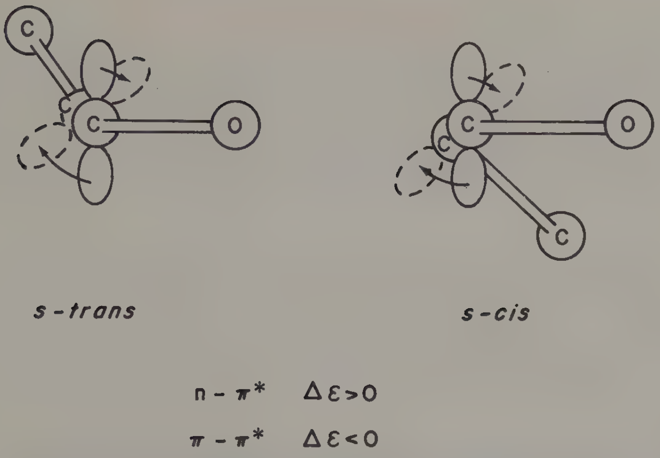


FIGURE 9. Orbital helicity rule applicable to either *s-cis* or *s-trans* enone. Reprinted with permission from D. N. Kirk, *Tetrahedron*, **42**, 777 (1986). Copyright (1986) Pergamon Journals Ltd

enone helicity defined by the sign of the angle ω is opposite in *s-cis* and *s-trans* conformations shown in Figure 9).

A number of semiempirical calculations were undertaken in an attempt to correlate the helicity of the skewed acrolein (**1a**) molecule with the rotational strength of its n–π* and π–π* transitions[124–126]. The results of the SCF–CNDO–CI calculations of Hug and Wagniere[124] are shown in Figure 10. Qualitatively the calculated rotational strengths R for the n–π* and π–π* transitions are of opposite sign for **1a** in the *s-trans* conformation, while they possess the same sign for the *s-cis* conformation. It should be noted that, according to the calculation neglecting perturbations by substituents in the vicinity of the acrolein chromophore, for $\omega = 90°$ rotational strength is zero for the n–π* transition and reaches a maximum for the π–π* transition.

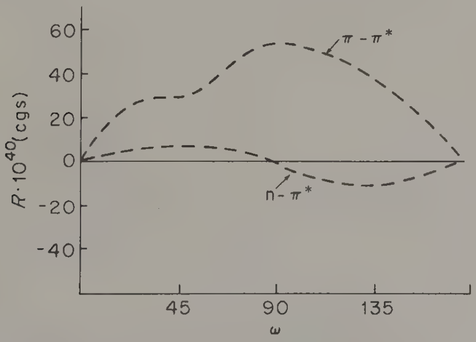


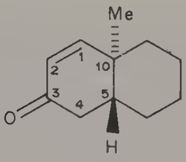
FIGURE 10. Calculated rotational strength R *vs.* the torsional angle ω in acrolein (**1a**) (redrawn from the data of Reference 124)

2. *Planar enones and dienones*

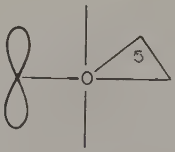
Nonplanar enones fall into the class of inherently dissymmetric chromophores, where local symmetry planes are lost and no sector rules, such as the octant rule for the n–π^* transition in saturated ketones, are applicable. In the case of a planar chromophore, nonzero rotational strength of a given transition must come from perturbation due to the closest chiral sphere and the use of a sector rule in such cases is justified. Chiroptical properties of planar *s-trans* enones ($\omega = 180°$) have indeed been considered in terms of sector rules.

The n–π^* transition is electrically forbidden and magnetically allowed, with the magnetic moment $\vec{m}$ directed along the C=O bond. Because the lowest-lying π^* orbital of enone contains two nodal surfaces (Figure 11a), the sign pattern has to change twice on going from the oxygen atom toward back sectors. Thus, according to Snatzke, a sector rule is obtained (Figure 11b) which has the sign pattern for the back octants opposite to that of the octant rule for saturated ketones[127–129]. The rule is also applicable to planar dienones of the **IIEt** type[130].

A planar chromophore is found in 2-cyclohexenones in a sofa S(5) conformation. In bicyclic 1-en-3-ones in a S(5) conformation $C_{(5)}$ is out of the plane formed by $C_{(1)}$–$C_{(4)}$ and $C_{(10)}$. The sector rule predicts a positive n–π^* Cotton effect for **86**, as is found experimentally.



(**86**)

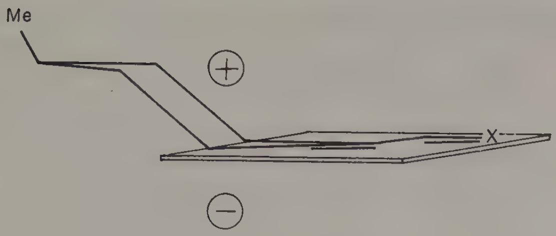


n–π^* +0.91 (349)
π–π^* −4.2 (227)
+6.3 (202)
(in heptane)

The planar diene rule proposed by Duraisamy and Walborsky (Figure 12, $X = CH_2$) apparently allows one to predict the sign of the π–π^* Cotton effect of planar enals ($X = O$), belonging to the group of cyclohexylideneacetaldehydes. When the molecule **87** of the

(a) (b)

FIGURE 11. Sector rule for the n–π^* transition of planar *s-trans* enones [128,129]. (a) Signs of contributions in upper sectors (large circles are for the signs in rear sectors). (b) Sign pattern for the rear sectors. Reproduced by permission of D. Reidel Publishing Company



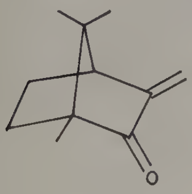
(87) X = O

n-π* −0.61 (347 nm)
π-π* +2.1 (230 nm)

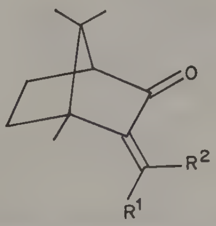
FIGURE 12. Planar rule for the π–π* Cotton effect of *s-trans* dienes ($X = CH_2$) and enals ($X = O$)[131]

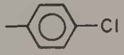
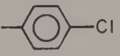
(R) absolute configuration is oriented as in Figure 12, bonds above the plane of the chromophore make a positive contribution to the π–π* transition Cotton effect[131]. Incidentally, the sign of the n–π* Cotton effect of **87** is correctly predicted by the sector rule mentioned earlier. Both rules can be used to determine the absolute configuration, if planarity of the chromophore is ascertained.

Derivatives of 2-bornanone (**88**) and 3-bornanone (**89–91**) are examples of planar *s-cis* enones. The near-planarity of the enone chromophore ($\omega = -4°$) in **90** and **91** was ascertained by X-ray analysis[132]. Thus the rotational power of the enone chromophore in **88** and **89** must originate from extrachromophoric perturbations in the bornane skeleton. A nearly mirror-image relationship between the CD curves for **88** and **89** results from the pseudoenantiomeric character of the perturbations in both enones (Table 25). In the *p*-chlorophenyl derivatives **90** and **91** the *p*-chlorostyrene part of the chromophore becomes nonplanar due to the twist of the aromatic ring from the plane of the C=C bond. The twist angle is +7° for the *Z*-isomer **90** and −146° for the *E*-isomer **91**. Thus the large π–π* Cotton effect of **91** is due to the significant nonplanarity of the *p*-chlorostyrene part of the conjugated enone chromophore[132].



(88)



	R1	R2
(89)	H	H
(90)	H	 Cl
(91)	 Cl	H

Rotational strength of planar dienals and dienones is influenced by their *E*/*Z* configuration. This is demonstrated by the CD data for the pairs of isomers: **3**, **5** and **4**, **6**. Opposite-sign π–π* Cotton effects are found for the *E*/*Z* isomers (data for cyclohexane solution)[6]:

3	Δε + 0.3 (277 nm)
5	− 0.4 (289 nm)
4	+ 1.2 (287 nm)
6	− 1.4 (290 nm)

(see page 59 for structural formulas)

TABLE 25. CD data for planar *s-cis* enones

	$\Delta\varepsilon$ (λ_{max}, nm)			
Compound	n–π^*	π–π^*	Solvent	Reference
88	+0.81 (344)	+4.99 (228)	*a*	52
89	−1.04 (346)	−5.54 (228)	*a*	52
90	−1.5 (389)	−11.2 (297)	*b*	132
91	+1.6 (348)	−41.2 (278)	*b*	132

[a] Methylcyclohexane.
[b] Dioxane.

This is apparently not related to *s-cis*/*s-trans* conformational changes, as both dienals **3** and **5** prefer *s-trans* conformation, but it is rather due to the change in the direction of the electric transition moment that is determined by the geometry of the π system.

3. Nonplanar enones and dienones

The empirical correlation between the helicity of *s-trans* enones and the sign of the n–π^* Cotton effect (Section III.B.1) has received support by the application of Snatzke's 'qualitative MO theory'[128,129]. It is shown in Figure 13 that for enones with $90^\circ < \omega < 180^\circ$ antiparallel arrangement of $\bar{m}$ and $\bar{\mu}$ transition moments is obtained, leading to the negative n–π^* Cotton effect. Since the n–π^* transition is electrically forbidden, the electric transition moment is obtained by the admixture of some π_2 character to the n orbital (left). The energy of the n MO is higher than that of π_2, thus HOMO consists of the energetically unfavored combination of the original n and π_2 orbitals. Formal multiplication by the LUMO (middle) yields an antiparallel arrangement of $\bar{\mu}$ and $\bar{m}$. This rule works well for *s-trans* enones in six- or seven-membered rings, but for 2-cyclopentenones, because of altered nodal properties, it has to be inverted[124,133].

An example of the application of CD measurements to conformational analysis of

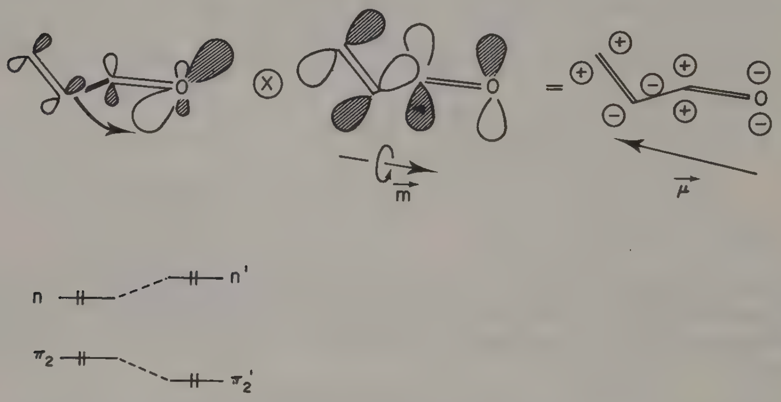


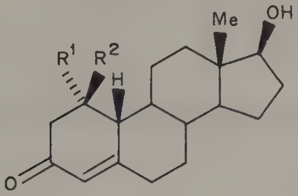
FIGURE 13. The rule for the n–π^* Cotton effect of nonplanar *s-trans* enones (the negative Cotton effect is obtained for the enone helicity shown). Taken from G. Snatzke, *Angew. Chem., Int. Ed. Engl.*, **18**, 363 (1979) and reproduced by permission of Verlag Chemie, GmbH, Weinheim

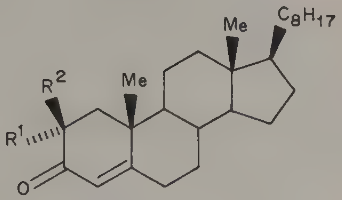
TABLE 26. CD data for steroidal 4-en-3-ones in various ring A conformations[120,134] (solvent ethanol)

	$\Delta\varepsilon$ (λ_{max}, nm)		
Compound	$n-\pi^*$	$\pi-\pi^*$	
92	−1.95 (316)	+8.2 (238)	+6.7 (219)
93	−3.1 (320)	+14.0 (243)	
94	+1.3 (325)	−21.5 (245)	
95	−1.48 (316)	+4.2 (240)[a]	+11.0 (217)
96	−2.45 (321)	+8.9 (235)[a]	+11.7 (215)
97	+1.43 (322)	−26.7 (244)	+11 (ca. 205)

[a] Shoulder.

steroidal 4-en-3-ones is shown in Table 26[134]. The usual conformation for unsubstituted steroidal 4-en-3-ones (**95**) is HC(1α, 2β)–S(1α) and for their 19-nor derivatives (**92**) it is HC(1α, 2β)–HC(1β, 2α) (Section II.E). The angle ω in 'normal' conformations is positive and increasing in the order: S(1α) < HC(1α, 2β) < S(2β); the $n-\pi^*$ and $\pi-\pi^*$ Cotton effects are respectively negative and positive. Introduction of 1α- or 2α-methyl group stabilizes the HC(1α, 2β) or S(2β) conformers, hence the increase in rotational strength of the enone chromophore in **93** and **96**. The epimeric derivatives **94** and **97** with a 1β- or 2β-methyl group prefer an 'inverted' HC(1β, 2α) conformation with a negative angle ω. In this conformation the repulsion between 1β-methyl and 11-methylene or 2β-methyl and 10β-methyl groups is reduced and the inversion of signs of the $n-\pi^*$ and long-wavelength $\pi-\pi^*$ Cotton effects is observed. Note that the second $\pi-\pi^*$ Cotton effect is invariably positive (*vide infra*).





(**92**) $R^1 = R^2 = H$ (**95**)
(**93**) $R^1 = Me$, $R^2 = H$ (**96**)
(**94**) $R^1 = H$, $R^2 = Me$ (**97**)

Quite similar conformational behavior of steroidal *s-trans* 4,9-dien-3-ones (**98**–**100**) is demonstrated by their CD spectra. 1α- and 1β-methyl-substituted dienones **99** and **100** give almost mirror-image $n-\pi^*$ (*ca* 350 nm) and $\pi-\pi^*$ (*ca* 290 nm) Cotton effects (Figure 14). As in the case of 4-en-3-ones, the CD curve reflects the conformation of ring A, i.e. HC(1α, 2β) for **99** and HC(1β, 2α) for **100**. The unsubstituted dienone **98** at room temperature exists as a mixture of conformers, roughly corresponding to $\frac{2}{3}$ HC(1β, 2α) and $\frac{1}{3}$ HC(1α, 2β), as confirmed by the calculated CD curve of **98** in Figure 14. At 83 K the CD of **98** becomes almost identical with that of **100**, which in turn does not change with

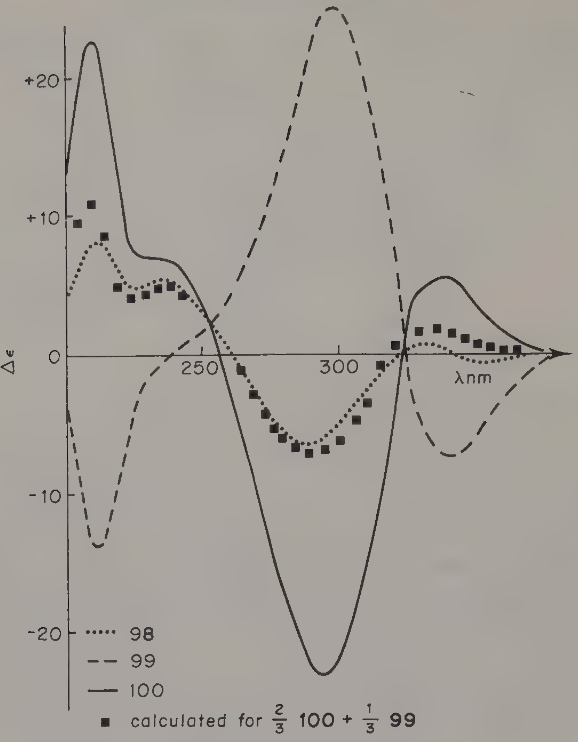
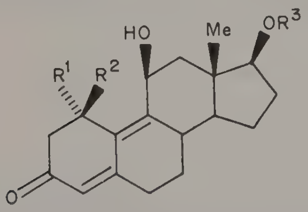


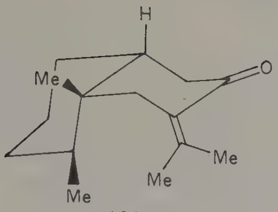
FIGURE 14. CD curves of 11β-hydroxy-4,9-dien-3-ones (solvent ethanol). Reprinted with permission from V. Delaroff, N. Dupuy, L. Nedelec and M. Legrand, *Tetrahedron*, **35**, 2681 (1979). Copyright (1979) Pergamon Journals Ltd

temperature. Thus, at 83 K the conformation of ring A in **98** is HC(1β,2α), with a negative torsional angle ω^{134}.



(**98**) $R^1 = R^2 = R^3 = H$
(**99**) $R^1 = Me$, $R^2 = H$, $R^3 = Ac$
(**100**) $R^1 = H$, $R^2 = Me$, $R^3 = Ac$

An example of application of CD measurements for the determination of the conformation of *s-cis* enones is the case of fukinone (**101**). Both n–π* and π–π* Cotton effects indicate, according to the orbital helicity rule (Section III.B.1), a negative helicity (i.e. $\omega < 0$) of the chromophore. From this it follows that the 'steroidal' conformation of (**101**), as shown, is preferred over the 'nonsteroidal' one. Variable-temperature CD measurements give the $\Delta G°$ value 0.9 kcal mol^{-1} ^{135}.

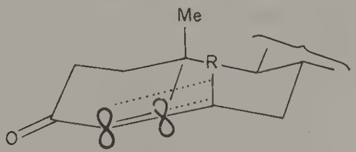


(101)

	297 K	83 K
n–π^*, $\Delta\varepsilon$ (325 nm)	-0.38	-0.46
π–π^*, $\Delta\varepsilon$ (243 nm)	$+3.4$	$+7.2$

4. Substitution effects

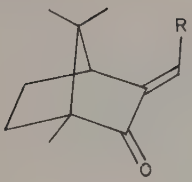
Nonplanar *s-cis* enones frequently give π–π^* Cotton effects of opposite sign to those predicted by the application of the enone helicity rule[122,136]. In order to eliminate the discrepancy Burgstahler and coworkers have proposed that chiral interactions of allylic axial bonds with the enone (or diene) chromophore in the excited state are the primary factors controlling the sign of the π–π^* Cotton effect[137]. Based on the experimental data of Kuriyama and coworkers[138] a strong influence of the allylic C—O bond on the π–π^* Cotton effect of enones has been shown by Beecham[139]. The effect of allylic axial bonds is particularly well documented for 6β-substituents in the steroidal 4-en-3-ones **102**–**107**[121,140]. As is seen from the data of Table 27, all donor substituents in the 6β position have a strong influence on the n–π^* and π–π^* Cotton effects. In fact the contribution is so strong that sign reversal is observed for both Cotton effects, with respect to the parent enone (R = H), the exception being the n–π^* Cotton effect in **102**–**104**. The 6β substituent is in an ideal orientation for overlap with the π orbital, the left-handed helicity of the R—C—C=C system giving rise to the strong negative contribution to the π–π^* Cotton effect. That the effect is of purely electronic origin is ascertained by the small influence exerted by equatorial 6α substituents on the chiroptical properties of 4-en-3-ones. In addition, X-ray data indicate that even in the 6β-bromo derivative ring A remains in S(1α) conformation, with a nearly planar ($\omega = -173.6°$) enone chromophore[141].



(102)–(107)

TABLE 27. Contributions of the allylic axial 6β substituents to the n–π^* and π–π^* Cotton effects of steroidal 4-en-3-ones (data from References 120 and 138)

		$\Delta\varepsilon_R - \Delta\varepsilon_H$	
Compound	R	n–π^*	π–π^* (*ca* 250 nm)
102	OAc	$+0.1$	-7.1
103	NHAc	$+0.4$	-7.8
104	OH	$+0.7$	-9.5
105	Me	$+2.1$	-12.8
106	Cl	$+2.1$	-18.8
107	Br	$+3.4$	-25.4



R	Δε (λ_{max}, nm)
H	+ 8.5 (225)
Me	+ 9.5 (235)
$OCH_2CH{=}CH_2$	+ 10.5 (255)
NHMe	+ 10.6 (295)

(solvent hexane)

SCHEME 5

If the heteroatom substituent is in the plane of the enone chromophore, only minor changes are observed in the π–π* Cotton effects, as exemplified by the CD data for the planar *s-cis* enones in Scheme 5.

5. *Short-wavelength Cotton effects of 2-cyclohexenones*

As soon as improved CD instruments allowed one to penetrate the spectral region down to 200 nm, it was recognized that two CD bands appear within the π–π* UV absorption envelope of polycyclic enones[136,142]. The long-wavelength (260–230 nm) CD band corresponds to the isotropic UV absorption band. The shorter-wavelength CD band (220–200 nm) was earlier thought to originate from the chiral perturbation of the enone carbonyl group by the α′-axial substituent[137]. Subsequently, reconsideration of the substitution and solvent effect has led to the assignment of the second π–π* band to the 220–200 nm Cotton effect[120,143]. Gawronski[120] has proposed a simple correlation between the sign of the 220–200 nm Cotton effect and the absolute configuration of the polycyclic enone (Figure 15). Enones whose structure falls into the general P-type formula (defined by the right-handed helicity of the C=C—C—R bond system) show a positive 220–200 nm Cotton effect, regardless of other conformational or substitution effects that may affect n–π* and π–π* (260–230 nm) Cotton effects. The negative Cotton effect is exhibited by enones of M-type (with left-handed helicity of the C=C—C—R bond system in Figure 15) (see Scheme 6).

In substituted 2-cyclohexenones a further Cotton effect appears below 200 nm, having no corresponding UV maximum. Contrary to the two π–π* Cotton effects at longer wavelength, its position is slightly blue-shifted in polar solvents. By analogy with saturated ketones it is considered as an n–σ* Cotton effect and it appears in the 195–185 nm range in 2-cyclohexenones having an α′-axial (R) or β′-axial (R′) substituent. The sign of this Cotton effect

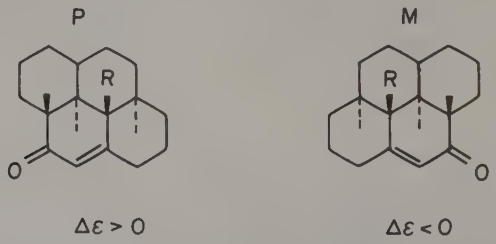
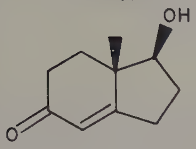
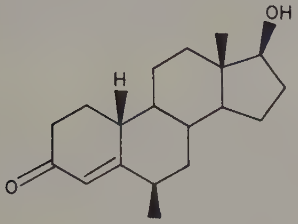
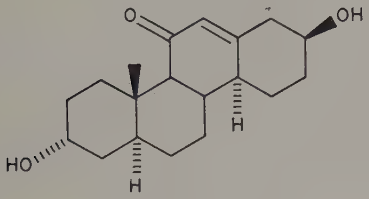
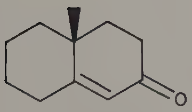
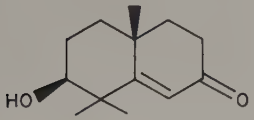
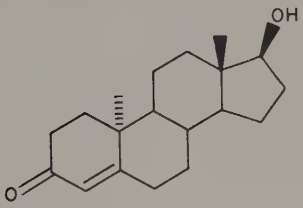


FIGURE 15. Configurational dependence of the 220–200 nm π–π* Cotton effect of polycyclic cyclohexenones[120]

	$\Delta\varepsilon$ (λ_{max}, nm; in methanol)	
	n–π^*	π–π^*
P-type		
	+ 2.7 (323)	− 10.3 (242) + 11.9 (204)
	− 1.5 (323)	− 5.2 (242) + 4.7 (210)[120]
	− 2.3 (339)	+ 5.8 (239) + 10.5 (212)[120]
M-type		
	+ 0.5 (339)	− 13.0 (230) − 6.6 (211)[a]
	− 1.8 (328)	+ 1.5 (252) − 7.1 (216)
	− 1.9 (331)	− 0.4 (251) − 11.3 (212)[120]

---

[a] Measured in heptane.

SCHEME 6

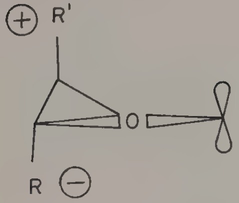
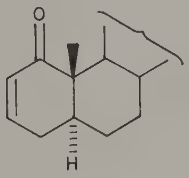


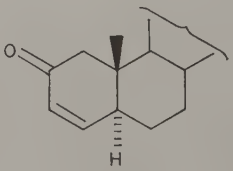
FIGURE 16. Substituent contributions to the Cotton effect below 200 nm of cyclohexenones with a planar enone chromophore. Reprinted with permission from J. Gawronski, *Tetrahedron*, **38**, 3 (1982). Copyright (1982) Pergamon Journals Ltd

is correlated with the absolute configuration of the substituents R and R′ (Figure 16). The Cotton effects below 200 nm of the two isomeric cholestenones **108** and **109** are shown below the structures[120]. In **108** the short-wavelength π–π^* and n–σ^* Cotton effects overlap in nonpolar solvents, but they move in opposite directions in the highly polar 1,1,1,3,3,3-hexafluoro-2-propanol.



(108)

in hexane: $\Delta\varepsilon + 28.0$(198 nm)
in $(CF_3)_2CHOH$: $\Delta\varepsilon + 12.3$ (207 nm)
$+ 11.4$ (191 nm)

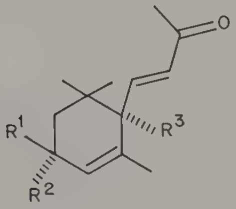


(109)

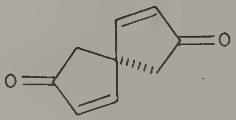
in MeCN: $\Delta\varepsilon + 2.3$ (189 nm)

6. Exciton interactions of enones

The interaction of the allylic substituent with the enone chromophore discussed in the preceding section is demonstrated in yet another way in the CD spectra of a series of homoconjugated enones **110**–**112** (Table 28). The enones **110**–**112** with the same chirality of the homoconjugated system display a strong positive Cotton effect at the wavelength just above their π–π^* UV maximum. The bis-enones **113** and **114** show even stronger π–π^* Cotton effects of opposite sign in the vicinity of the UV maximum.



(110)–(114)



(115)

The appearance of strong Davydov-split Cotton effects in the vicinity of the isotropic absorption maximum of the electrically allowed transition in bi- or multichromophoric systems is indicative of chiral exciton interaction of the chromophores[149]. This interaction has been applied by Nakanishi and Harada to various stereochemical problems in a form

TABLE 28. π–π^* Bands of homoconjugated enones

Enone	R^1	R^2	R^3	$\Delta\varepsilon$ (nm)	ε (nm)	Solvent	Ref.
110	H	H	OH	+13.6 (235)	13,000 (228)	MeCN	144
111	H	OMe	H	+20.2 (233)	13,000 (225)	ethanol	145
112	H	OH	H	+25.4 (237)		dioxane	146
113	O		H	+35.9 (240) [a]	19,300 (237)	ethanol	147
114	O		OH	+38.4 (242) −30.2 (208)	21,300 (234)	methanol	147
115				+38 (228) −16 (210)	16,000 (223)	isooctane	148

[a] Second band not reported.

of the 'exciton chirality method'[150]. In a simple formulation, positive chirality of the system consisting of the electric transition moments of the two chromophores gives rise to the Davydov-split CD curve having a positive first (i.e. lower energy) Cotton effect (Figure 17). The interacting chromophores having electrically allowed π–π^* transitions include enones, α,β-unsaturated esters, benzoates and other aromatic chromophores[151]. The direction of the electric transition moment of the chromophore can be determined by measurements of linear dichroism (Section III.A) or by semiempirical MO calculations. It is conventionally assumed that in enones the point-dipole transition moment is located at the mid-point of the central C—C bond.

The application of the exciton chirality method for determination of the absolute configuration of two naturally occurring compounds having an enone chromophore, i.e. quassin (**116**) and abscissic acid (**117**), is shown below. The observed bisignate Cotton effect of quassin (around 250 nm) is due to the Davydov splitting of the π–π^* transitions of the planar 2-methoxyenone chromophores. Figure 18 shows the experimental and calculated CD curves of **116**, the negative band at 330 nm in the experimental curve being due to the n–π^* transition. Excellent agreement between the measured and calculated CD curves allowed one to establish the absolute configuration of quassin as shown in Figure 18[151].

Unlike the case of the rigid skeleton of quassin, determination of the absolute configuration of (+)-*cis*-abscissic acid (**117**) requires consideration of ring and side-chain conformations, in order to estimate the directions of the transition moments of the enone and dienic acid chromophores. As a model compound, (+)-*trans*-abscissic acid (**118**) was used for experimental studies and semiempirical calculations. From the presence of the W-type coupling in the proton NMR spectra of **118** ($J_{2\beta,4} = 1$ Hz) it follows that the

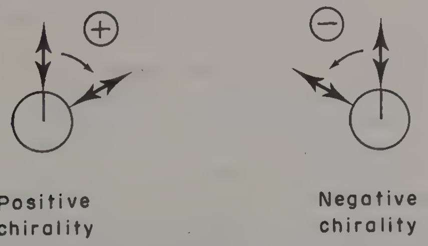


FIGURE 17. Qualitative definition of exciton chirality

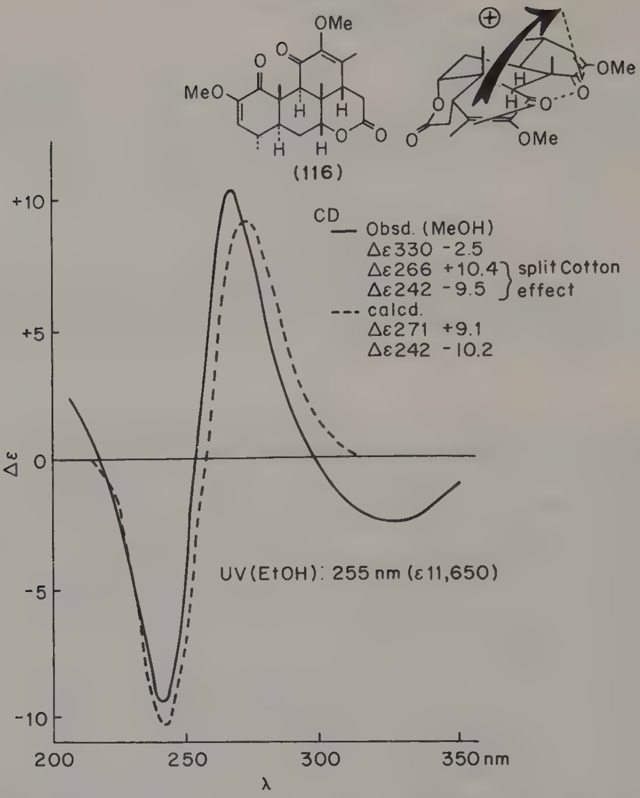
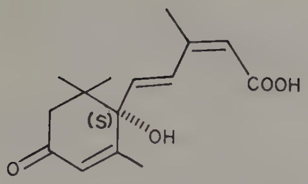


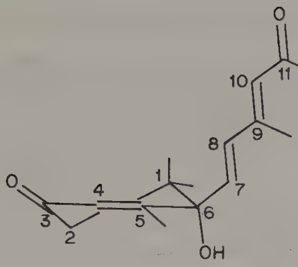
FIGURE 18. CD spectra of quassin (**116**):——observed (in methanol), – – – calculated. Reprinted with permission from M. Koreeda, N. Harada and K. Nakanishi, *J. Am. Chem. Soc.*, **96**, 266 (1974). Copyright (1974) American Chemical Society

cyclohexenone ring adopts the HC(1β, 2α) conformation. The best fit between the experimental and calculated CD curves of **118** was obtained for (*S*)-configuration (as shown), and the side-chain conformation defined by the torsional angle $O—C_{(6)}—C_{(7)}—C_{(8)} = +150°$. According to calculations, changes of the side-chain conformation have no effect on the assignment of the absolute configuration of **118**. Thus, based on the observed signs of the exciton Cotton effect, the absolute configuration of natural abscissic acid (**117**) is also (*S*)[147].

The absolute configuration of a molecule containing a single enone chromophore can be determined by the exciton chirality method if the second chromophore necessary for exciton interaction is introduced by chemical modification. A common technique is to transform the hydroxy group into the benzoate[151]. Benzoates of steroidal 17-hydroxy-4-en-3-ones were the first extensively studied examples of exciton coupling between two different chromophores[152]. The benzoates of the two axially chiral and stereochemically correlated derivatives of adamantane, the hydroxyenal **119** and the hydroxyenone **120**, display exciton Cotton effects in the region of the π–π* transitions of the enone (enal) and benzoate chromophores. The pattern of signs of the measured Davydov-split Cotton



(117)

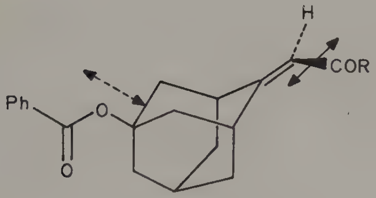


(118)

$\Delta\varepsilon$	$+34.5\,(261)$	$+25.5\,(254)$
	$-28.0\,(229)$	$-12.6\,(221)$
ε	$24{,}800\,(245)$	$28{,}400\,(241)$

(in methanol)

effects of **119** and **120** is due to the negative chirality of the two transition moments, from which the (S) absolute configuration of the two molecules can be deduced. The uniformity of signs of the Cotton effects of **119** and **120** proves that exciton interactions are not significantly altered by *s-cis/s-trans* conformational differences between the enal and enone chromophores[153].



(119) R = H $\Delta\varepsilon\ -15.6\,(237)$
$+3.0\,(221)$
$\varepsilon\ 35{,}000\ (232)$
(120) R = Me $\Delta\varepsilon\ -12.9\,(239)$
$+9.1\,(223)$
$\varepsilon\ 27{,}700\,(230)$

(in cyclohexane)

IV. ACKNOWLEDGEMENTS

Thanks are due to Prof. K. Mori for supplying the author with samples of compounds for the CD measurements. Some of the enones for which spectral data are provided were prepared within the RP II.13.2.10 research grant.

V. REFERENCES

1. R. J. Loncharich, T. R. Schwartz and K. N. Houk, *J. Am. Chem. Soc.*, **109**, 14 (1987).
2. S. Marriott and R. D. Topsom, *J. Mol. Struct.*, **106**, 277 (1984).
3. C. E. Blom, G. Grassi and A. Bauer, *J. Am. Chem. Soc.*, **106**, 7427 (1984).
4. E. A. Cherniak and C. C. Costain, *J. Chem. Phys.*, **45**, 104 (1966).
5. T. Liljefors and N. L. Allinger, *J. Am. Chem. Soc.*, **98**, 2745 (1976).
6. J. K. Gawronski and H. M. Walborsky, *J. Org. Chem.*, **51**, 2863 (1986).
7. H. O. House, in *Stereochemistry and Reactivity of Systems Containing π Electrons* (Ed. W. H. Watson), Verlag Chemie Int., Deerfield Beach, 1983, pp. 279–317.
8. E. A. Braude and C. J. Timmons, *J. Chem. Soc.*, 3766 (1955).

9. F. H. Cottee, B. P. Straugham, C. J. Timmons, W. F. Forbes and R. Shilton, *J. Chem. Soc. (B)*, 1146 (1967).
10. K. Noack, *Spectrochim. Acta*, **18**, 1625 (1962).
11. H.-J. Oelichmann, D. Bougeard and B. Schrader, *J. Mol. Struct.*, **77**, 179 (1981); **77**, 149 (1981).
12. H. N. A. Al-Jallo and E. S. Waight, *J. Chem. Soc. (B)*, 73 (1966); 75 (1966).
13. R. L. Erskine and E. S. Waight, *J. Chem. Soc.*, 3425 (1960).
14. K. Noack and R. N. Jones, *Can. J. Chem.*, **39**, 2201 (1961).
15. (a) J. G. Angyan, A. Kucsman, R. A. Poirier and I. G. Csizmadia, *J. Mol. Struct. (Theochem)*, **123**, 189 (1985).
    (b) F. S. Jorgensen, L. Carlsen and F. Duus, *J. Am. Chem. Soc.*, **103**, 1350 (1981).
16. H. Martens, G. Hoornaert and S. Toppet, *Tetrahedron*, **29**, 4241 (1973).
17. H. Dodziuk, K. Kamienska-Trela and J. Dabrowski, *Roczniki Chem.*, **44**, 393 (1970).
18. A. R. Katritzky, R. F. Pinzelli and R. D. Topsom, *Tetrahedron*, **28**, 3449 (1972).
19. R. Mecke and K. Noack, *Chem. Ber.*, **93**, 210 (1960).
20. E. S. Waight and R. L. Erskine, in *Steric Effects in Conjugated Systems* (Ed. G. W. Gray), Butterworths, London, 1958, pp. 73–81.
21. A. Bienvenüe, *J. Am. Chem. Soc.*, **95**, 7345 (1973).
22. A. Bienvenüe and B. Duchatellier, *Tetrahedron*, **28**, 833 (1972).
23. W. P. Hayes and C. J. Timmons, *Spectrochim. Acta*, **24A**, 323 (1968).
24. C. E. Blom, R. P. Müller and H. H. Günthard, *Chem. Phys. Lett.*, **73**, 483 (1980).
25. K. Noack and R. N. Jones, *Can. J. Chem.*, **39**, 2225 (1961).
26. A. J. Bowles, W. O. George and W. F. Maddams, *J. Chem. Soc. (B)*, 810 (1969).
27. A. F. Kluge and C. P. Lillya, *J. Org. Chem.*, **36**, 1977 (1971).
28. H.-J. Oelichmann, D. Bougeard and B. Schrader, *Angew. Chem., Int. Ed. Engl.*, **21**, 639 (1982).
29. H. Junge, *Spectrochim. Acta*, **24A**, 1965 (1968).
30. J. Dabrowski and K. Kamienska-Trela, *Bull. Chem. Soc. Jpn.*, **39**, 2565 (1966).
31. J. Dabrowski and M. Tencer, *Bull. Chem. Soc. Jpn.*, **48**, 1310 (1975).
32. J. Dabrowski and K. Kamienska-Trela, *Spectrochim. Acta*, **22**, 211 (1966).
33. W. R. Benson and A. E. Pohland, *J. Org. Chem.*, **29**, 385 (1964).
34. L. Kania, K. Kamienska-Trela and M. Witanowski, *J. Mol. Struct.*, **102**, 1 (1983).
35. D. Smith and P. J. Taylor, *Spectrochim. Acta*, **32A**, 1477 (1976).
36. D. W. Boerth, *J. Org. Chem.*, **47**, 4085 (1982) and references cited therein.
37. C. F. Dykstra, *J. Am. Chem. Soc.*, **98**, 7182 (1976).
38. E. R. Davidson and L. E. Nitzsche, *J. Am. Chem. Soc.*, **101**, 6524 (1979).
39. J. C. D. Brand and D. G. Williamson, *Discuss. Faraday Soc.*, **35**, 184 (1963).
40. R. C. Cookson and S. H. Dandegaonker, *J. Chem. Soc.*, 1651 (1955).
41. M. F. Nicol, *Appl. Spectrosc. Rev.*, **8**, 183 (1974).
42. S. Iwata and K. Morokuma, *J. Am. Chem. Soc.*, **97**, 966 (1975).
43. R. B. Woodward, *J. Am. Chem. Soc.*, **63**, 1123 (1941); **64**, 76 (1942).
44. J. M. Hollas, *Spectrochim. Acta*, **19**, 1425 (1963).
45. W. F. Forbes and R. Shilton, *J. Am. Chem. Soc.*, **81**, 786 (1959).
46. H. O. House and R. S. Ro, *J. Am. Chem. Soc.*, **80**, 2428 (1958).
47. P. K. Das and R. S. Becker, *J. Phys. Chem.*, **82**, 2081 (1978).
48. T. Takemura, P. K. Das, G. Hug and R. S. Becker, *J. Am. Chem. Soc.*, **98**, 7099 (1976).
49. L. F. Fieser and M. Fieser, *Steroids*, Van Nostrand–Reinhold, Princeton, 1959, pp. 15–21.
50. T. Liljefors and N. L. Allinger, *J. Am. Chem. Soc.*, **100**, 1068 (1978).
51. (a) E. A. Braude and C. J. Timmons, *J. Chem. Soc.*, 3766 (1955).
    (b) E. A. Braude and F. Sondheimer, *J. Chem. Soc.*, 3754 (1955).
52. D. A. Lightner, M. J. Flores, B. V. Crist and J. K. Gawronski, *J. Org. Chem.*, **45**, 3518 (1980).
53. A. F. Cameron and G. Jamieson, *J. Chem. Soc. (B)*, 1581 (1971).
54. H. O. House, R. F. Sieloff, T. V. Lee and M. B. De Tar, *J. Org. Chem.*, **45**, 1800 (1980).
55. W. E. Thiessen, H. A. Levy, W. G. Dauben, G. H. Beasley and D. A. Cox, *J. Am. Chem. Soc.*, **93**, 4312 (1971).
56. J. Dabrowski and K. Kamienska-Trela, *J. Am. Chem. Soc.*, **98**, 2826 (1976).
57. C. Skötsch and E. Breitmaier, *Chem. Ber.*, **113**, 795 (1980).
58. J. Dabrowski and M. Tencer, *Tetrahedron*, **32**, 587 (1976).
59. L. Bardon, J. Elquero and R. Jacquier, *Bull. Soc. Chim. France*, 297 (1967).

60. G. Quinkert, G. Dürner, E. Kleiner, F. Adam, E. Haupt and D. Leibfritz, *Chem. Ber.*, **113**, 2227 (1980).
61. N. Boccara and P. Maitte, *Tetrahedron Lett.*, 4031 (1977).
62. W. K. Chan, K. Nakanishi, T. G. Ebrey and B. Honig, *J. Am. Chem. Soc.*, **96**, 3642 (1974).
63. R. Gilardi, I. L. Karle, J. Karle and W. Sperling, *Nature*, **232**, 187 (1971); R. Gilardi, I. L. Karle and J. Karle, *Acta Crystallogr., Sect. B*, **28**, 2605 (1972); T. Hamanaka, T. Mitsui and M. Kakudo, *Acta Crystallogr., Sect. B*, **28**, 214 (1972).
64. A. Warshel and M. Karplus, *J. Am. Chem. Soc.*, **96**, 5677 (1974).
65. I. Naito, A. Kinoshita and T. Yonemitsu, *Bull. Chem. Soc. Jpn.*, **49**, 339 (1976).
66. J. E. Baldwin, *J. Org. Chem.*, **30**, 2423 (1965).
67. D. D. Faulk and A. Fry, *J. Org. Chem.*, **35**, 364 (1970).
68. C. J. Timmons, *Chem. Commun.*, 576 (1965).
69. F. H. Cottee and C. J. Timmons, *J. Chem. Soc. (B)*, 326 (1968).
70. D. H. Williams, *Tetrahedron Lett.*, 2305 (1965).
71. P. Bass and H. Cerfontain, *Tetrahedron*, **33**, 1509 (1977).
72. J. Ronayne, M. V. Sargent and D. H. Williams, *J. Am. Chem. Soc.*, **88**, 5288 (1966).
73. G. Montaudo, V. Librando, S. Caccamese and P. Maravigna, *J. Am. Chem. Soc.*, **95**, 6365 (1973).
74. T. M. Filippova, A. R. Bekker and B. D. Lavrukhin, *Org. Magn. Reson.*, **14**, 337 (1980).
75. J. Dabrowski and L. J. Kozerski, *Org. Magn. Reson.*, **4**, 137 (1972).
76. T. Toda, M. C. Woods and K. Takahashi, *Tetrahedron*, **27**, 5391 (1971).
77. K. Müllen, S. Bender, E. Kotzamani, H. Schmickler, B. Frei and H. R. Wolf, *Tetrahedron Lett.*, **22**, 3513 (1981).
78. M. L. Filleux-Blanchard, F. Mabon and C. J. Martin, *Tetrahedron Lett.*, 3907 (1974).
79. M. Tencer and J. Dabrowski, *Spectroscopy Lett.*, **16**, 351 (1983).
80. D. H. Marr and J. B. Stothers, *Can. J. Chem.*, **43**, 596 (1965).
81. S. Braun, *Org. Magn. Reson.*, **11**, 197 (1978).
82. M. W. Barrett, R. D. Farrant, D. N. Kirk, J. D. Mersh, J. K. M. Sanders and W. L. Duax, *J. Chem. Soc., Perkin Trans. 2*, 105 (1982).
83. F. Pavelčik, K. Havetta and V. Suchy, *Acta Crystallogr., Sect. C*, **41**, 1272 (1985).
84. K. Tokuno, M. Matsui, F. Miyoshi, Y. Asao and T. Ohashi, *Acta Crystallogr., Sect. C*, **42**, 85 (1986).
85. D. Rabinovich, *J. Chem. Soc. (B)*, 11 (1970).
86. S. K. Branch and I. W. Nowell, *Acta Crystallogr., Sect. C*, **41**, 769 (1985).
87. A. E. Jungk and G. M. J. Schmidt, *J. Chem. Soc. (B)*, 1427 (1970).
88. A. Hoser, Z. Kałuski, H. Małuszynska and V. D. Orlov, *Acta Crystallogr., Sect. B*, **36**, 1256 (1980).
89. Z. Kałuski, E. Skrzypczak-Jankun, V. D. Orlov and A. I. Borovoi, *Bull. Acad. Pol. Sci., Ser. Chim.*, **26**, 869 (1978).
90. A. Katrusiak, M. Ratajczak-Sitarz, Z. Kałuski and V. D. Orlov, *Acta Crystallogr., Sect. C*, **43**, 103 (1987).
91. A. Katrusiak, M. Ratajczak-Sitarz, Z. Kałuski, V. D. Orlov, U. A. Borovoi and E. I. Mihedkina, *Acta Crystallogr., Sect. C*, **43**, 342 (1987).
92. V. Zabel, W. H. Watson, S. Alvarado, J. F. Ciccio and J. Calzada, *Acta Crystallogr. Sect. B*, **36**, 2816 (1980).
93. Mazhar-Ul-Haque, D. Rogers and C. N. Caughlan, *J. Chem. Soc., Perkin Trans. 2*, 223 (1974).
94. M. J. Bovill, M. H. P. Guy, G. A. Sim, D. N. J. White and W. Herz, *J. Chem. Soc., Perkin Trans. 2*, 53 (1979).
95. M. Soriano-Garcia, B. Ortiz and R. A. Toscano, *Acta Crystallogr., Sect. C*, **40**, 479 (1984).
96. W. L. Duax, C. Eger, S. Pokrywiecki and Y. Osawa, *J. Med. Chem.*, **14**, 295 (1971).
97. P. J. Cox and G. A. Sim, *Acta Crystallogr., Sect. B*, **38**, 1360 (1982).
98. C. M. Weeks, W. L. Duax and Y. Osawa, *Acta Crystallogr., Sect. B*, **31**, 1502 (1975).
99. A. Cooper, C. T. Lu and D. A. Norton, *J. Chem. Soc. (B)*, 1228 (1968).
100. (a) *Atlas of Steroid Structure*, Vol. 1 (Eds. W. L. Duax and D. A. Norton), IFI–Plenum, New York, 1975; Vol. 2 (Eds. J. F. Griffin, W. L. Duax and C. M. Weeks), IFI–Plenum, New York, 1984.
    (b) W. L. Duax, C. M. Weeks and D. C. Rohrer, *Top. Stereochem.*, **9**, 271 (1976).
101. C. Romers, C. Altona, H. J. C. Jacobs and R. A. G. de Graaf, *Terpenoids and Steroids*, **4**, 531 (1974).

102. P. J. Roberts, J. C. Coppola, N. W. Isaacs and O. Kennard, *J. Chem. Soc., Perkin Trans. 2*, 774 (1973).
103. H. Campsteyn, L. Dupont and O. Dideberg, *Acta Crystallogr., Sect. B*, **30**, 90 (1974).
104. M. M. Bhadbhade and K. Venkatesan, *Acta Crystallogr. Sect. C*, **40**, 1905 (1984).
105. G. Precigoux, B. Busetta, C. Courseille and M. Hospital, *Acta Crystallogr., Sect. B*, **31**, 1527 (1975).
106. W. L. Duax, V. Cody, J. F. Griffin, J. Hazel and C. M. Weeks, *J. Steroid Biochem.*, **9**, 901 (1978).
107. M. J. Begley, E. A. Frecknall and G. Pattenden, *Acta Crystallogr., Sect. C*, **40**, 1745 (1984).
108. H. Irngartinger, M. Nixdorf, W. Dobler and R. Gleiter, *Acta Crystallogr., Sect. C*, **40**, 1481 (1984).
109. J. D. M. Asher and G. A. Sim, *J. Chem. Soc.*, 6041 (1965).
110. D. N. J. White and G. A. Sim, *J. Chem. Soc., Perkin Trans. 2*, 1826 (1975).
111. A. T. McPhail and K. D. Onan, *J. Chem. Soc., Perkin Trans. 2*, 332 (1976).
112. B. Norden, *Appl. Spectrosc. Rev.*, **14**, 157 (1978).
113. J. Michl and E. W. Thulstrup, *Spectroscopy with Polarized Light. Solute Alignment by Photoselection, in Liquid Crystals, Polymers, and Membranes*, Verlag Chemie, New York, 1986.
114. (a) A. Yogev, L. Margulies, D. Amar and Y. Mazur, *J. Am. Chem. Soc.*, **91**, 4558 (1969).
    (b) A. Yogev, J. Riboid, J. Marero and Y. Mazur, *J. Am. Chem. Soc.*, **91** 4559 (1969).
115. J. Gawronski, T. Liljefors and B. Norden, *J. Am. Chem. Soc.*, **101**, 5515 (1979).
116. L. Velluz, M. Legrand and M. Grosjean, *Optical Circular Dichroism*, Chapt. 4, Academic Press, New York, 1965.
117. G. Snatzke, in *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry* (Ed. G. Snatzke), Chap. 13, Heyden, London, 1967.
118. G. Snatzke and F. Snatzke, in *Fundamental Aspects and Recent Developments in Optical Rotatory Dispersion and Circular Dichroism* (Eds. F. Ciardelli and P. Salvadori), Heyden, London, 1973, pp. 109–116., 121–123.
119. M. Legrand and M. J. Rougier, in *Stereochemistry, Fundamentals and Methods*, Vol. 2 (Ed. H. B. Kagan), G. Thieme, Stuttgart, 1977, pp. 123–127.
120. J. Gawronski, *Tetrahedron*, **38**, 3 (1982).
121. D. N. Kirk, *Tetrahedron*, **42**, 777 (1986).
122. C. Djerassi, R. Records, E. Bunnenberg, K. Mislow and A. Moscowitz, *J. Am. Chem. Soc.*, **84**, 870 (1962).
123. W. B. Whalley, *Chem. Ind.*, 1024 (1962).
124. W. Hug and G. Wagniere, *Helv. Chim. Acta*, **54**, 633 (1971).
125. Kam-khow Cheong, A. Oshita, D. J. Caldwell and H. Eyring, *Proc. Natl. Acad. Sci. U.S.A.*, **67**, 1727 (1970); *Topics Modern Phys.*, 93 (1971).
126. T. Aoyama and H. Yamakawa, *Nippon Kagaku Kaishi*, **1** (1976).
127. G. Snatzke, *Tetrahedron*, **21**, 413 (1965).
128. G. Snatzke, *Angew. Chem., Int. Ed. Engl.*, **18**, 363 (1979).
129. G. Snatzke, in *Optical Activity and Chiral Discrimination* (Ed. S. F. Mason), D. Reidel, Dordrecht, 1979, pp. 53–54.
130. G. Snatzke, *Tetrahedron*, **21**, 439 (1965).
131. M. Duraisamy and H. M. Walborsky, *J. Am. Chem. Soc.*, **105**, 3264 (1983).
132. F. Labruyere, C. Bertrand, C. Metge, A. Dubourg, R. Roques, J. P. Declercq and G. Germain, *Acta Crystallogr., Sect. C*, **40**, 277 (1984).
133. G. Snatzke, *Tetrahedron*, **21**, 421 (1965).
134. V. Delaroff, N. Dupuy, L. Nedelac and M. Legrand, *Tetrahedron*, **35**, 2681 (1979).
135. T. Sato, M. Tada, T. Takahashi, I. Horibe, H. Ishii, T. Iwata, K. Kuriyama, Y. Tamura and K. Tori, *Chem. Lett.*, 1191 (1977); M. Tada, T. Sato, T. Takahashi, K. Tori, I. Horibe and K. Kuriyama, *J. Chem. Soc., Perkin Trans. 1*, 2695 (1981).
136. H. Ziffer and C. H. Robinson, *Tetrahedron*, **24**, 5803 (1968).
137. A. W. Burgstahler and R. C. Barkhurst, *J. Am. Chem. Soc.*, **92**, 7601 (1970); A. W. Burgstahler, R. C. Barkhurst and J. K. Gawronski, in *Modern Methods of Steroid Analysis* (Ed. E. Heftmann), Chap. 16, Academic Press, New York, 1973.
138. K. Kuriyama, M. Moriyama, T. Iwata and K. Tori, *Tetrahedron Lett.*, 1661 (1968).
139. A. F. Beecham, *Tetrahedron*, **27**, 5207 (1971).
140. R. N. Totty and J. Hudec, *Chem. Commun.*, 785 (1971).

141. E. M. Gopalakrishna, A. Cooper and D. A. Norton, *Acta Crystallogr., Sect. B*, **25**, 639 (1969).
142. L. Velluz, M. Legrand and R. Viennet, *C.R. Hebd. Seances Acad. Sci.*, **261**, 1687 (1965).
143. R. D. Burnett and D. N. Kirk, *J. Chem. Soc., Perkin Trans. 1*, 1460 (1981).
144. W. Eschenmoser, P. Uebelhart and C. H. Eugster, *Helv. Chim. Acta*, **64**, 2681 (1981).
145. R. Buchecker, P. Hamm and C. H. Eugster, *Chimia*, **25**, 192 (1971).
146. H. Mayer and A. Ruettimann, *Helv. Chim. Acta*, **63**, 1451 (1980).
147. M. Koreeda, G. Weiss and K. Nakanishi, *J. Am. Chem. Soc.*, **95**, 239 (1973); N. Harada, *J. Am. Chem. Soc.*, **95**, 240 (1973).
148. M. Sumiyoshi, H. Kuritani and K. Shingu, *Chem. Commun.*, 812 (1977).
149. S. F. Mason, *J. Chem. Soc.* (*B*), 370 (1966); S. F. Mason, in *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry* (Ed. G. Snatzke), Heyden, London, 1967, p. 71.
150. N. Harada and K. Nakanishi, *Circular Dichroic Spectroscopy—Exciton Coupling in Organic Stereochemistry*, University Science Books, Mill Valley, 1983.
151. M. Koreeda, N. Harda and K. Nakanishi, *J. Am. Chem. Soc.*, **96**, 266 (1974).
152. V. Delaroff and R. Viennet, *Bull. Soc. Chim. France*, 277 (1972).
153. J. K. Gawronski, S. M. Reddy and H. M. Walborsky, *J. Am. Chem. Soc.*, **109**, 6726 (1987).

The Chemistry of Enones
Edited by S. Patai and Z. Rappoport

CHAPTER **4**

Thermochemistry of enones and related species

JOEL F. LIEBMAN and RALPH M. POLLACK

Department of Chemistry, University of Maryland Baltimore County, 5401 Wilkens Avenue, Baltimore, MD 21228, USA and Center for Advanced Research in Biotechnology, 9600 Gudeslky Drive, Rockville, MD 20850, USA

I. INTRODUCTION

For all the importance of enones, there is surprisingly little reliable data concerning their thermochemistry. Although Hine and coworkers[1–4] have performed an elegant set of equilibration experiments that provided information on the relative values of ΔG for a set of 57 substituents in and out of conjugation with a carbon–carbon double bond ('Hine's 57 varieties'), there is much less information on the other simple thermochemical parameters, such as heats and entropies of formation, heat capacities and phase-change enthalpies. Since concepts of resonance and strain energy are ultimately derived from heats of formation, we will concentrate on this last thermochemical quantity for the molecules of interest. However, even here, there is a paucity of data, particularly in the gas phase for which these derived concepts are even more fundamental than in condensed phases, i.e. solid, liquid or solution.

Table 1 lists literature values of the heats of formation of enones that are available; quinones, enolized β-diketones and aromatic aldehydes and ketones are included. These latter compounds are included as there is substantial evidence that they can be treated in an analogous manner. Other unsaturated carbonyl derivatives (esters, acids, nitriles, etc.) are largely ignored in this chapter.

Unlike the thermochemistry chapters in most of the volumes in this series, we will not derive or otherwise present a Benson-like group increment analysis[30]. This is not due to

TABLE 1. Heats of formation of enones and their derivatives

In this table we place square brackets around the heat of formation of a condensed-phase species to indicate that this value is for the solid. When no brackets appear for the heat of formation of a condensed-phase species, the value is for the liquid. The presence of a plus, +, as a reference for a heat of formation of a gaseous species means that the heat of sublimation was taken directly from Reference 25. That is, we did not make any correction of the data to STP. Though the heat of sublimation is not for 298 K, we nonetheless derived the heat of formation of the gaseous species by adding the heat of formation for the solid and the reported heat of sublimation. The year of the reference is for the most trusted (either from Reference 8 or our best choice) direct measurement of the condensed-phase heat of formation. For the gas phase the year refers either to most-trusted direct measurement of the heat of formation of the gaseous species or to the heat of vaporization or sublimation. Structures of some of the compounds are given at the end of the Table.

Formula	Name	$\Delta H_f(s)$ or $\Delta H_f(lq)$ (kcal mol^{-1})	Ref.	Year	$\Delta H_f(g)$ (kcal mol^{-1})	Ref.	Year
C_3H_4O	acrolein	−25.1	5	1915			
$C_3H_4O_3$	hydroxymalonaldehyde (enol)	−120.7	10	1933			
$C_4H_2O_4$	3,4-dihydroxycyclobutenedione (squaric acid)[a] (**1**)	[−143.0(0.1)]	6	1971	−106.1	+	1983
C_4H_4O	1-butyn-3-one	6.7(0.2)	7	1986	−15.7(0.2)	7	1986
$C_4H_4O_2$	cyclobutane-1,3-dione (enol)	[−62.1(0.5)]	8	1978	−44.5(0.7)	8	1978
C_4H_6O	crotonaldehyde	−33.2(0.4)	8	1970	−24.0(0.3)	8	1936
$C_5H_3NO_4$	5-nitrofurfural	[−54.2(0.1)]	8	1980	−35.2(0.6)	8	1980
$C_5H_4O_2$	furfural	−48.2(1.1)	8	1929	−36.1(1.1)	8	1926
$C_5H_5F_3O_2$	trifluoroacetylacetone (enol)	−248.6(0.8)	9	1984	−239.8(0.8)	9	1984
C_5H_5NO	2-pyrrolaldehyde	[−25.4(0.6)]	8	1933			
C_5H_5NO	4-pyridone[b]	[−39.7(0.3)]	8	1982	−19.0(0.5)	8	1982
C_5H_8O	(*E*)-2-methyl-2-butenal	−54.5	10	1932			
C_5H_8O	3-penten-2-one	−17.5	10	1932			
$C_5H_8O_2$	acetylacetone (enol)[c]	−102.2(0.3)	11	1979	−91.9(0.3)	11	1970
$C_6Cl_4O_2$	tetrachloro-*p*-benzoquinone	[−68.0(2.0)]	8	1953	−44.4(2.8)	8	1927
$C_6HCl_3O_2$	trichloro-*p*-benzoquinone	[−64.4(2.0)]	8	1953	−43.2(2.8)	8	1927
$C_6H_2Cl_2O_2$	2,3-dichloro-*p*-benzoquinone	[−59.3(2.0)]	8	1953			
$C_6H_2Cl_2O_2$	2,5-dichloro-*p*-benzoquinone	[−58.6(2.0)]	8	1953			
$C_6H_2Cl_2O_2$	2,6-dichloro-*p*-benzoquinone	[−58.4(2.0)]	8	1953	−41.7(2.8)	8	1927
$C_6H_2Cl_2O_4$	2,5-dichloro-3,6-dihydroxy-*p*-benzoquinone	[−157.6]	5	1900 1925			
$C_6H_3ClO_2$	chloro-*p*-benzoquinone	[−52.7(2.0)]	8	1953	−36.2(2.8)	8	1927

$C_6H_4O_2$	*p*-benzoquinone	[−44.4(0.3)]	8	1954 1956	−29.4(0.8)	8	1956
$C_6H_5NO_2$	*p*-benzoquinone oxime[d]	−21.1	5	1900 1925			
C_6H_6O	2,4-cyclohexadienone				−17.(3)	12	1986
C_6H_6O	2,5-cyclohexadienone				−13(3)	12	1986
C_6H_7NO	2-methyl-4-pyridone[b]	[−44.1(0.3)]	8	1982	−17.1(0.4)	8	1982
$C_6H_{10}O$	mesityl oxide	−59.3	10	1961			
$C_6H_{10}O_2$	acetylacetone enol *O*-methyl ether	−87.5	5	1927			
$C_6H_{10}O_2$	3-methylpentane-2,4-dione (enol)				−105.1	13	1974
$C_6H_{10}O_2$	hexane-2,4-dione (enol)				−102.5	13	1974
C_7H_5ClO	*o*-chlorobenzaldehyde	−28.3(2.0)	8	1953	−15.0(2.1)	8	1949
C_7H_5ClO	*m*-chlorobenzaldehyde	−30.1(2.0)	8	1953			
C_7H_5ClO	*p*-chlorobenzaldehyde	[−35.0(2.0)]	8	1953			
$C_7H_5ClO_2$	chlorosalicylaldehyde[e]	−88.4	5	1897			
$C_7H_5NO_3$	*m*-nitrobenzaldehyde	[−28.2]	5	1895			
$C_7H_5NO_3$	*p*-nitrobenzaldehyde	[−36.1]	10	1930			
$C_7H_5NO_4$	3-(5-nitrofuryl)acrolein	[−38.3(0.3)]	8	1980	−15.4(0.3)	8	1980
C_7H_6O	benzaldehyde	−20.8(0.5)	8	1975	−8.8(0.7)	8	1975
C_7H_6O	cycloheptatrienone (tropone)	−2.4(0.8)	8	1971	10.5(0.8)	8	1971
$C_7H_6O_2$	*o*-hydroxybenzaldehyde	−67.9	14	1899			
$C_7H_6O_2$	*m*-hydroxybenzaldehyde	[−73.2]	5	1923			
$C_7H_6O_2$	*p*-hydroxybenzaldehyde	[−70.6]	5	1899			
$C_7H_6O_2$	2-methyl-*p*-benzoquinone	[−59.5]	5	1900 1925			
$C_7H_6O_2$	2-hydroxycycloheptatrienone (tropolone)	[−57.2(0.3)]	8	1951 1952 1956	−37.1(0.4)	8	1951 1971
$C_7H_6O_2$	3-furylacrolein	[−43.5(0.2)]	8	1980	−25.3(0.5)	8	1980
C_7H_7NO	2-aminotropone	[−7.6(0.6)]	8	1971	9.4(0.6)	8	1971
$C_7H_{10}O$	3-methyl-2-cyclohexenone	−57.0	5	1912			
$C_7H_4O_7 \cdot 3H_2O$	3-hydroxy-4-pyrone-2,6-dicarboxylic acid trihydrate (meconic acid trihydrate)	[−304.3]	5	1900			
$C_7H_{12}O_2$	acetylacetone enol *O*-ethyl ether	−99.5	5	1927			
$C_7H_{12}O_2$	3-ethylpentane-2,4-dione (enol)				−105.1	13	1974
$C_7H_{12}O_2$	5-methylhexane-2,4-dione (enol)				−105.1	13	1974

TABLE 1. *(continued)*

Formula	Name	ΔH_f(s) or ΔH_f(lq) (kcal mol^{-1})	Ref.	Year	ΔH_f(g) (kcal mol^{-1})	Ref.	Year
$C_7H_{12}O_2$	heptane-3, 5-dione (enol)				– 109.2	13	1974
C_8H_5NO	benzoyl cyanide	[9.3(0.1)]	8	1969	28.1(1.0)	8	1969
$C_8H_5NO_2$	2, 3-indolinedione (isatin)	[– 64.2(0.9)]	8	1933			
$C_8H_6O_3$	3, 4-methylenedioxybenzaldehyde	[– 85.9]	5	1892	– 64.2	+	1953 1960
$C_8H_6O_3$	phenylglyoxylic acid	[– 115.3]	14	1932			
C_8H_8O	acetophenone	– 34.1(0.2)	8	1961	– 20.7(0.4)	8	1970
$C_8H_8O_2$	*o*-anisaldehyde	[– 63.7(1.8)]	8	1940			
$C_8H_8O_2$	*m*-anisaldehyde	– 66.0(1.8)	8	1940			
$C_8H_8O_2$	*p*-anisaldehyde	– 63.9(1.2)	8	1940	– 48.4(1.3)	8	1947
$C_8H_8O_2$	*o*-hydroxyacetophenone	[– 85.5(0.9)]	8	1937			
$C_8H_8O_2$	*m*-hydroxyacetophenone	[– 88.6(1.0)]	8	1937			
$C_8H_8O_2$	*p*-hydroxyacetophenone	[– 87.1(1.0)]	8	1937			
$C_8H_8O_2$	furylideneacetone	[– 57.4(0.4)]	8	1978			
$C_8H_8O_3$	3-hydroxy-4-methoxybenzaldehyde (isovanillin)	[– 108.4(1.4)]	8	1940			
$C_8H_8O_3$	4-hydroxy-3-methoxybenzaldehyde (vanillin)	[– 107.3]	10	1940	– 86.1	+	1953 1960
$C_8H_8O_3$	2, 4-dihydroxyacetophenone	[– 137.1(0.9)]	8	1937			
$C_8H_8O_4$	3, 4-diethoxycyclobutenedione (diethyl squarate)[a]	– 132.0(0.3)	6	1971			
C_8H_9NO	*m*-aminoacetophenone	[– 41.4(0.1)]	8	1971			
		– 38.5(0.2)	8	1971			
C_8H_9NO	*p*-aminoacetophenone	[– 43.5(0.1)]	8	1971			
		– 39.7(0.2)	8	1971			
$C_8H_{12}O$	3, 5-dimethyl-2-cyclohexenone	– 59.9	5	1920			
$C_8H_{14}O$	2-ethyl-2-hexenal				– 64.2(0.4)	8	1960
$C_8H_{14}O_2$	3-propylpentane-2, 4-dione (enol)				– 108.3	13	1974
$C_8H_{14}O_2$	3-isopropylpentane-2, 4-dione (enol)				– 107.3	13	1974
$C_8H_{14}O_2$	3, 5-dimethylhexane-2, 4-dione (enol)				– 110.1	13	1974
$C_8H_{14}O_2$	6-methylheptane-2, 4-dione (enol)				– 109.2	13	1974

$C_8H_{14}O_2$	octane-2, 4-dione (enol)				−108.2	13	1974
C_9H_6O	3-phenylpropynal	29.8	5	1914			
$C_9H_6O_2$	chromone (**2**)	[−54.9(0.7)]	15	1988	−35.5(0.7)	15	1988
$C_9H_6N_2O_3$	3-benzoyl-5-hydroxy-1, 2, 4-oxadiazole (**3a**)	[−64.5(1.9)]	8	1931			
$C_9H_6N_2O_3$	5-benzoyl-3-hydroxy-1, 2, 4-oxadiazole (**3b**)	[−10.2(2.0)]	8	1931			
C_9H_7NO	benzoylacetonitrile	[−5.3(0.1)]	8	1969	16.8(1.0)	8	1969
$C_9H_7N_3O_2$	3-amino-4-benzoylfurazan^f (**4a**)	[18.9(1.2)]	8	1931			
C_9H_8O	cinnamaldehyde	−6.4	5	1982			
C_9H_8O	1-indanone	−31.8	5	1927			
$C_9H_8N_2O$	2, 2′-dipyrrolyl ketone	[−6.0(1.1)]	8	1932			
$C_9H_{10}O$	propiophenone	−40.0(0.3)	8	1961	−26.0(0.5)	8	1970
$C_9H_{10}O_2$	2-hydroxy-3-methylacetophenone	−95.3	10	1961			
$C_9H_{10}O_3$	2-hydroxy-4-methoxyacetophenone	[−127.6]	10	1961			
$C_9H_{11}NO$	*p*-dimethylaminobenzaldehyde	[−32.9(0.2)]	8	1956			
$C_9H_{13}NO$	4-ethyl-3, 5-dimethyl-2-pyrrol-aldehyde	[−60.9(1.2)]	8	1933			
$C_9H_{14}O$	3, 5, 5-trimethylcyclohexenone (isophorone)	−76.1	5	1920			
$C_9H_{16}O_2$	3-butylpentane-2, 4-dione (enol)				−110.2	13	1974
$C_9H_{16}O_2$	2, 2-dimethyl-3, 5-heptanedione (enol)	−126.1(0.6)	11	1981	−112.5(0.6)	11	1975
$C_9H_{16}O_2$	2, 6-dimethyl-3, 5-heptanedione (enol)	−126.0(0.5)	11	1981	−112.4(0.6)	11	1975
$C_{10}H_6O_2$	phenylcyclobutenedione	[−20.1(0.2)]	16	1960	−7.1(0.3)	16	1960
$C_{10}H_6O_2$	1, 2-naphthoquinone	[−38.1]	5	1900 1925			
$C_{10}H_6O_2$	1, 4-naphthoquinone	[−43.8(0.5)]	8	1956	−26.5(1.0)	8	1956
$C_{10}H_6O_4$	furil (**5**)	[−80.3]	5	1925			
$C_{10}H_7F_3O_2$	benzoyltrifluoroacetone (enol)	−227.7(1.0)	9	1984	−209.2	9	1984
$C_{10}H_7NO_2$	1, 2-naphthoquinone 1-oxime^d	[−12.1(0.5)]	8	1968	8.6(1.1)	8	1968
$C_{10}H_7NO_2$	1, 2-naphthoquinone 2-oxime^d	[−14.8(1.1)]	8	1968	−1.3(1.5)	8	1968
$C_{10}H_7NO_2$	1, 4-naphthoquinone oxime^d	[−25.8(0.6)]	8	1968	−4.9(1.2)	8	1968
$C_{10}H_8N_2O_2$	3-benzoyl-4-methylfurazan (**4b**)	[28.5(1.4)]	8	1931			
$C_{10}H_8O$	3-phenylcyclobutenone	[6.7]	10	1958			

TABLE 1. *(continued)*

Formula	Name	$\Delta H_f(s)$ or $\Delta H_f(lq)$ (kcal mol^{-1})	Ref.	Year	$\Delta H_f(g)$ (kcal mol^{-1})	Ref.	Year
$C_{10}H_8O$	4-phenyl-1-butyn-3-one	21.5	5	1914			
$C_{10}H_8O_4$	furoin (**6**)	[−98.9]	5	1925			
$C_{10}H_9NO$	6-benzoylpropionitrile	[−17.1(0.1)]	8	1969	7.2(1.0)	8	1969
$C_{10}H_9N_3O_2$	3-amino-4-(*p*-toluyl)furazan[f] (**4c**)	[10.1(1.3)]	8	1931			
$C_{10}H_{10}O$	1-tetralone	[−50.1(5.0)]	8	1951			
$C_{10}H_{10}O$	benzalacetone	−23.6	10	1958			
$C_{10}H_{10}O_2$	benzoylacetone (enol)	[−80.1(0.7)]	11	1981	−60.1(0.7)	11	1959
$C_{10}H_{10}O_4$	2, 4-diacetylresorcinol	[−180.1(1.5)]	8	1937			
$C_{10}H_{10}O_4$	4, 6-diacetylresorcinol	[−185.6(1.6)]	8	1937			
$C_{10}H_{10}O_5$	2-formyl-5, 6-dimethoxy-benzoic acid	[−192.4]	5	1900			
$C_{10}H_{12}O$	3a, 4, 7, 7a-tetrahydro-4, 7-methano-inden-1-one (**7**)	[−3.8]	17	1964			
$C_{10}H_{12}O_2$	4-isopropyltropolone	[−81.4(0.9)]	8	1956			
$C_{10}H_{12}O_2$	2-isopropyl-5-methyl-*p*-benzoquinone	[−78.1]	5	1900 1925			
$C_{10}H_{13}NO_2$	2-isopropyl-5-methyl-*p*-benzoquinone oxime[d,e]	[−51.7]	5	1920 1925			
$C_{10}H_{13}N_3$	4-formyl-3, 5-dimethylpyrrole-2-carboxylic acid ethyl ester	[−153.2(1.2)]	8	1932			
$C_{10}H_{13}NO_3$	5-formyl-2, 4-dimethylpyrrole-3-carboxylic acid ethyl ester	[−154.4(1.2)]	8	1932			
$C_{10}H_{14}O$	carvone (**8**)	−43.1	5	1886			
$C_{10}H_{14}O$	eucarvone (**9**)	−43.1	5	1913			
$C_{10}H_{16}O$	carvenone (**10**)	−76.6	5	1911			
$C_{10}H_{16}O$	geranial (citral) (**11**)	−47.4	5	1923			
$C_{10}H_{16}O$	dihydrocarvone (**12**)	−74.6	5	1899 1911			
$C_{10}H_{16}O$	pulegone (**13**)	−72.3	5	1899 1911 1920			

$C_{10}H_{18}O_2$	2,2,6-trimethyl-3,5-heptanedione (enol)	−135.9(0.5)	11	1981	−122.1(0.5)	11	1975
$C_{11}H_8O_2$	2-methyl-1,4-naphthoquinone	[−54.8]	10	1946			
$C_{11}H_{10}O_2$	1-phenyl-1-pentyn-3-one	9.7	5	1910			
$C_{11}H_{10}O_2$	1,4,4a,8a-tetrahydro-1,4-methanonaphthalene-5,8-dione (**14a**)	[36.1]	17	1964			
$C_{11}H_{12}O$	α-methylbenzalacetone	[−29.7]	5	1927			
		−25.5	5	1927			
$C_{11}H_{14}O$	isovalerophenone	−52.6(0.4)	8	1961	−36.1(0.5)	8	1970
$C_{11}H_{14}O$	pivalophenone	−48.9(0.5)	8	1961			
$C_{11}H_{14}O$	2,4,5-trimethylacetophenone	−60.3(1.0)	8	1941	−45.2(1.1)	8	1970
$C_{11}H_{14}O$	2,4,6-trimethylacetophenone	−63.9(0.7)	8	1941	−49.0(0.9)	8	1970
$C_{11}H_{15}NO_3$	4-acetyl-3,5-dimethylpyrrole-2-carboxylic acid ethyl ester	[−156.4(1.2)]	8	1933			
$C_{11}H_{20}O_2$	2,2,6,6-tetramethyl-3,5-heptane dione (enol)	−140.5(0.9)	11	1981	−126.2(0.9)	11	1975
$C_{12}H_{10}O$	1-phenyl-1-hexyn-3-one	−0.3	5	1910			
$C_{12}H_{10}O_4$	quinhydrone (**15**)	[−134.7]	5	1925	−114.5	+	1981
$C_{12}H_{12}O_3$	*β*-benzallevulinic acid (**16a**)	[−124.0]	5	1890			
$C_{12}H_{12}O_3$	*δ*-benzallevulinic acid (**16b**)	[−127.3]	5	1890			
$C_{12}H_{17}NO_3$	2,4-dimethyl-5-propionylpyrrole 3-carboxylic acid ethyl ester	[−169.3(1.5)]	8	1932			
$C_{12}H_{17}NO_3$	3,5-dimethyl-4-propionylpyrrole 2-carboxylic acid ethyl ester	[−162.3(1.5)]	8	1932			
$C_{12}H_{10}O_2$	1,4,4a,8a-tetrahydro-1,4-ethanonaphthalene-5,8-dione (**14b**)	[−53.1]	17	1964			
$C_{13}H_5N_5O_{11}$	2,2′,4,4′,6-pentanitrobenzophenone	[−27.3(1.0)]	8	1976			
$C_{13}H_8O_2$	xanthone (**17**)	[−47.0(0.9)]	18	1988	−23.5(0.9)	18	1988
$C_{13}H_{10}O$	benzophenone	[−8.2(0.5)]	8	1959	13.1(1.1)	8	1972
							1978
$C_{13}H_{10}O_2$	furylideneacetophenone	[−72.4]	19	1963			
$C_{13}H_{10}O_2$	2,4-dihydroxybenzophenone	[−117.8(0.4)]	20	1979			
$C_{13}H_{10}O_3$	difurylideneacetone	[−48.1(0.6)]	8	1978			
$C_{13}H_{12}O$	2,6-dimethylbenzotropone (**18**)	[−19.2(0.9)]	8	1956	−0.5(2.6)	8	1970
$C_{13}H_{14}O$	1-phenyl-3-heptyn-5-one	−14.1	5	1910			
$C_{13}H_{14}O$	5-methyl-1-phenyl-1-hexyn-3-one	20.0	5	1910			

TABLE 1. *(continued)*

Formula	Name	$\Delta H_f(s)$ or $\Delta H_f(lq)$ (kcal mol^{-1})	Ref.	Year	$\Delta H_f(g)$ (kcal mol^{-1})	Ref.	Year
$C_{13}H_{14}O$	4,4-dimethyl-1-phenyl-1-pentyn-3-one	– 0.3(1.0)	21	1986	15.4	21	1986
$C_{13}H_{17}NO_5$	ethyl 5-carbethoxy-2,4-dimethyl-pyrrole-2-glyoxylate	[– 242.6(1.6)]	8	1932			
$C_{13}H_{20}O$	α-ionone (**19**)	– 67.0	5	1923			
$C_{13}H_{20}O$	β-ionone (**20**)	– 62.5(0.8)	22	1985			
$C_{13}H_{20}O$	ψ-ionone (**21**)	– 51.0(0.7)	22	1985			
$C_{14}H_8O_2$	9,10-anthraquinone (**22a**)	[– 49.6(0.8)]	8	1956	– 22.8(1.6)	8	1956
$C_{14}H_8O_2$	9,10-phenanthraquinone (**23a**)	[– 55.2(0.3)]	8	1956	– 33.2(1.1)	8	1956
$C_{14}H_8O_3$	hydroxy-9,10-anthraquinone^e	[– 107.0]	5	1900 1925			
$C_{14}H_8O_4$	1,2-dihydroxy-9,10-anthraquinone (**22b**)	[– 139.9]	5	1900	– 110.2	+	1973
$C_{14}H_8O_5$	1,2,4-trihydroxy-9,10-anthraquinone (**22c**)	– 186.8	5	1900 1925			
$C_{14}H_8O_8$	1,2,3,5,6,7-hexahydroxy-9,10-anthraquinone	[– 340.0]	5	1900 1925			
$C_{14}H_9NO_4$	*p*-nitrobenzil	[– 22.0]	5	1925			
$C_{14}H_{10}O_2$	benzil	[– 36.8(0.7)]	8	1959	– 13.3(1.1)	8	1962
$C_{14}H_{12}O$	*p*-methylbenzophenone	– 18.6(0.5)]	8	1959			
$C_{14}H_{12}O$	2-phenylacetophenone	[– 17.1]	10	1962			
$C_{14}H_{12}O$	deoxybenzoin	[– 17.0(0.7)]	8	1962	5.3(1.2)	8	1947
$C_{14}H_{12}O_2$	benzoin	[– 59.2(0.7)]	8	1962			
$C_{14}H_{16}O$	1-phenyl-1-octyn-3-one	– 29.5	5	1910			
$C_{14}H_{21}NO_2$	3,5-diethyl-2,4-dipropionyl pyrrole	[– 114.9(1.9)]	8	1932			
$C_{15}H_{10}O$	1,3-diphenyl-3-propynone	[35.3]	5	1914			
$C_{15}H_{12}O$	diphenylcyclopropenone	[47.3(0.5)]	23	1985	75.7(2.0)	23	1985
$C_{15}H_{12}O_2$	dibenzoylmethane (enol)	[– 53.7(0.4)]	11	1965	– 35.7	11	1967
$C_{15}H_{14}O$	4-ethylbenzophenone	– 15.4(0.5)	8	1959			
$C_{15}H_{18}O_3$	santonin (**24**)	[– 141.2(0.5)]	8	1964			
$C_{15}H_{18}O_3$	β-santonin	[– 140.4(0.5)]	8	1964			
$C_{15}H_{18}O_3$	6-α(*H*)-santonin	[– 139.7(0.4)]	8	1964			

$C_{15}H_{18}O_3$	6, 11-α(*H*)-santonin	[− 144.1(0.6)]	8	1964			
$C_{16}H_{10}N_2O_2$	indigotin (**25**)	[− 32]	14	1893			
$C_{16}H_{10}N_2O_3$	3, 4-dibenzoylfurazan (**4d**)	[− 24.9(2.2)]	8	1931			
$C_{16}H_{11}NO_5$	*p*-nitroacetylbenzoin[e]	[− 14.8]	5	1925			
$C_{16}H_{12}O_2$	1, 2-dibenzoylethylene	[− 27.4(0.6)]	8	1954			
$C_{16}H_{14}O_2$	1, 2-dibenzoylethane	[− 61.1(0.4)]	8	1954			
$C_{16}H_{16}O$	4-isopropylbenzophenone	− 28.3(0.5)	8	1959			
$C_{16}H_{16}O$	2, 6-pentamethylenebenzotropone (**26a**)	[12.2(1.5)]	8	1956	32.8(2.9)	8	1970
$C_{17}H_{14}O$	dibenzalacetone	[12.8]	5	1910			
$C_{17}H_{16}O_2$	dibenzoylmethane enol *O*-methyl ether (*β*-ethoxychalcone)	[− 45.5(0.4)]	8	1965			
$C_{17}H_{18}O$	4-*t*-butylbenzophenone	− 32.4(0.5)	8	1959			
$C_{17}H_{24}N_2O$	bis(4-ethyl-3, 5-dimethyl-2-pyrryl) ketone	[− 60.7(2.4)]	8	1932			
$C_{17}H_{32}O$	(*E*)-2-cycloheptadecenone (civetone)	[− 115.7(3.2)]	8	1933	− 97.6(3.2)	8	1970
$C_{18}H_{10}O_2$	5, 12-naphthacenoquinone	[− 34.1(0.8)]	8	1956	− 8.1(1.5)	8	1956
$C_{18}H_{10}O_2$	9, 10-benzanthraquinone	[− 55.4(0.8)]	8	1956	− 35.6(1.3)	8	1956
$C_{18}H_{14}N_2O_3$	3, 4-di(*p*-toluyl)furazan (**4e**)	[4.9(3.1)]	8	1931			
$C_{18}H_{16}O_2$	7-isopropyl-3-methyl-9, 10-phenanthraquinone (**23b**)	[− 85.1]	5	1900 1925			
$C_{18}H_{18}O_2$	cinnamoin	− 30.9	10	1936			
$C_{19}H_{26}O_2$	4-androstene-3, 17-dione (**27a**)	[− 103]	14	1969			
$C_{19}H_{28}O_2$	testosterone (**27b**)	[− 94]	14	1969			
$C_{20}H_{12}O_2$	perylene-1, 12-quinone	[− 10.4]	10	1929			
$C_{20}H_{12}O_2$	perylene-3, 10-quinone[g]	[− 65.9]	24	1929			
$C_{21}H_{13}NO_5$	*p*-nitrobenzoylbenzoin[e]	[26.3]	5	1925			
$C_{21}H_{26}O$	1, 3, 3-triphenylpropenone	24.3	5	1924			
$C_{21}H_{28}O_2$	3-hydroxy-3, 3-diphenyl-propiophenone	− 51.6	5	1924			
$C_{21}H_{28}O_5$	cortisone (**27c**)	[− 255]	14	1969			
$C_{21}H_{30}O_2$	progesterone (**27d**)	[− 132]	14	1969			
$C_{21}H_{30}O_2$	desoxycorticosterone (**27e**)	[− 124]	14	1969			
$C_{21}H_{30}O_3$	cortisol (**27f**)	[− 256]	14	1969			
$C_{22}H_{12}O_2$	6, 13-pentacenoquinone	[− 17.4(1.5)]	8	1956	− 10.4(2.1)	8	1956
$C_{22}H_{28}O$	2, 4, 6-triisopropylbenzophenone	[− 72.8(0.5)]	8	1982	− 45.1(1.7)	8	1982
$C_{23}H_{30}O$	2, 6-decamethylenebenzotropone (**26b**)	[− 62.9(2.7)]	8	1956	− 38.2(3.7)	8	1970

TABLE 1. *(continued)*

Formula	Name	ΔH_f(s) or ΔH_f(lq) (kcal mol^{-1})	Ref.	Year	ΔH_f(g) (kcal mol^{-1})	Ref.	Year
$C_{23}H_{27}NO_8 \cdot 2H_2O$	narceine dihydrate (**28**)·$2H_2O$	[−421.2]	14	1899 1900			
$C_{24}H_{12}O_2$	dibenzopyrenequinone (**29**)	[−60.0(1.6)]	8	1956	^−33.1(2.1)	8	1956
$C_{24}H_{16}O_2$	3, 9-diacetylperylene (**30a**)	[−22.4]	10	1929			
$C_{26}H_{20}O$	α, α, α-triphenylacetophenone	[52.0]	10	1934			
$C_{26}H_{20}O_2$	3, 9-dipropionylperylene (**30b**)	[−47.3]	10	1929			
$C_{28}H_{24}O_2$	3, 9-dibutyrylperylene (**30c**)	[−55.9]	10	1929			
$C_{33}H_{42}N_4O_2$	2, 9-diacetyl-1, 3, 5, 6, 8, 10-hexamethyl-4, 7-diethyl-tetrapyrro-14-ene (**31**)	[−71.6(4.5)]	8	1933			
$C_{34}H_{20}O_2$	3, 9-dibenzoylperylene	[19.7]	24	1929			
$C_{34}H_{36}N_4O_3$	pyropheophorbide-a monomethyl ester (**33b**)	[−89.6(4.3)]	8	1933			
$C_{36}H_{36}N_4O_6$	methylpheophorbide-b (**32b**)	[−206.0(4.4)]	8	1933			
$C_{36}H_{38}N_4O_5$	pheoporphyrin-a5 dimethyl ester (**33a**)	[−169.4(4.5)]	8	1933			
$C_{36}H_{38}N_4O_5$	methylpheophorbide-a (**32a**)	[−161.1(4.5)]	8	1933			
$C_{36}H_{24}O_2$	3, 9-di-*o*-toluylperylene (**30e**)	[9.1]	10	1929			

---

[a] It should be noted (with admitted regret) that Reference 8 erroneously gives the heat of formation of squaric acid and its diethyl ester in the gas phase as well as in the condensed phase when Reference 6 'merely' estimates phase-change heats.

[b] It is generally assumed that the isomeric 4*H*-pyridones and 4-pyridinols are close in energy. See, for example, the discussion in Reference 26 in which these data were reported. For these compounds we take the experimentally determined heats of formation to be for the 4*H*-pyridone form.

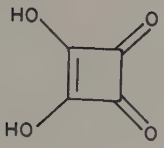
[c] While it is safe to assume that β-diketones are predominantly in their enol form, to the authors' knowledge only for acetylacetone are there separate thermochemical data on both the keto and enol forms. (See the discussion in References 11 and 27).

[d] There is considerable uncertainty as to whether these species are benzo/naphthoquinone oximes or nitroso phenols/naphthols. For an article that presents calorimetric data supporting the latter, see Reference 28, which is the primary source of information on the naphthoquinone oximes.

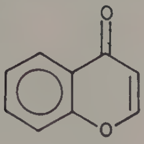
[e] Substitution site was unspecified.

[f] These two compounds are misnamed in Reference 8 (cf. the primary reference source, Reference 29).

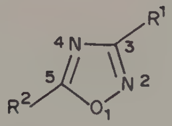
[g] These two numbers, like all the other perylene derivative thermochemical data, are taken from Reference 24, but somehow were omitted from our archival sources. The value for the 3, 10-quinone was derived by adding the difference of the heats of formation of the isomeric perylenequinones to the value for the 1, 12-isomer given in the archival source, Reference 10. The value for the 3, 9-dibenzoylperylene was derived from the energetics of the macroincrementation reaction dipropionylperylene + ditoluylperylene → dibutyrylperylene + dibenzoylperylene using experimental heats of combustion for all four compounds and the archival heats of formation of the three listed therein.



(1)

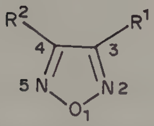


(2)



(3) (a) $R^1 = PhCO$, $R^2 = OH$

(b) $R^1 = OH$, $R^2 = PhCO$



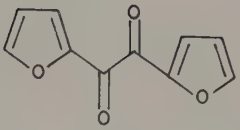
(4) (a) $R^1 = NH_2$, $R^2 = PhCO$

(b) $R^1 = PhCO$, $R^2 = Me$

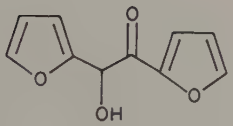
(c) $R^1 = NH_2$, $R^2 = p\text{-}MeC_6H_4CO$

(d) $R^1 = R^2 = PhCO$

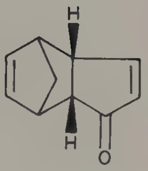
(e) $R^1 = R^2 = p\text{-}MeC_6H_4CO$



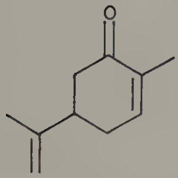
(5)



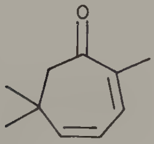
(6)



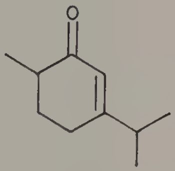
(7)



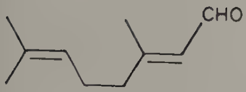
(8)



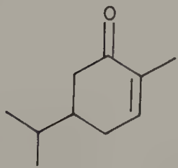
(9)



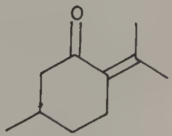
(10)



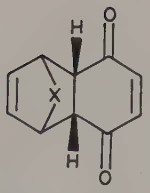
(11)



(12)

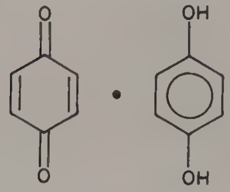


(13)

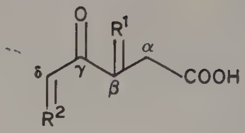


(14) **(a)** $X = CH_2$

(b) $X = CH_2CH_2$

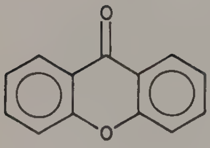


(15)

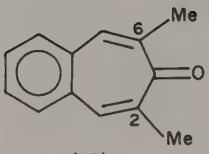


(16) **(a)** $R^1 = PhCH, R^2 = H$

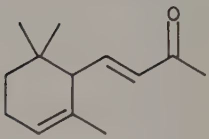
(b) $R^1 = H, R^2 = PhCH$



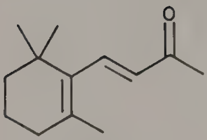
(17)



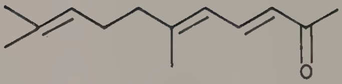
(18)



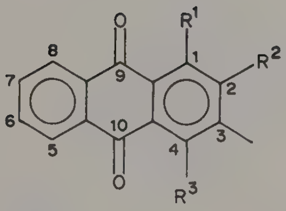
(19)



(20)



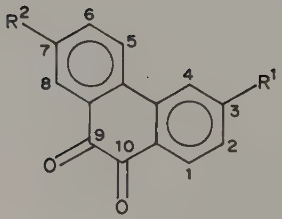
(21)



(22) **(a)** $R^1 = R^2 = R^3 = H$

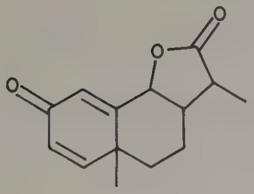
(b) $R^1 = R^2 = OH, R^3 = H$

(c) $R^1 = R^2 = R^3 = OH$

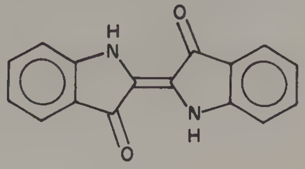


(23) **(a)** $R^1 = R^2 = H$

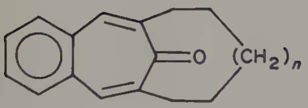
(b) $R^1 = Me, R^2 = i\text{-}Pr$



(24)

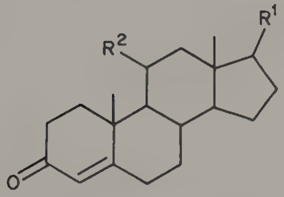


(25)



(26) (a) $n = 1$

(b) $n = 6$



(27) (a) R^1=O, R^2=H

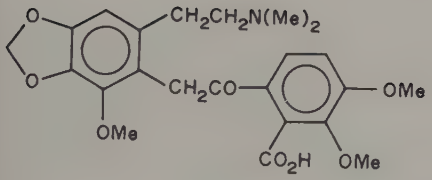
(b) R^1=β-OH, R^2=H

(c) R^1=β-$COCH_2OH$, α-OH, R^2=O

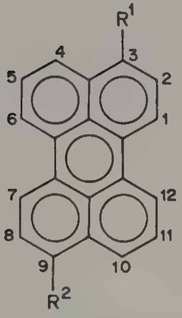
(d) R^1=β-COMe, R^2=H

(e) R^1=β-$COCH_2OH$, R^2=H

(f) R^1=β-$COCH_2OH$, α-OH, R^2=β-OH



(28)



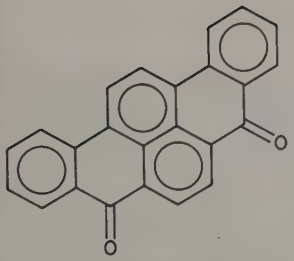
(30) (a) R^1=R^2=COMe

(b) R^1=R^2=COEt

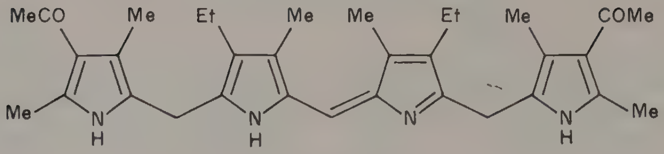
(c) R^1=R^2=COPr

(d) R^1=R^2=PhCO

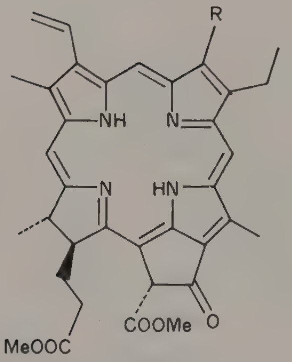
(e) R^1=R^2=p-MeC_6H_4CO



(29)

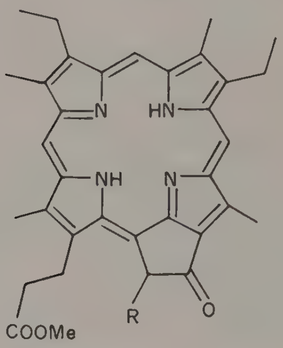


(31)



(32) (a) R = Me

(b) R = CHO



(33) (a) R = CO_2Me

(b) R = H

lack of space, but rather to the lack of sufficient data on related compounds to enable a useful comparison of theory and experiment to be made. We will instead present brief analyses of the thermochemistry of a variety of these enones, with comments on relationships with other, better understood, species. Although data are presented in Table 1 for gases, liquids and solids, only data for gases and liquids will be analyzed in the text. Clearly, gas-phase data are preferable, as intermolecular interactions are negligible; liquid-phase data are, however, surprisingly useful because, within about 1 kcal mol^{-1}, the heat of vaporization depends only on the number and type of heavy atoms and not the degree of unsaturation[31].

II. STABILIZATION OF ENONES

A. Simple Enones

The simplest enone for which heats of formation are available in both condensed and gaseous phases is crotonaldehyde. A value for the resonance energy of the aldehyde group, compared to methyl, may be derived from the results of the following macroincrementation reaction[32,33] along with the observed heats of formation (equation 1). *Trans* compounds are used in all cases. The calculated values (ΔH_f) are based on a decoupling of the olefinic and carbonyl groups and thus represent the heats of formation for the hypothetical nonconjugated species. The differences between these values and the experimental ones represent the stabilization energies for the relevant species. The heat of formation of crotonaldehyde in the gas phase is -24.0 kcal mol^{-1}*, whereas in the liquid phase it is $-33.1\,\mathrm{kcal\,mol^{-1}}$, leading to values of the stabilization energy for crotonaldehyde of $2.4\,\mathrm{kcal\,mol^{-1}}$(g) and $3.1\,\mathrm{kcal\,mol^{-1}}$(l), relative to *trans*-2-butene.

$$\begin{array}{lccccccc}
 & \mathrm{MeCH{=}CHCHO} & = & \mathrm{MeCH{=}CHMe} & + & \mathrm{MeCH_2CH_2CHO} & - & \mathrm{MeCH_2CH_2Me} \\
\Delta H_\mathrm{f}(\mathrm{g}) & -21.6 & = & -2.7 & & +(-48.9) & & -(-30.0) \\
\Delta H_\mathrm{f}(\mathrm{l}) & -30.0 & = & -7.9 & & +(-57.1) & & -(-35.0) \\
(\mathrm{kcal\,mol^{-1}}) & & & & & & &
\end{array} \qquad (1)$$

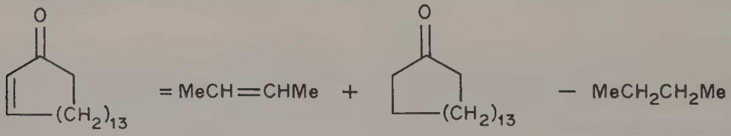
These values are surprisingly small for a conjugating substituent. Similarly, Hine and coworkers[1–4] have found that the corresponding $\Delta\Delta G$ for the difference in stabilization of a double bond by a formyl group and an alkyl group ($D_{\mathrm{CHO}} - D_{\mathrm{R}}$) is *ca* $1.3\,\mathrm{kcal\,mol^{-1}}$. They also find that the stabilization (ΔG) of a double bond by an acetyl group is similar to that by an alkyl group. They have attributed the similarity of the stabilization due to these groups to the destabilizing inductive effect of the carbonyl, competing with the expected stabilization of the resonance interaction.

It is of interest that the vaporization enthalpies of butane and 2-butene are approximately the same ($5.0\,\mathrm{kcal\,mol^{-1}}$ and $5.2\,\mathrm{kcal\,mol^{-1}}$, respectively), whereas that of crotonaldehyde ($9.1\,\mathrm{kcal\,mol^{-1}}$) is somewhat higher than butyraldehyde ($8.2\,\mathrm{kcal\,mol^{-1}}$)[8]. How much this is due to the dipolar resonance structure stabilizing crotonaldehyde in the liquid phase compared to the gas phase is moot. Although the difference is small, it appears to be outside the limits of error of measurement in this case ($\pm 0.4\,\mathrm{kcal\,mol^{-1}}$ for crotonaldehyde and $\pm 0.3\,\mathrm{kcal\,mol^{-1}}$ for butyraldehyde).

Similarly, the stabilization energy of a carbonyl *vs* a vinyl group may be obtained by an analysis of the macroincrementation reaction of equation 2. The difference between experimental and calculated values ($1.6\,\mathrm{kcal\,mol^{-1}}$ and $0.9\,\mathrm{kcal\,mol^{-1}}$ for gas phase and liquid, respectively) in both cases suggests that the formyl group is destabilizing relative to vinyl. That is, enones enjoy less stabilization than conjugated dienes. This conclusion, based upon heats of formation, corroborates results of Hine and coworkers[1–4] based on free energies. They found that a vinyl group is $1.7\,\mathrm{kcal\,mol^{-1}}$ better at stabilizing a double bond than a formyl group. Presumably, the stronger inductive destabilization of the double bond by the carbonyl than by the vinyl group accounts for this observation. This conclusion is supported by the greater barrier to rotation about the sp^2–sp^2 bond in acrolein[34] than in butadiene[35] (*ca* 8 *vs* $6\,\mathrm{kcal\,mol^{-1}}$). Since in the perpendicular form the inductive effect is essentially unchanged from the ground-state planar form, the barriers to rotation measure the difference in resonance between the two forms. If we assume that the resonance energy of the perpendicular forms in negligible, then the difference in the barriers to rotation can be directly used to get the resonance energy difference of the two molecules.

$$\begin{array}{lccccccc}
 & \mathrm{MeCH{=}CHCHO} & = & \mathrm{MeCH{=}CHCH{=}CH_2} & + & \mathrm{MeCH_2CH_2CHO} & & \\
 & & & & - & \mathrm{MeCH_2CH_2CH{=}CH_2} & & \\
\Delta H_\mathrm{f}(\mathrm{g}) & -25.6 & = & 18.2 & & +(-48.9) & & -(-5.1) \\
\Delta H_\mathrm{f}(\mathrm{l}) & -34.0 & = & 11.9^{36} & & +(-57.1) & & -(-11.2) \\
(\mathrm{kcal\,mol^{-1}}) & & & & & & &
\end{array} \qquad (2)$$

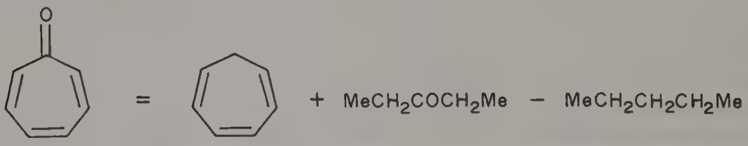
Although there are equilibrium data for the interconversion of conjugated and unconjugated cycloalkenones[37], there is no heat of formation data on these compounds, with the exception of (*E*)-2-cycloheptadecenone. Calculation of the heat of formation in the absence of conjugation (equation 3) gives a value of $-82.7\,\mathrm{kcal\,mol^{-1}}$ compared to the experimental value of $-97.6\,\mathrm{kcal\,mol^{-1}}$. Despite the potential idiosyncracies of 17-membered rings, the resulting stabilization energy of nearly $15\,\mathrm{kcal\,mol^{-1}}$ seems excessive, even considering the $\pm 3\,\mathrm{kcal\,mol^{-1}}$ error limits for both cycloalkanones. A prediction of the heat of formation of cycloheptadecanone by assuming it is strainless gives a value of -111 to $-113\,\mathrm{kcal\,mol^{-1}}$, suggesting that the measured value for this compound is likely to be correct. That of cycloheptadecenone is therefore somewhat suspect. More work on cycloalkenones is clearly required.



(3)

ΔH_f(g) $-82.7 = -2.7$ $+(-110)$ $-(-30.0)$
(kcal mol^{-1})

It is apparent from the above discussion that the resonance energy of a simple enone is small. Much as butadiene is less conjugated than benzene, it might be expected that crotonaldehyde has less conjugation than tropone (equation 4). The experimental heats of formation of tropone are $10.5\,\mathrm{kcal\,mol^{-1}}$ (g) and $-2.4\,\mathrm{kcal\,mol^{-1}}$ (l). Thus, the stabilization energy of tropone is *ca* 6–7 kcal mol^{-1}, substantially higher than crotonaldehyde. This small stabilization energy and the comparable heats of vaporization of tropone ($12.9\,\mathrm{kcal\,mol^{-1}}$) and cycloheptanone ($12.4\,\mathrm{kcal\,mol^{-1}}$) argue against viewing tropone as 'tropylium oxide', although the dipolar resonance structure is clearly important. In contrast, cyclopropenone appears to be considerably more aromatic (*ca* 20 kcal mol^{-1}), as determined from the heat of formation of its diphenyl derivative and related analysis[23,38], although both systems satisfy the Huckel $4n+2$ rule. We remind the reader that as n increases, aromaticity decreases[39], so this result is not altogether surprising.



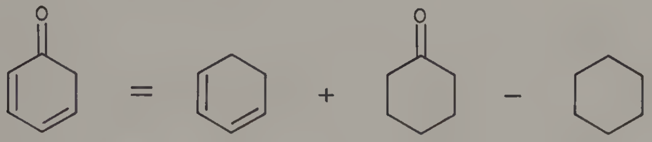
(4)

ΔH_f(g) $16.7 = 43.2$ $+(-61.6)$ $-(-35.1)$
ΔH_f(l) $4.6 = 34.0$ $+(-70.9)$ $-(-41.5)$
(kcal mol^{-1})

Although there are no thermochemical data on benzotropone itself, measurements have been made on the 2, 6-dimethyl derivative (**18**) and two 2, 6-polymethylene derivatives **26**. An analysis analogous to the above has shown that the pentamethylene derivative (**26a**) is highly strained owing to loss of conjugation energy and distortion of the tropone ring itself, while the decamethylene derivative (**26b**) is essentially strainless[40].

The two isomeric cyclohexadienones have recently been investigated in the gas phase by Shiner and coworkers[12] using the flowing afterglow technique. These measurements result in the heat of formation of the 2, 4-isomer equal to $-17 \pm 3\,\mathrm{kcal\,mol^{-1}}$ and of the 2, 5-isomer equal to $-13 + 3\,\mathrm{kcal\,mol^{-1}}$. Several comparisons have been made by these authors. The heat of formation of phenol is $-23\,\mathrm{kcal\,mol^{-1}}$, making it only 6–10 kcal mol^{-1} more stable than the isomeric cyclohexadienones. This difference is surprisingly low. The heat of formation of 2, 4-cyclohexadienone may be estimated to be *ca* 1 kcal mol^{-1} from the macroincrementation reaction of equation 5. Although the conjugation between the double bonds and the carbonyl group is not taken into account by this method, the stabilization energy should be only *ca* 3 kcal mol^{-1} (*vide supra*) and should not appreciably alter the disparity between theory and experiment (-2 kcal mol^{-1} *vs* -17 kcal mol^{-1}).

Solution phase O—H bond strength measurements of phenols[41] and the C–C dimerization enthalpy of the resulting phenoxy radicals[42] may be combined to give heats of formation of bis(cyclohexadienone). Suitable macroincrementation reactions and estimates[43] of heats of vaporization and solution result in heats of formation of simple cyclohexadienones that are more in accord with our suggested values than those of Shiner *et al.*[12]. Thermochemical measurements, such as the heats of rearrangement of the isomeric 4,4-dimethylcyclohexadienones to the corresponding phenols, or heats of hydrogenation to form the cyclohexanone and/or cyclohexanol, would be of interest in disentangling the conflicting values.


(5)

$$\Delta H_f(g)\ (\text{kcal mol}^{-1})\qquad 0.9 = 25.4 + -54.0 - (-29.5)$$

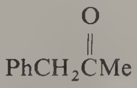
B. Buried Enones

As has been recently noted[33,44], there appears to be a constancy in the difference between the heats of formation of vinyl-X and phenyl-X for a wide variety of substituents X. This suggests that, in some sense, the phenyl group is equivalent to a double bond in its substituent effects. In this light, it is possible to consider aromatic aldehydes and ketones, such as benzaldehyde and acetophenone, as equivalent to enones. We will refer to such species as buried enones. A simple demonstration of this relationship is the near equality of the difference in heats of formation of benzaldehyde and toluene with crotonaldehyde and propene (equations 6 and 7). Similarly, the difference in the heats of formation of the isomeric compounds propiophenone and benzyl methyl ketone gives the effect of conjugation of a phenyl ring with a carbon–oxygen double bond (1.9 kcal mol^{-1}, equation 8). This result compares to the value for the stabilization energy of a carbon–carbon double bond of 2.4 kcal mol^{-1} given earlier for crotonaldehyde.

$$\begin{array}{lcccccc} & \text{PhCHO} & & \text{PhMe} & & & \\ \Delta H_f(g) & -8.8 & - & 12.0 & = & -20.8 & (6) \\ (\text{kcal mol}^{-1}) & & & & & & \end{array}$$

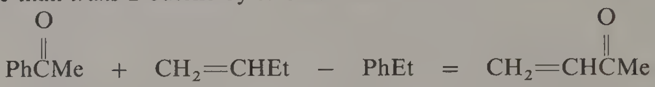
$$\begin{array}{lcccccc} & CH_2{=}CHCHO & & CH_2{=}CHMe & & & \\ \Delta H_f(g) & -24.0 & - & (-2.7) & = & -21.3 & (7) \\ (\text{kcal mol}^{-1}) & & & & & & \end{array}$$


$\overset{\displaystyle O}{\overset{\|}{\text{PhCEt}}}$


$\text{PhCH}_2\overset{\displaystyle O}{\overset{\|}{\text{C}}}\text{Me}$

$$\begin{array}{lcccccc} \Delta H_f(g) & -26.0 & - & (-24.1) & = & -1.9 & (8) \\ (\text{kcal mol}^{-1}) & & & & & & \end{array}$$

This equivalence between the effects of phenyl and vinyl substituents can be used to predict heats of formation of substituted vinyl ketones of the type C═C—C(═O)R because of the availability of data for the corresponding phenyl ketones. For example, the heat of formation of methyl vinyl ketone may be derived from that of acetophenone by macroincrementation reaction 9. The greater stability of methyl vinyl ketone compared to the isomeric crotonaldehyde (3.8 kcal mol^{-1}) is due to the greater ability of alkyl groups than hydrogen to stabilize a carbonyl compared to internal *vs* external olefins. For example, butyraldehyde is less stable than methyl ethyl ketone by *ca* 8 kcal mol^{-1} and 1-butene is less stable than *trans*-2-butene by *ca* 3 kcal mol^{-1}.

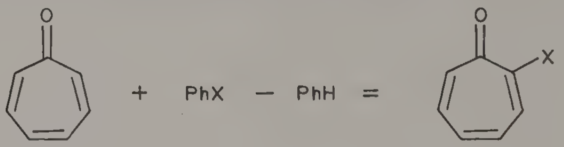


$$\mathrm{Ph\overset{\overset{O}{\|}}{C}Me} \;+\; \mathrm{CH_2{=}CHEt} \;-\; \mathrm{PhEt} \;=\; \mathrm{CH_2{=}CH\overset{\overset{O}{\|}}{C}Me}$$

ΔH_f(g) (kcal mol^{-1}): $-20.7 \;+\; 0 \;-\; 7.1 \;=\; -27.8$ (9)

C. Substituent Effects

Let us now turn to substituted tropones. The stabilizing effects of 2-hydroxy and 2-amino substituents on tropone (**34**) are quite small. The macroincrementation reactions of equation 10 suggest that the stabilization energy due to a 2-hydroxy substituent is *ca* 5 kcal mol^{-1} and that from a 2-amino substituent is *ca* 2 kcal mol^{-1}. (We have used aniline and phenol as mimics of vinyl amine and vinyl alcohol in these schemes, since we judge these data to be more reliable. This choice is valid due to the previously demonstrated equivalence of these two groups.) If 2-hydroxy and 2-aminotropone should best be viewed as substituted cycloheptatrienones, then these compounds are vinylogous esters and amides, respectively. However, in contrast to the low stabilization energy found here, the resonance stabilization in acids and amides is considerably larger (*ca* 20 kcal mol^{-1}), as determined by analogous macroincrementation reactions[44,45] (equations 11 and 12).



(10)

(34)

X = OH

ΔH_f(g) (kcal mol^{-1}): $10.5 + (-23.0) - 19.7 = -32.2$ (calcd)

-37.1 (expt)

$\Delta = 4.9$

X = NH_2

ΔH_f(g) (kcal mol^{-1}): $+10.5 + 20.8 - 19.7 = 11.6$ (calcd)

9.4 (expt)

$\Delta = 2.2$

$$\mathrm{MeCHO + PhOH - PhH = MeCO_2H} \qquad (11)$$

X = OH

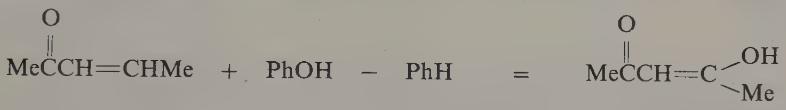
ΔH_f(g) (kcal mol^{-1}): $-39.7 + (-23.0) - 19.7 = -82.4$ (calcd)

-103.4 (expt)

$\Delta = 21.0$

$$\begin{array}{lcccccccl} & \mathrm{MeCHO} & + & \mathrm{PhNH_2} & - & \mathrm{PhH} & = & \mathrm{MeCONH_2} & \\ \mathrm{X = NH_2} & & & & & & & & \\ \Delta H_f(\mathrm{g}) & -39.7 & + & 20.8 & - & 19.7 & = & -38.6\,(\mathrm{calcd}) & (12) \\ (\mathrm{kcal\,mol^{-1}}) & & & & & & & -57.0\,(\mathrm{expt}) & \\ & & & & & & & \Delta = 18.4 & \end{array}$$

Another enone that can be considered as a vinylogous acid is the enol form of acetylacetone. We may estimate its heat of formation from macroincrementation reaction 13, where the necessary pentenone is itself estimated by reaction 14, In this case, a calculated value was used instead of making use of the experimental value of -17.5 kcal mol^{-1} for the liquid phase[10] because the measured value appears to be in error when compared with the known values for crotonaldehyde and 2-pentanone. This stabilization energy (*ca* 13 kcal mol^{-1}, which is an upper bound due to the neglect of hydrogen bonding) is intermediate between that of the hydroxytrienone and a carboxylic acid itself, suggesting that resonance in vinylogous acids is substantially less important than in carboxylic acids themselves.



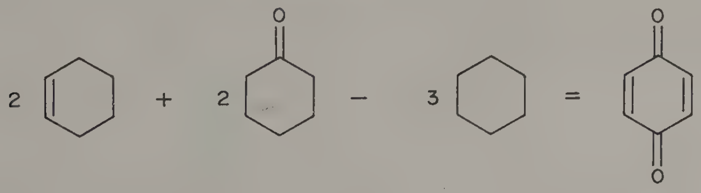
$$\mathrm{MeC(=O)CH{=}CHMe + PhOH - PhH = MeC(=O)CH{=}C(OH)Me}$$

$$\begin{array}{lcccccccl} \Delta H_f(\mathrm{g}) & -35.4 & + & (-23.0) & - & 19.7 & = & -78.1\,(\mathrm{calcd}) & (13) \\ (\mathrm{kcal\,mol^{-1}}) & & & & & & & -91.1\,(\mathrm{expt}) & \\ & & & & & & & \Delta = 13.0 & \end{array}$$

$$\mathrm{PhC(=O)Me + (\mathit{E})\text{-}MeCH{=}CHMe - PhMe = MeC(=O)CH{=}CHMe}$$

$$\begin{array}{lcccccccl} \Delta H_f(\mathrm{g}) & -20.7 & + & (-2.7) & - & 12.0 & = & -35.4\,(\mathrm{calcd}) & (14) \\ (\mathrm{kcal\,mol^{-1}}) & & & & & & & & \end{array}$$

We now turn from enones with electron-donating substituents to those with electron-withdrawing substituents. The first case is that of 3-acylenones for which *para* quinones qualify as an appropriate example that has the necessary available thermochemical data in the gas phase. In particular, consider *p*-benzoquinone (**35**). The macroincrementation reaction 15, which explicitly ignores all of the ene-one interactions, suggests that *p*-benzoquinone enjoys reasonable stabilization (7–8 kcal mol^{-1}) due to conjugation. These results are consonant with the earlier calculations for crotonaldehyde, which suggest 4 × 2.4 = 9.6 kcal mol^{-1} for the four independent enone parts of *p*-benzoquinone. This



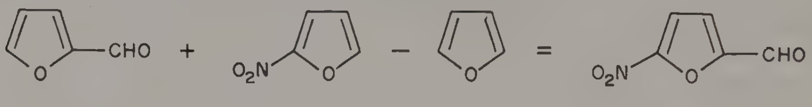
(15)

(**35**)

$$\begin{array}{lccccccl} \Delta H_f(\mathrm{g}) & 2\times(-1.2) & + & 2\times(-54.0) & - & 3\times(-29.5) & = & -21.9\,(\mathrm{calcd}) \\ (\mathrm{kcal\,mol^{-1}}) & & & & & & & -29.4\,(\mathrm{expt}) \\ & & & & & & & \Delta = 7.5 \end{array}$$

assumption, however, may be overly generous since the interaction of one double bond with two carbonyls is likely to be less energetically favorable than twice the interaction with one.

The second case we will consider is 5-nitrofurfural (**36**) with its accompanying macroincrementation reaction (equation 16). The nearly identical theoretical and experimental heats of formation suggest that a rather distant electron-withdrawing substituent has only a small electronic effect on enones. A larger effect might be expected for a nearby substituent, although no thermochemical data exist on any isomer of 5-nitrofurfural, nor on any other appropriately substituted furfural derivative.



(36)

ΔH_f(g) −36.0 + (−6.9) − (−8.3) = −34.6 (calcd)
(kcal mol^{-1}) −35.2 (expt) (16)
$\Delta =$ 0.6

D. Comparison of Enones with Related Species

The stabilization energy of enones may be compared to that for other substituents on a double bond by using hydrogenation enthalpies. This quantity is a measure of the difference in heats of formation of unsaturated and corresponding saturated compounds. Tables 2 and 3 give hydrogenation enthalpies for the gas and liquid phases of a variety of substituted (*E*)-olefins. Unfortunately, no simple relationship between the electronic and steric properties of the substituents and the hydrogenation enthalpy is apparent. The two extrema are vinyl and ethynyl, two nonpolar, classical conjugating groups that should have similar resonance and inductive effects. Furthermore, the hydrogenation enthalpy of the compound with the one unequivocally electron-donating substituent, methyl, lies between that for compounds with the electron-withdrawing substituents cyano and carbo-n-butoxy.

TABLE 2. Gas-phase hydrogenation enthalpies[a]

X	ΔH_f (g, $MeCH{=}CHX$)	ΔH_f (g, $MeCH_2CH_2X$)	ΔH_{H_2} (g)
$CH{=}CH_2$	18.2	−5.1	23.3
CHO	−24.0	−48.9	24.9
CN	33.6	8.0	25.6
Me	−2.7	−30.0	27.3
COOBu	−99.4[b]	−127.5[b]	28.1
H	4.8	−25.0	29.8
$C{\equiv}CH$	60.9[c]	30.7[d]	30.2

[a] In kcal mol^{-1}.

[b] The heat of formation of butyl butanoate was approximated by that of propyl pentanoate.

[c] Estimated heat of vaporization (condensation) using the method of Reference 36.

[d] D. D. Wagman, J. E. Kilpatrick, K. S. Pitzer and F. D. Rossini, *J. Res. Natl. Bur. Stand.*, 35, 467 (1945).

TABLE 3. Liquid-phase hydrogenation enthalpies[a]

X	ΔH_f (l, MeCH=CHX)	ΔH_f (l, $MeCH_2CH_2X$)	ΔH_{H_2} (l)
$CH=CH_2$	11.8[b]	−11.2	23.0
CHO	−33.2	−57.2	24.0
CN	24.0	−1.4	25.4
Me	−7.1	−35.0	27.9
COOBu	−111.8[c]	−139.3[c]	27.5
H	0.4	−29.1[b]	29.5
C≡CH	54.5	24.3[b,d]	30.2

[a] In kcal mol^{-1}.

[b] Estimated heat of vaporization (condensation) using the results of ref. 36.

[c] The heat of formation of butyl butanoate was approximated by that of propyl pentanoate.

[d] D. D. Wagman, J. E. Kilpatrick, K. S. Pitzer and F. D. Rossini, *J. Res. Natl. Bur. Stand.*, **35**, 467 (1945).

E. Conclusion

In spite of the seeming presence of considerable data (cf. Table 1) on the thermochemistry of enones and "buried" enones, it is still impossible to offer many meaningful predictions or explanations about the energetics of numerous enones of interest as found elsewhere in this volume. More research is clearly needed in this area.

III. REFERENCES

1. J. Hine, S.-M. Linden, A. Wang and V. Thiajarajan, *J. Org. Chem.*, **45**, 2821 (1980).
2. J. Hine, V. M. Kanajasabapathy and P. Ng, *J. Org. Chem.*, **47**, 2745 (1982).
3. J. Hine and M. J. Skoglund, *J. Org. Chem.*, **47**, 4758 (1982).
4. J. Hine and M. J. Skoglund, *J. Org. Chem.*, **47**, 4766 (1982).
5. D. R. Stull, E. F. Westrum, Jr. and G. C. Sinke, *The Chemical Thermodynamics of Organic Compounds*, Wiley, New York, 1969, evaluating the data archived in M. S. Kharasch, *Bur. Stand. J. Res.*, **2**, 359 (1929) (RP41).
6. P. Sellers, *Acta Chem. Scand.*, **25**, 2184 (1971).
7. R. Fuchs, personal communication.
8. J. B. Pedley, R. D. Naylor and S. P. Kirby, *Thermochemical Data of Organic Compounds*, Chapman and Hall, New York, 1986.
9. P. A. Erastov, V. P. Kolesov and I. K. Igumenov, *Russ. J. Phys. Chem.*, **54**, 2144 (1984).
10. D. R. Stull, E. F. Westrum, Jr. and G. C. Sinke, *The Chemical Thermodynamics of Organic Compounds*, Wiley, New York, 1969, presenting data not found in M. S. Kharasch, *Bur. Stand. J. Res.*, **2**, 359 (1929) (RP41).
11. M. A. Ribeiro da Silva, in *Thermochemistry and its Applications to Chemical and Biochemical Systems* (Ed. M. A. Ribeiro da Silva), D. Reidel Publ. Co., Dordrecht, 1982, p. 317.
12. C. S. Shiner, P. E. Vorndan and S. R. Kass, *J. Am. Chem. Soc.*, **108**, 5699 (1986).
13. K. Conrath, C. Van de Sande and M. Vandewalle, *Org. Mass. Spectom.*, **9**, 585 (1974).
14. E. S. Domalski, *J. Phys. Chem. Ref. Data*, **1**, 221 (1972).
15. R. Sabbah and L. El Watik, *Bull. Soc. Chim. Fr.*, **4**, 626 (1988).
16. E. J. Smutny, M. C. Caserio and J. D. Roberts, *J. Am. Chem. Soc.*, **82**, 1793 (1960).
17. R. C. Cookson, E. Crundwell, R. R. Hill and J. Hudec, *J. Chem. Soc.*, 3062 (1964).
18. C. E. Johnson, personal communication: update of K. Y. Kim, R. E. Winan and C. E. Johnson, *J. Phys. Chem.*, **82**, 450 (1978), and R. Sabbah and L. El Watik, *Bull. Soc. Chim. Fr.*, **4**, 626 (1988).
19. A. A. Vaprintseva and A. V. Finkel'shtein, *Tr. Sib. Tekhnol. Inst.*, **36**, 75 (1963); *Chem. Abstr.*, **61**, 11393b (1964).
20. I. Contineanu and D. I. Marchidan, *Rev. Chim. (Roum.)*, **30**, 1096 (1979); *Chem. Abstr.*, **92**, 128248d (1980).

21. T. V. Siretskaya, V. V. Takhistov, S. M. Pimenova, V. M. Orlov and V. N. Pustobuev, *React. Kinet. Catal. Lett.* **31**, 15 (1986); *Chem. Abstr.*, **106**, 40860w (1987).
22. P. A. Gerasimov, A. I. Gubareva, V. V. Beregovykh and E. I. Blokh, *Russ. J. Phys. Chem.*, **59**, 2861 (1985).
23. These results are a composite of two contemporaneous thermochemical studies that derived nearly identical heats of formation for diphenylcyclopropenone: combustion calorimetry, W. V. Steele, B. E. Gammon, N. K. Smith, J. S. Chickos, A. Greenberg and J. F. Liebman, *J. Chem. Thermodyn.*, **17**, 505 (1985); reaction calorimetry, H. E. Davis, N. L. Allinger and D. W. Rogers, *J. Org. Chem.*, **50**, 3601 (1985).
24. A. Pongrantz and F. Griengl, *Monatsh. Chem.*, **53**, 256 (1929).
25. J. S. Chickos, in *Molecular Structure and Energetics: Physical Measurements* (Eds. J. F. Liebman and A. Greenberg), VCH Publishers, Inc., Deerfield Beach and New York, 1987.
26. S. Suradi, N. El-Saiad, G. Pilcher and H. A. Skinner, *J. Chem. Thermodyn.*, **14**, 45 (1982).
27. J. M. Hacking and G. Pilcher, *J. Chem. Thermodyn.*, **11**, 1015 (1979).
28. J. V. Hamilton and T. F. Fagley, *J. Chem. Eng. Data*, **13**, 523 (1968).
29. M. Milone and A. Allaavena, *Gazz. Chim. Ital.*, **61**, 75 (1931).
30. S. W. Benson, *Thermochemical Kinetics*, 2nd edn., Wiley, New York, 1976.
31. This is derivable from the results in J. S. Chickos, D. G. Hesse, J. F. Liebman and S. Y. Panshin, *J. Org. Chem.*, **53**, 3424 (1988).
32. H. M. Rosenstock, J. Dannacher and J. F. Liebman, *Radiat. Phys. Chem.*, **20**, 7 (1982).
33. J. F. Liebman, in *Molecular Structure and Energetics: Studies of Organic Molecules* (Eds. J. F. Liebman and A. Greenberg), VCH Publishers, Inc. Deerfield Beach and New York, 1986, p. 267.
34. G. R. de Maré, Y. N. Pachenko and A. V. Abramenkov, *J. Mol. Struct.*, **160**, 327 (1987).
35. Y. N. Pachenko, A. V. Abramenkov and C. W. Bock, *J. Mol. Struct.*, **140**, 87 (1986).
36. The requisite heat of condensation of (*E*)-1,3-pentadiene was estimated using rule 2 of J. S. Chickos, L. H. Ladon, A. S. Hyman and J. F. Liebman, *J. Org. Chem.*, **46**, 4294 (1981).
37. D. L. Whalen, J. F. Weimaster, A. M. Ross and R. Radhe, *J. Am. Chem. Soc.*, **98**, 7319 (1976).
38. J. F. Liebman and A. Greenberg, in *The Chemistry of the Cyclopropyl Group* (Ed. Z. Rappoport), Wiley, Chichester, 1987, p. 1083.
39. See, for example, J. H. Lowry and K. S. Richardson, *Mechanism and Theory in Organic Chemistry*, 3rd edn., Harper & Row, New York, 1987, pp. 41–51.
40. See the discussion in J. F. Liebman, in *The Cyclophanes* (Eds. P. M. Keehn and S. M. Rosenfeld), Academic Press, New York, 1983, p. 23.
41. L. R. Mahoney and M. A. DaRooge, *J. Am. Chem. Soc.*, **97**, 4722 (1975).
42. L. R. Mahoney and S. A. Weiner, *J. Am. Chem. Soc.*, **97**, 585 (1975).
43. J. F. Liebman, unpublished results.
44. P. George, C. W. Bock and M. Trachtman, in *Molecular Structure and Energetics: Biophysical Aspects* (Eds. F. Liebman and A. Greenberg), VCH Publishers, Inc., New York, 1987, p. 163.
45. J. F. Liebman and A. Greenberg, *Biophys. Chem.*, **1**, 222 (1974).

The Chemistry of Enones
Edited by S. Patai and Z. Rappoport

CHAPTER **5**

NMR spectroscopy of enones

HUGO E. GOTTLIEB
Department of Chemistry, Bar-Ilan University, Ramat-Gan 52100, Israel

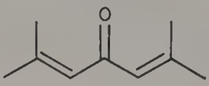
I. INTRODUCTION

A discussion on the NMR spectroscopy of enones must address itself primarily to how the presence of adjacent carbonyl and double-bond functions affects the spectral data (such as chemical shifts and coupling constants) of the involved nuclei. On a more fundamental level, the question is really how to rationalize these data in terms of molecular parameters, or, better yet, to be able to say something about the degree of conjugation, the conformation, etc., from the analysis of NMR spectra.

II. BASIC NMR DATA

A. ^1H NMR

α,β-Unsaturated aldehydes and ketones were among the first organic compounds to be investigated by NMR. Thus, in 1953, Meyer, Saika and Gutowski[1] reported data (taken at 17.8 MHz) for acrolein, crotonaldehyde and tiglaldehyde. The aldehyde hydrogen signal was found at 4.4 to 4.6 ppm lower field than H_2O, and the olefinic protons were shown to be deshielded by 0.5 to 1.0 ppm relative to cyclohexene. In 1959, Martin and Martin[2] studied eighteen α,β-unsaturated ketones at 25 MHz. Among their findings were the deshielding of CH_3, CH_2 and olefinic hydrogens when located α to carbonyl groups. They also showed that in a molecule like phorone (**1**) the two types of methyl groups are non-equivalent and give two distinct peaks. In the case of methyl vinyl ketone, the two β hydrogens were also seen to be non-equivalent, but the olefinic proton pattern was too complex to be analysed in detail. This task was performed in 1965 by Douglas and Goldstein[3] on spectra of acrolein and three of its methylated derivatives (at 60 MHz). A full analysis was now possible and all proton chemical shifts and proton–proton coupling constants are given. In addition, values of $^1J_{CH}$ were measured from ^{13}C satellites. A comparison of the NMR data of acrolein with that of butadiene shows that while J_{HH} values and the chemical shift of H-2 are similar in both substances, the β protons are deshielded in acrolein by *ca* 1 ppm due to conjugation with the carbonyl. This deshielding increases by another 0.3 to 0.4 ppm in concentrated solutions; this is interpreted as a further polarization of the π system when molecules of the aldehyde can associate. Similar results were obtained in the same year by Kossanyi[4], for several alkyl vinyl ketones.



(1)

The signal of an aldehyde proton is easily spotted by its low field location. *A priori*, an α,β double bond might be expected to affect this chemical shift by deshielding through a magnetic anisotropic effect and/or by decreasing the partial charge of the carbonyl carbon (a shielding effect). Klinck and Stothers[5] show that the latter contribution is dominant, since the CHO is *ca* 0.2 ppm at higher field in unsaturated aldehydes than in saturated ones. They also find a curious dependence on ring size, which is absent in cyclic saturated aldehydes. Specifically, while the aldehyde proton absorption is at δ 9.33 in 1-cyclohexenecarboxaldehyde (similar to acyclic cases), the equivalent value for 1-cyclopentenecarboxaldehyde is δ 9.72; no good explanation for this effect is given.

Proton chemical shift data on many unsaturated aliphatic compounds, including aldehydes and ketones, have been presented in chart form[6].

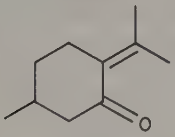
B. ^{13}C NMR

The chemical shift of carbon is less affected than that of hydrogen by medium and anisotropy effects, and therefore it is more indicative of the degree of conjugation and charge delocalization. This was recognized by the group of Stothers already in early papers reporting carbon shifts for an appreciable number of unsaturated aldehydes and ketones[7–9]. For example[9], the carbonyl of 2-cyclohexenone is 12 ppm at higher field than the one in cyclohexanone. This increased electron density comes, as might be expected, at the expense of the β olefinic carbon, which is deshielded by 23 ppm relative to cyclohexene. The actual chemical shifts for cyclohexenone are 197.1 (C=O), 128.4 (C_α) and 149.8 ppm (C_β)[8]. Alkyl substitution tends to have a downfield effect similar to that in simple olefins; also, the intensity of the shielding of the carbonyl and the deshielding of the β-carbon depends on the degree of conjugation, and is therefore reduced by branching when this causes deviations from planarity (steric inhibition to resonance)[8].

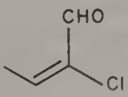
More recently, Loots, Weingarten and Levin used carbon shifts quantitatively in order to calculate electron deficiencies at the β-carbon (they estimated a ratio of 240 ppm per unit charge) in a variety of α,β-unsaturated carbonyl compounds, cyclic and acyclic[10,11]. For acyclic aldehydes and ketones, the value is usually of the order of 0.1 unit charges. For cyclic enones, the partial charge depends inversely on ring size, increasing from 0.05 in the eight-membered ring to 0.15 in 2-cyclopentenone. This is explained by increased planarity of the π-system and decreased distance between the β-carbon and the (negatively charged) oxygen in smaller rings. For cyclopropenone the high value (0.20) reflects the important contribution of a cyclopropyl cation canonic form; conversely, cyclopentadienone is the only compound examined with a negative partial charge on the β-carbons (a total of -0.11 units). This is attributed to the contribution of a canonic structure with a cyclopentadienyl anion moiety bound to a positively charged oxygen. Partial charges calculated in this manner correlate well also with ^{17}O chemical shifts for a series of α,β-unsaturated carbonyl compounds, including fourteen aldehydes and ketones[12]. Extrapolation of the oxygen shifts permits the authors to estimate an increase of 530 ppm for the loss of one electron; the data show that the electron density lost by the β-carbon is indeed gained by the carbonyl oxygen atom.

A heteroatom such as nitrogen or oxygen linked to the β-position of an enone system will of course also conjugate with the chromophore. For example, Still, Plavac, McKinnon and Chauhan report ^{13}C data on 4-pyrones and a variety of sulphur or nitrogen analogues and benzo derivatives thereof[13]. Introduction of the heteroatom deshields the β carbon but shields both the α carbon and the carbonyl.

^{18}O isotope shifts (the chemical shift difference between the ^{18}O and ^{16}O isotopomers) for the carbon linked to the oxygen are larger for aldehydes and ketones (30–50 ppb) than for alcohols (10–30 ppb)[14]. The shifts are smaller for conjugated ketones than for saturated ones; examples of specific values are 52 ppb for methyl cyclohexyl ketone, 47 ppb for acetophenone, 45 ppb for pulegone (**2**) and 37 ppb for tropone.



(**2**)



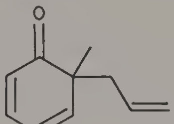
(**3**)

The geminal coupling constant between the aldehyde proton and the α carbon is unusually large, a feature which is often useful in spectral assignment. Yamamoto, Watabe and Kikuchi have reported values for several such $^2J_{CH}$ (from ^{13}C satellites in the ^1H spectra)[15], which are *ca* + 25 Hz for both saturated and α,β-unsaturated aldehydes; the value is larger (33 Hz) for propynal. The coupling constant also increases on α chlorination (being e.g. 40 Hz for **3**) both for sp^3- and sp^2-hybridized α carbons.

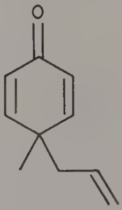
C. Special Classes of Compounds

1. Dienones

The group of von Philipsborn has reported extensive data on the NMR of many cyclohexadienones such as **4** and **5**, representing '*ortho*' and '*para*' systems, respectively; some acyclic compounds are also represented. Proton[16,17] and carbon[18] chemical shifts are interpreted in terms of charge distribution and substituent effects. The vicinal, olefinic proton–proton couplings are 'normal' (10.0–10.2 Hz, like in cyclohexenones) for the '*para*' but smaller (9.5–9.8 Hz) for '*ortho*' compounds. The vicinal coupling across the single bond of derivatives of **4** falls in the 5.7–6.2 Hz range, which is smaller than in open-chain (transoid) compounds. Almost all possible long-range proton–proton and carbon–proton coupling constants are listed; especially large are the α,α' (1.6–2.0 Hz) and β, β' (2.7–3.0 Hz) proton–proton interactions in the '*para*' structures, which represent $^4J_{HH}$ in a W-type arrangement. A few fluorinated compounds are included, together with ^{19}F chemical shifts, and values of J_{HF} and J_{CF}.



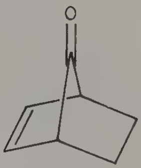
(4)



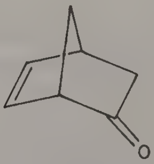
(5)

2. β,γ-Unsaturated ketones

In 1965, Savitsky, Namikawa and Zweifel[19] reported the fact that the carbonyl chemical shift for **6** was 10 ppm at higher field than that of its saturated analogue; no such difference, however, exists for **7**[19]. This was interpreted in terms of molecular strain. A few years later, Gurudata and Stothers[20] confirmed these observations, but looked also at several more acyclic, mono- and bicyclic β,γ-unsaturated ketones. They show that in most cases the carbonyl carbons are shielded by 1 to 3 ppm relative to their saturated analogues, and explain these observations in terms of a homoconjugative interaction, which depends on the geometry of the possible orbital overlap. In 1975 the same group reported full ^{13}C chemical shifts for a variety of polycyclic β,γ- and γ,δ-unsaturated ketones[21], comparing these to the corresponding olefins and saturated ketones. These investigators find qualitative evidence for the presence of homoconjugation, but attempts to correlate carbon shifts with charge densities derived from molecular orbital calculations were not very successful. It seems that other effects must be included if a full understanding of the carbon shifts is desired.



(6)



(7)

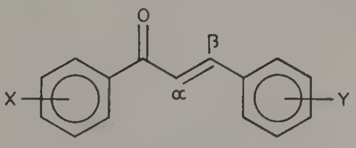
3. Acetylenic systems

In 1963, Jouve and Simonnin reported the ^1H chemical shifts for propynal, methyl ethynyl ketone and phenyl ethynyl ketone[22]. In these substances, the acetylenic proton absorbs at 3.03, 3.28 and 3.33 ppm, respectively, more than 1 ppm lower field than acetylenes which are not conjugated to carbonyls, a result of charge delocalization. In fact, Kalabin, Proidakov, Gavrilov and Vereshchagin claim that the degree of delocalization is even higher in acetylenic aldehydes and ketones than in their ethylenic analogues[23]. They base their conclusion on a ^{13}C study of several such compounds, where it is seen that the carbonyl is shielded by 10 to 20 ppm in the former group relative to the latter.

Bohlmann and Brehm have extended these observations to diynes as opposed to dienes; in each case an aldehyde is compared to $—CH_2OH$ as a substituent[24]. In both series, the δ carbons are deshielded by *ca* 10 ppm, while the β carbons are deshielded by *ca* 20 ppm in the dienes but only by *ca* 10 ppm in the diynes. A few triynes were also examined; while the β and δ carbons are strongly deshielded, as in the diynes, the ζ carbon moves downfield by only some 4 ppm. Thus it is concluded that charge distribution is of the same order of magnitude in acetylenic and ethylenic systems. While this seems to contradict the results of the Soviet group[23], here as well the aldehyde carbonyls are very shielded (*ca* 18 ppm) in the diynes as compared to the corresponding dienes. Since the evidence based on the shifts of the β and δ carbons is quite compelling, it would seem that effects other than charge delocalization must be responsible for the high-field absorption of carbonyls when connected to triple-bonded carbons.

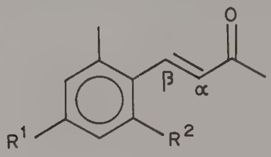
4. Aryl-substituted enones

In enone systems that are substituted by aryl groups, the effect of the conjugation of these peripheral rings with the central chromophore has to be taken into account. A measure of this type of influence can be found in a ^{13}C study of chalcones which are *meta*- or *para*-substituted in one of the two phenyl rings (**8**)[25]. The chemical shifts of C-α and C-β correlate well with Hammett parameters for X or Y. The effects are strong on Y substitution, with $\rho_{C\text{-}\alpha} = +5.3$ and $\rho_{C\text{-}\beta} = -2.7$, reflecting direct conjugation of the olefinic and aryl moieties. This type of behaviour is common to styrene derivatives (see e.g. Ref. 26 and other papers cited therein). Substituents X, on the other hand, can only cross-conjugate with C-α and C-β and therefore the effect is weaker and of opposite sign ($\rho_{C\text{-}\alpha} = -0.9$ and $\rho_{C\text{-}\beta} = +2.8$). The same group reported later on the ^1H NMR of such chalcones[27], with similar results. The fits for such correlations are generally better for carbon than for hydrogen shifts, due to the larger relative influence of medium and anisotropy effects in the latter. Carbon chemical shifts for several naturally occurring flavonoids, which are biogenetically related to chalcones, have been reported[28,29].

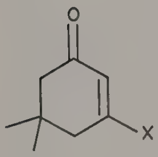


(**8**)

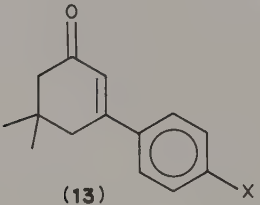
In aryl-substituted systems, one has to give some thought also to the planarity of the extended cromophore. This is illustrated by the olefinic proton chemical shifts for compounds **9**–**11**, which were reported by Unterhalt[30]. While these are identical for **9** and **10** ($\delta_{H\text{-}\alpha} = 6.50$ and $\delta_{H\text{-}\beta} = 7.67$), further *ortho*-substitution (to **11**) causes shielding ($\delta_{H\text{-}\alpha} = 6.21$ and $\delta_{H\text{-}\beta} = 7.58$), obviously resulting from tilting of the aryl moiety away from the plane of the enone. Geribaldi and Azzaro addressed the issue more quantitatively, in correlating olefinic proton shifts in the **12–14** series with Hammett constants for the X substituents[31]. They find that the transmission of electronic effects is less efficient in compounds **13** than in **12** or **14**, and interpret their results in terms of possible loss of planarity. The angle between the planes of the enone and aryl moieties is estimated to increase from 0° ($X = NH_2$) to almost 40° ($X = NO_2$) for the **13** system.



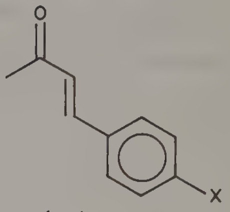
(**9**) $R^1 = R^2 = H$
(**10**) $R^1 = H, R^2 = CH_3$
(**11**) $R^1 = R^2 = CH_3$



(**12**)



(**13**)



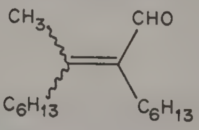
(**14**)

D. Geometrical Isomerism

One of the questions the chemist often wants the NMR spectrum to clarify is the configuration of the double bond. Of course, if the enone system is singly β-substituted, the answer is obtained very easily by inspection of the coupling constant between the two olefinic hydrogens: *ca* 12 Hz for *cis*, 16 Hz for *trans*. The problem becomes more difficult when the olefin is trisubstituted: Is the remaining hydrogen *cis* or *trans* to the carbonyl?

In the case of aliphatic aldehydes, the chemical shift of the aldehyde hydrogen provides a direct answer. Frost and Barzilay[32], and later Grigor'eva, Prokof'ev and Semenovskii[33] have shown that this is always in the 9.3–9.6 ppm range for the *E* isomer and at lower field (9.9–10.3 ppm) for the *Z*. The former group also show that the $^3J_{\beta\text{-H},\gamma\text{-H}}$ tends to be smaller in *trans*- (5.8–6.8 Hz) than in *cis*- (7.0–8.2 Hz) alkylated aldehydes[32], but since this must be due to a conformational preference of the alkyl substituent, this result may not be readily extrapolated to differently substituted compounds.

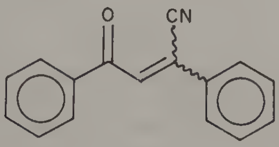
A more general criterion is the chemical shift of the allylic protons, which usually appear at lower field when *cis* to the carbonyl than when they are *trans*[33,34]. Of course, the applicability of this observation depends on the nature of the α-substituent, but in principle it allows the assignment even of enones which have no hydrogen left on the double bond. For instance, Grigor'eva, Prokof'ev and Semenovskii[33] report chemical shifts of 2.20 and 1.93 ppm for the methyl groups of the *E* and *Z* isomers of **15**, respectively.



(**15**)

Probably the most reliable means to determine the configuration of a trisubstituted olefin is to examine the three-bond coupling constants between the allylic carbons and the olefinic hydrogen. Several groups have reported long-range carbon–hydrogen coupling data for many olefins, including tens of α, β-unsaturated aldehydes and ketones[35–38]. In all cases, the *trans* coupling constant is larger than the *cis* for a pair of isomers. In addition, the ranges of the *trans* and *cis* coupling constants are separated enough to allow unambiguous structural assignment even if only one isomer is available, especially if one compares one's own data with similar models in the literature. The coupling constants seem to depend mainly on the state of hybridization of the allylic carbon in question, slightly decreasing in the series sp (*ca* 14 Hz for *trans*, *ca* 8 Hz for *cis*) to sp^2 (10–17 Hz for *trans*, 4–10 Hz for *cis*) to sp^3 (6–8 Hz for *trans*, 8–11 Hz for *cis*). Vogeli and von Philipsborn[35] show that there is a good correlation between the value of $^3J_{\underline{C}H_3,H}$ and the corresponding $^3J_{HH}$ for the analogous compound where the methyl group has been replaced by a hydrogen, with $^3J_{CH} \cong 0.6 \times {}^3J_{HH}$.

The main problem in the applicability of this criterion is the extraction of these $^3J_{CH}$ values from fully coupled carbon spectra, since other long-range coupling constants may obscure the desired splitting. When this difficulty can be overcome, the results are usually unambiguous. For instance, for the pair of β-cyanochalcones **16**, the cyano signal for the two separated isomers gave well-resolved doublets, with $J = 14.5$ Hz and $J = 9.5$ Hz, respectively. It was therefore clear that the former was the *E*- and the latter the *Z*-cyanochalcone[39].



(16)

III. CONFORMATIONAL ANALYSIS

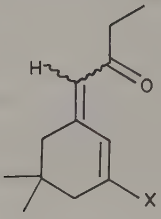
An interesting question that has occupied many researchers is the conformational preference around the single bond joining the olefinic carbons to the carbonyl. If the system is to be fully conjugated, the chromophore has to be planar and, therefore, two possibilities exist: a C=C—C=O dihedral angle of 180° (s-*trans*) or of 0° (s-*cis*). As already mentioned above, a high degree of branching may lead to loss of planarity, i.e. angles that deviate significantly from these.

In this section we will deal first with the NMR techniques for conformational assignment (useful information is also obtained from other spectroscopic methods such as UV or IR) and then with the results reported in the literature.

A. Methods

1. Chemical shifts

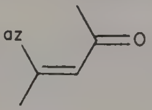
The ^1H chemical shift of the β substituent which is *cis* to the carbonyl is deshielded when the conformation is s-*cis*. This has been stated by Kossanyi already in 1965[4], and employed by other groups for conformational assignment[40–43]. The method is particularly useful when both β substituents are hydrogens; the *trans* proton then serves as an internal reference, and the Δδ values can be correlated directly to conformational populations. Most authors use an estimated $\Delta\delta = 0.15$ ppm for pure s-*cis* and *ca* 0.65 ppm for pure s-*trans*, in the case of alkyl-substituted α, β-unsaturated aldehydes and ketones. If only one β hydrogen is left, Barlet, Pierre and Arnaud use its chemical shift to calculate populations[41], but then the values for pure conformers have to be estimated from compounds with different configurations (*cis* and *trans*), and the results seem slightly less reliable. When pairs of *cis* and *trans* isomers are available, they can serve as models for each other, and then even more highly substituted enones can be analysed[44]. Rouillard, Geribaldi and Azzaro[45] have used this technique in a more quantitative vein by estimating the anisotropy and electric-field effects of the carbonyl on the various hydrogens in the molecule for both possible configurations and concluded that the conformation of dienones **17** (where X = H, Me, Ph, but also a few heteroatoms) is always s-*cis* as shown in the formula.



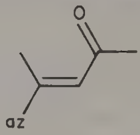
(17)

2. *Coupling constants*

The use of proton–proton coupling constants for this type of conformational assignment requires a hydrogen substituent on the carbonyl, i.e. an aldehyde. It is then shown[46] that the $^3J_{HH}$ between the aldehyde and α protons is 7.7 ± 0.1 Hz for s-*trans*; the value would presumably be smaller for an s-*cis* conformation. Otherwise $^3J_{CH}$ may be employed; this has been demonstrated by Braun[37], who finds that the coupling between the $\underline{C}H_3$ α to the carbonyl and the α-H is 2.7 Hz for **18** (s-*trans*, dihedral angle 180°) but too small to be measured in **19** (s-*cis*, dihedral angle 0°). In both formulas, az stands for a 4,6,8-trimethyl-1-azulenyl substituent. Vicinal proton–proton coupling constants are particularly important for polyenones[40,46–48]. The C═CH—CH═C coupling is *ca* 10 Hz for s-*trans*; this should be compared with cyclic dienones such as **4**, which are fixed in an s-*cis* conformation and where the corresponding value is of the order of 6 Hz[16].



(18)

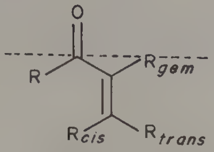


(19)

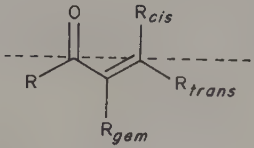
3. *Solvent shifts*

Information on molecular parameters may be derived not only from the study of NMR chemical shifts, but also from a comparison between the shifts of the same individual nucleus in different solvents (for a review, see Ref. 49). In this way, intramolecular effects are canceled out, and only the influence of solvation remains. For enones, the main application of this principle is the so-called aromatic-solvent induced shift (ASIS) in the ^1H NMR. The ASIS in usually defined as δ (aliphatic solvent) $-\,\delta$ (aromatic solvent), where the former is $CDCl_3$ or CCl_4 and the latter is benzene. Other aromatic solvents have been used in this context (*vide infra*).

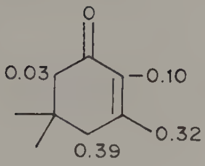
Several authors in the mid 1960s showed that the ASIS for carbonyl compounds can assume both positive or negative values[50–53]. The nodal surface (the locus of $\Delta\delta = 0$) is roughly a plane perpendicular to the C=O bond which passes through the carbonyl carbon atom. Protons located in space on the oxygen side of this plane are deshielded ($\Delta\delta < 0$) and those on the other side are shielded ($\Delta\delta > 0$). The absolute value of $\Delta\delta$ initially increases with distance from the nodal plane, goes through a maximum, and then decays to zero. The result of this behaviour on enones is illustrated on formulas **20** and **21**. The ASIS values for protons of the three substituents on the double bond (or the olefinic protons themselves) have different signs and magnitudes in the s-*trans* (**20**) and s-*cis* (**21**) cases and are therefore very conformation-dependent. The ASIS for R_{cis} is of greatest diagnostic importance, being positive or negative if s-*trans* or s-*cis* conformations, respectively, predominate. Examples of some benzene-induced shifts[50] are shown on formulas **22–25** and seem to leave no doubt that the main conformer for the two acyclic enones is the one depicted.



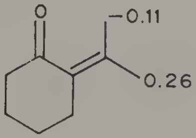
(**20**)



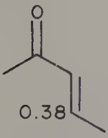
(**21**)



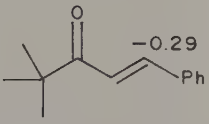
(**22**)



(**23**)



(**24**)



(**25**)

Since the reason for the solvent effect is the association of at least one benzene molecule with the carbonyl (Ichikawa and Matsuo argue in favour of more extensive clustering)[54] lower temperatures should lead to more stable complexes and therefore to stronger shifts. This has been demonstrated by Ronayne, Sargent and Williams[55] with deuteriated toluene as the solvent. Other solvents have also been examined for their ASIS behaviour[56], but the only one with appreciable popularity is pyridine, maybe because of its relatively easy availability in deuteriated form. The results are similar to those for benzene, but the nodal plane is somewhat shifted, passing roughly through the α carbons rather than the carbonyl[51,53]. This feature sometimes allows a clear-cut answer when groups are near the benzene nodal plane, and therefore have ASIS values for this solvent which are close to zero.

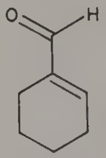
While ASIS is a powerful method, its applicability to enones with substituents other than alkyl groups may be problematic. It has been shown, for instance, that the nodal plane in aryl vinyl ketones is significantly tilted from the perpendicular plane to the C=O bond[57]. The position and shape of the nodal surface when other functionalities are present is unpredictable, especially since these may also have specific interactions of their own with the aromatic solvent.

4. Lanthanide-induced shifts

The carbonyl group of an enone is a potential complexing site for a lanthanide. The magnitude of lanthanide-induced shifts, usually through the pseudocontact interaction, is well understood and depends strongly on geometrical parameters. It should be possible, therefore, to fit observed shifts to expected molecular conformations, such as s-*cis*/s-*trans*, for the enone system[58]. If a fast-equilibrating mixture of conformers is present, the lanthanide-induced shifts will be a weighted average. An analysis of the data, preferably with the aid of a computer to optimize variables such as the coordinates of the lanthanide atom, may provide conformational populations[59,60]. Of course, this method is limited to molecules containing no other complexing site for the lanthanide. It is furthermore based on the assumption that the conformations of the complexes are essentially the same as those for the free enones, and this may not always be valid.

5. Nuclear Overhauser effects

The measurement of NOEs between protons belonging to substituents on the carbonyl and the olefinic parts of the enone may also provide important conformational information. The geometrical dependence of the NOE is solely a function of the distance between the protons in question, and conclusions are usually unambiguous. For instance, irradiation at the aldehyde hydrogen frequency of **26** leads to a 21% increase in the intensity of the olefinic hydrogen peak, but no change is noticed for the signal of the allylic hydrogens on C-6[61]. This proves an s-*trans* conformation as drawn.



(26)

Unfortunately, few workers seem to have attempted to analyse the conformation of enones by this method (see also Refs. 47 and 48), which does not have the main drawback of all the others mentioned above, i.e. possible interference from other functional groups in the molecule. The one minor problem is that in the case of a fast equilibrium, each conformer contributes to the NOE to a different extent. The conversion of NOE ratios to conformational populations requires the estimation of H–H distances, for which the assumption of particular geometries is required.

6. Low-temperature investigations

The most unambiguous way of determining conformational populations is of course to lower the temperature until the rotation around the C=C—C=O single bond is slow on the NMR time-scale. The identity of each of the pure conformers may then be established by other methods (e.g. coupling constants, NOE). While this has indeed been done for many aromatic aldehydes and ketones[62,63], we could find no mention in the literature of analogous work for simple olefinic cases. The reason is most probably the low energy barrier for such a process, which should be less than the 7.9 and 5.4 kcal mol^{-1} found for benzaldehyde[62] and acetophenone[63], respectively. It is not impossible, however, that such an investigation could be performed at the high magnetic fields now available in commercial spectrometers.

Additional functional groups may lead to increased rotation barriers and therefore easier observation of the separated conformers. For dienones, one such study has been reported; also, enones with electron-donating β substituents will have much higher barriers. For all these, results will be described in the appropriate sections.

B. Results

The results of conformational analyses for a representative collection of enones, as reported in the chemical literature, are presented in Tables 1 and 2. Our purpose in this section is, however, also to try to rationalize these findings, and for this it is useful to start by examining the structures of the s-*trans* (**20**) and s-*cis* (**21**) conformers. In the former, the steric interaction which is of most interest to us is that between R (the substituent on the carbonyl) and R_{cis}. To be sure, strain may result from the proximity of other groups around the double bond, but such interactions are either unavoidable in the s-*trans* conformer (between R_{gem} and C=O) or are not primarily affected by rotation around the C=C—C=O single bond (between R_{cis} and R_{trans} or between R_{gem} and R_{trans}). Conversely, in the s-*cis* form (**21**), we should focus on the interaction between R_{cis} and R_{gem}. The steric contribution to the conformational equilibrium depends, therefore, mainly on the balance between these two potentially destabilizing effects.

1. *Alkylated enones*

The conformation of acrolein (Table 1, entry 1) is s-*trans*. This is understood by making the general statement that, for electronic reasons, enone systems prefer an s-*trans* conformation unless forced into s-*cis* by steric hindrance. Gem-alkylation might be expected to destabilize the s-*trans* form in aldehydes by interaction with the carbonyl oxygen, but clearly a methyl group (entry 2) is not enough. It is possible that larger geminally substituted groups may tilt the balance in favour of s-*cis*, but no such results were revealed by our literature search. One may thus state with good generality that all aldehydes are mainly s-*trans*; alkylation at other positions (entries 3–5) has only a minor effect, as expected.

Methyl vinyl ketone (entry 6) is still mainly s-*trans*, but more of the s-*cis* conformer is now present. Increasing the size of R (entries 7 to 9) destabilizes the s-*trans* form, and by the time R = *t*-Bu, the molecule is mainly s-*cis*. These data indicate that a bulky substituent prefers to point away from the double bond, even though it is by no means obvious from inspection of molecular models that this should be preferred on steric grounds. Methyl-substituted analogues of methyl vinyl ketone are also s-*trans* (entries 10, 12, 13) unless methylation is at the *cis* position. If $R_{cis} = H$ but $R_{gem} \neq H$, s-*cis* predominates (entries 11, 14). If both R_{cis} and R_{gem} are not hydrogens (entry 15), reported results are not consistent, but it seems likely that a non-planar conformation is dominant (*vide infra*).

In general, other n-alkyl groups differ little from methyl as far as steric constraints are concerned, since the rest of the carbon chain can usually bend away and escape other major steric interactions. Conformational data for higher homologues such as ethyl or n-propyl[41,42,44,65] differ therefore little from the corresponding methylated enones and were not included in Tables 1 and 2.

2. *Arylated enones*

If aryl groups affect conformational preference just in virtue of their bulk, they should not lead to conformational populations which are very different from the corresponding

TABLE 1. Conformation of alkyl and aryl enones[a]

	R	$\mathrm{R}_{\mathrm{gem}}$	R_{cis}	R_{trans}	% s-*cis* conformation[b] (Reference)
1.	H	H	H	H	2 (43)
2.	H	Me	H	H	0 (59)
3.	H	H	Me	Me	1 (59)
4.	H	Me	H	Me	10 (59)
5.	H	H	H	Me	9 (59)
6.	Me	H	H	H	21 (60), 25 (43), 27 (59), mainly s-*trans* (55), s-*trans* (37)
7	Et	H	H	H	38 (43)
8.	*i*-Pr	H	H	H	63 (43)
9.	*t*-Bu	H	H	H	92 (43)
10.	Me	Me	H	H	2 (43), 11 (60), 12 (59), s-*trans* (42, 50)
11.	Me	H	Me	H	s-*cis* (41)
12.	Me	H	H	Me	16 (41), mainly s-*trans* (55), s-*trans* (37, 50)
13.	Me	Me	H	H	15 (60), 18 (59), s-*trans* (41, 50)
14.	Me	H	Me	Me	72 (59), 74 (60), s-*cis* (37, 44, 50, 52, 55)
15.	Me	Me	Me	Me	s-*cis* (50), a lot of non-planar (44)
16.	H	H	H	Ph	14 (59), s-*trans* (64)
17.	Me	H	H	Ph	63 (59), 69 (60), s-*trans* + s-*cis* (64), mainly s-*trans* (55), s-*trans* (50)
18.	*t*-Bu	H	H	Ph	s-*cis* (50)
19.	Me	H	Me	Az	s-*cis* (37)
20.	H	H	Ph	H	s-*trans* (64)
21.	Me	H	Ph	H	s-*cis* + s-*trans* (64)
22.	Me	H	Az	Me	s-*trans* (37)
23.	Ph	H	H	Ph	83 (59), mainly s-*cis* (64)
24.	Ph	H	Ph	H	s-*cis* (64)
25.	Ph	Me	Me	Me	non-planar (65)

[a] Az = 4, 6, 8-trimethyl-1-azulenyl.
[b] Unless otherwise indicated.

alkyl enones. Thus, cinnamaldehyde (entry 16) is mainly s-*trans*, just as crotonaldehyde (entry 5). The corresponding methyl ketone (entry 17) should also be mainly s-*trans* (cf. entry 12), but the results of various authors are not consistent. Two other cases of *trans*-aryl groups conform to expectations: entries 18 (cf. 9) and 19 (cf. 14).

When the aryl group is located at the position *cis* to the carbonyl, differences from the alkyl case start to emerge. The aldehyde (entry 20) is indeed s-*trans*, in accordance with the general rule (*vide supra*), but it seems that the methyl ketones are less sterically hindered by the planar *cis*-aromatic system than by a *cis*-methyl and have larger s-*trans* contributions (entries 21 and 22). A better understanding of this point would require a much larger number of examples.

Phenyl ketones (entries 23–25) are either s-*cis* or non-planar in view of the bulk of the aromatic moiety (cf. entries 8, 9) but again the planarity of the molecule in entry 24 is quite surprising and would seem to require further confirmation.

3. Halogenated enones

Data for such compounds (see Table 2) conform to expectations if one assumes that halogens act mainly sterically, and are comparable in bulk to alkyl groups such as methyl. Thus all the aldehydes (entries 1–7) are s-*trans*; methyl and phenyl ketones are s-*cis* if

TABLE 2. Conformation of haloenones

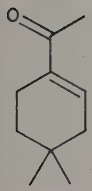
	R	R_{gem}	R_{cis}	R_{trans}	Results[a] (Reference)
1.	H	Cl	H	Me	12% (59)
2.	H	Br	H	Me	19% (59)
3.	H	Me	Cl	Me	6% (59), mainly s-*trans* (65)
4.	H	Me	Me	Cl	4% (59), mainly s-*trans* (65)
5.	H	H	Cl	Me	11% (59)
6.	H	H	Br	Me	5% (59)
7.	H	H	Me	Cl	9% (59)
8.	Me	H	Me	Cl	mainly s-*cis* (65)
9.	Me	H	Cl	Me	mainly s-*cis* (65)
10.	Me	H	Cl	Cl	mainly s-*cis* (65)
11.	Ph	H	Me	Cl	mainly s-*cis* (65)
12.	Ph	H	Cl	Me	mainly s-*cis* (65)
13.	Ph	H	Cl	Cl	mainly s-*cis* (65)
14.	Me	Me	H	Cl	mainly s-*trans* (65)
15.	Ph	Me	H	Cl	mainly s-*trans* (65)
16.	Ph	Me	Cl	H	mainly s-*trans* (65)
17.	Me	Me	Me	Cl	non-planar (65)
18.	Me	Me	Cl	Me	non-planar (65)
19.	Me	Me	Cl	Cl	non-planar (65)
20.	Ph	Me	Me	Cl	non-planar (65)
21.	Ph	Me	Cl	Me	non-planar (65)
22.	Ph	Me	Cl	Cl	non-planar (65)

[a] Percentage of s-*cis*, unless otherwise indicated.

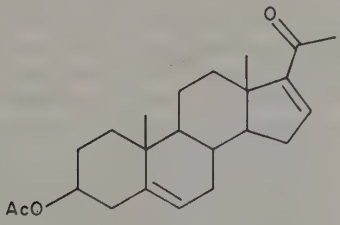
$R_{gem} = H$ and $R_{cis} \neq H$ (entries 8–13), and s-*trans* in the opposite case, $R_{gem} \neq H$ and $R_{cis} = H$ (entries 14, 15). Persubstituted systems (entries 17–22) are non-planar, while entry 16 is somewhat puzzling. The nature of the halogen (compare entry 1 to 2 or 5 to 6) seems to be unimportant.

4. *Cyclic enones*

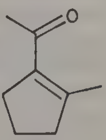
If both the carbonyl and the α-olefinic carbon belong to the same ring, the conformation is fixed; indeed, such compounds were often used as models to establish the validity of techniques such as ASIS (*vide supra*). If, however, the carbonyl is exocyclic, the enone is conformationally mobile, and a few results have been reported for such substances. Thus **26**, an aldehyde, is s-*trans* as expected[61] (*vide supra*), and so are methyl ketones **27**[50] and **28**[55]. *Cis*-methylation leads to s-*cis* conformations for **29**[55] and **30**[50] rather than to non-planar forms as might be predicted. Since results for **27–30** were obtained by the use of ASIS, confirmation by NOE would seem appropriate.



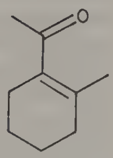
(**27**)



(**28**)



(**29**)

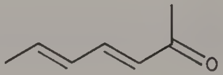


(**30**)

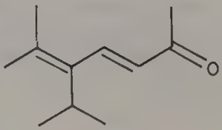
5. Dienones and polyenones

Conformational studies on $\alpha, \beta, \gamma, \delta$-unsaturated methyl ketones substituted only on the δ position were performed by Kluge and Lillya using chemical shift and coupling information[40] and by Filippova, Bekker and Lavrukhin using lanthanide-induced shifts[58]. Despite the different techniques employed, the two groups agree in their results. When the α, β-double bond has *cis* configuration, the C=C—C=O is mainly s-*cis*; when the dienone is α, β-*trans*, the conformation is a mixture of s-*cis* and s-*trans*. This is as expected from the simple alkyl enone data (*vide supra*) and is independent of the γ, δ configuration. The conformation of the C=C—C=C single bond is s-*trans* in all the unsubstituted cases, for all possible isomers; all-*trans* polyene aldehydes have also s-*trans* conformations[46]. In agreement with the data in Table 1, β-alkyl substitution leads to a predominance of s-*cis* enone, while α substitution leads to s-*trans*; more highly branched derivatives are non-planar[40].

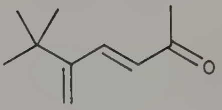
Confirmation for methyl ketone conformational preferences is provided by Mullen and coworkers, who recorded ^{1}H-NMR spectra of **31**–**34** at low temperatures[66]. For all four dienones, the behaviour is similar: the spectrum starts to broaden below −90 °C, and splits into a 3:1 mixture of two species below *ca* −150 °C. Chemical shift information indicates the major isomer to be the enone s-*trans* and the minor the corresponding s-*cis* conformer, in excellent agreement with, e.g., entries 6 and 12 in Table 1. For **32**, the rotation barrier at −144 °C is 6.6 kcal mol^{-1} with a 0.27 kcal mol^{-1} ground-state energy difference between the s-*cis* and s-*trans* isomers. Derivatives of **31** methylated at α or β do not show any broadening down to −160 °C, and are supposed to be exclusively s-*cis* or s-*trans*, respectively. No evidence is found for mobility of the diene moiety; from $^3J_{HH}$, **31** is known to be s-*trans*. NOE results indicate that **32** is s-*trans* but **33** is s-*cis*, in analogy to β-ionone (**34**).



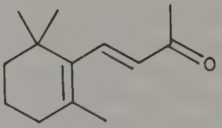
(31)



(32)

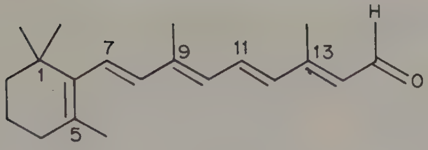


(33)



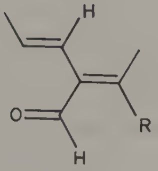
(34)

The latter ketone is important as a model for retinal (**35**), the aldehyde derived from the visual pigments of many animals, including man. Rowan, Sykes and coworkers have extensively investigated retinal and its 9-, 11- and 13-*cis* isomers using ^{1}H chemical shifts, coupling constants, relaxation times and NOEs[47,48]. With the exception of 11-*cis* retinal, the other aldehydes are shown to be all planar, with s-*trans* conformations from C-7 to C-15. 11-*Cis* retinal deviates slightly from planarity around the 10, 11 bond and is a mixture of distorted s-*trans* and s-*cis* conformers around the 12, 13 bond. Of course, the visual pigments are immonium salts of retinal, and work has been done recently[67] correlating charge distribution through the chromophore of such derivatives, as determined by ^{1}H and ^{13}C chemical shifts, with their UV-visible spectra.



(**35**)

Wiemann and coworkers found a $^4J_{HH} = 1.8$ Hz between the marked protons of **36**, which indicates a conformation as drawn for this and similar cross-conjugated dienones[53]. This large W-coupling is absent, however, for **37** and the equivalent ethyl derivative, suggesting that a different conformation predominates, though none is suggested by the authors.



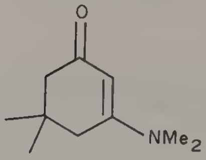
(**36**) R = H
(**37**) R = CH_3

IV. *β*-AMINOENONES

The substitution of an electron-rich heteroatom at position *β* in the enone system introduces marked changes in its behaviour. The contribution of canonic forms with a positive charge on the carbonyl oxygen and a negative charge on C_α or the carbonyl oxygen (i.e. electron delocalization through the five-atom system) has to be taken into account. Also, if the heteroatom has at least one hydrogen substituent, tautomerism becomes an important issue.

The best-studied examples of such systems are the *β*-hydroxyenones, i.e. the enolic forms of *β* diketones. However, two very good and extensive review articles on this subject have been published. The first, by Kol'tsov and Kheifets, presents the study of keto-enol tautomerism by NMR, including *α* and *β* diketones[68]. A more recent review by Emsley deals with the structure of *β* diketones by different techniques, and NMR is an important part thereof[69]. In both, sulphur analogues are also covered. We have decided, therefore, not to include these families of compounds in this chapter, and concentrate only on the third main case, *β*-aminoenones.

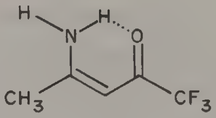
The first question of interest in this field is the degree of electron delocalization. Dabrowski, Skup and Sonelski have looked at the ^{14}N NMR chemical shifts of several R—CO—CH=CH—NR′R″ systems and shown that they fall between the values for the corresponding amides (R—CO—NR′R″) and amines (R—NR′R″) and, in fact, are usually closer to the former than to the latter[70], so that a fair amount of charge delocalization is present. The other side of the coin is the carbon part of the chromophore. ^{13}C shifts for **38**[71], as compared to cyclohexenone[9], indicate that the carbonyl carbon is indeed shielded, but only by 3 ppm, while it is the double bond which is strongly polarized (α carbon: − 32 and *β* carbon: + 15 ppm relative to the simple enone). These data seem to indicate that the canonic form with a negative charge on C-α contributes far more to the overall structure than that with a negatively charged oxygen.



(38)

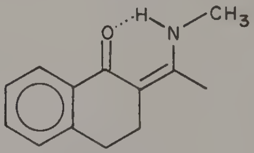
A. Tautomerism

If the nitrogen bears at least one hydrogen atom, three tautomeric forms are in principle possible: a ketoimine, a ketoenamine and an enolimine. Aizikovich and coworkers show from the study of ^{1}H and ^{13}C chemical shifts that for **39** the ketoenamine form predominates[72]. In fact, as the temperature is lowered, the signal for the NH_2 group splits into two: the absorption of the free hydrogen is at high field (5.3 ppm), while the chelated one is deshielded (9.8 ppm). The barrier for exchange between the two protons, i.e. for the rotation of the NH_2 group, is *ca* 14 kcal mol^{-1}. If CD_3OD is added, both signals slowly disappear, indicating that the exchange process is slower than the rotation. The analogue of **39** where the CF_3 and CH_3 moieties are switched shows this splitting even at room temperature; in fact, no significant spectral change is noticed in the range −50 to +125 °C. Addition of CD_3OD now makes the signal for the free NH disappear immediately, but that for the chelated hydrogen survives for several hours, pointing to a very stable hydrogen bond.



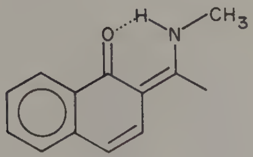
(39)

In fact, simple β-aminoenones exist mainly in the ketoenamine form, as proved in the case of **40** by a 5 Hz coupling constant between the N-methyl and NH protons[73–75]. In these hydrogen chelates, the NH signal appears within a wide range of chemical shifts (5 to 20 ppm), which correlate well with IR N—H and C=O stretching frequencies, and are indicative of the strength of the hydrogen bond[76].

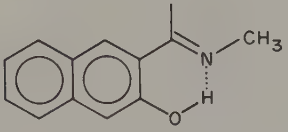


(40)

The ketoenamine tautomer predominates even in systems such as **41** where the enolimine would be aromatic[73,77]. The energy balance is then quite subtle, however, since some of the phenol tautomer is present in this and similar compounds, and **42** is exclusively phenolic[77]. In this study, Dudek and Dudek determined the tautomeric equilibrium by synthesizing the ^{15}N isotopomers and looking for ^{1}H, ^{15}N coupling in the proton spectrum[77,78]. For the N—H signal, formamide ($J = 88$ Hz) is taken as a model, and smaller values are interpreted as resulting from fast equilibration with some imine tautomer.

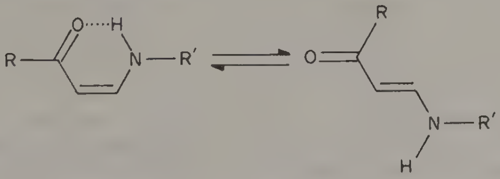


(41)



(42)

Filleux-Blanchard and coworkers extended the ^{15}N technique to acyclic enaminoketones such as 43[79]. For $R = R' = Ph$, in $CDCl_3$ solution, they can see, in addition to a $^1J_{NH} = 91$ Hz, a $^3J_{NH} = 4.2$ Hz with the α-olefinic proton, indicating a *trans* relationship between the two nuclei. Other useful vicinal couplings are $^3J_{HH} = 8$ Hz between the olefinic hydrogens and 13 Hz for the β-olefinic proton and the N—H, which all favour isomer **43a**. If the solvent is made more basic, however, additional peaks appear; the coupling constant between the two olefinic hydrogens in this other species is 12 Hz, indicating a *trans* relationship, while the $^3H_{\beta\text{-H,NH}}$ remains 13 Hz. For this form, structure **43b** is suggested, even though this s-*trans* conformation seems unlikely (*vide infra*). Of course, such an isomerization can be easily visualized to occur through the intermediacy of the ketoimine form. The *trans/cis* equilibrium constant, which is near 0 in $CDCl_3$, becomes 0.05 in acetone, 0.72 in DMSO and 2.6 in HMPA, as the hydrogen-bond acceptor ability of the solvent is increased. Similar results had been obtained previously by Dudek and Volpp[80]. These investigators see *trans* isomers even in 1 M $CDCl_3$ for $R = R' = CH_3$; the equilibrium constant changes from 0.34 to *ca* 1 as the solute concentration is increased up to the neat liquid. They also show that a bulkier R′ favours the *cis* conformer, as does β-methylation, while α methylation shifts the equilibrium towards the *trans*. All these results can be explained by taking steric interactions into account.



(43a) (43b)

Kashima and coworkers have reported ^1H NMR data on many tens of enaminoketones, both fixed into *cis* or *trans* stereochemistries or potentially mobile[81]. Of the latter, the mono-N-alkylated compounds are reported as *cis*, and the di-N-alkylated ones as *trans* isomers. Mono-N-alkylated aminoenones fixed in a *trans* configuration all seem to have the N—H bond transoid to the double bond, unlike what is suggested in structure **43b**. ^{13}C chemical shift data on this class of compounds have been reported for both *cis* and *trans* isomers[82,83].

B. Conformational Analysis

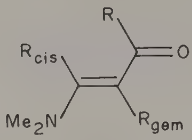
1. s-cis, s-trans *Isomerism*

Conformational population data for several *trans*-β-dimethylamino enones (**44**), as reported by different investigators, are compiled in Table 3. Different methods were used

TABLE 3. Conformation of β-aminoenones

	R	R_{gem}	R_{cis}	% *cis* (Reference)
1.	H	H	H	5 (87), 14 (84)
2.	Me	H	H	60 (87), 63 (85), 70 (84)
3.	Et	H	H	77 (84), 85 (84)
4.	n-Pr	H	H	80 (87)
5.	*i*-Pr	H	H	75 (85), 82 (84)
6.	*t*-Bu	H	H	100 (84, 85)
7.	Ph	H	H	99 (87)
8.	H	Me	H	99 (87)
9.	H	H	Me	0 (84)
10.	Me	Me	H	100 (84)
11.	Me	H	Me	0 (84)

in obtaining these results. Kozerski and Dabrowski employ aromatic solvent induced shifts to a variety of substances[84]. The same group also used low temperature to freeze out individual conformers[85,86]. Of course, the problem of identifying the separate s-*cis* and s-*trans* forms remains. These researchers used a consistent difference in the olefinic coupling (*ca* 12.5 Hz for s-*cis*, 13.6 Hz for s-*trans*) and the expected increase in s-*cis* population as R is made bulkier for this purpose[85]; carbon chemical shifts are less useful as a diagnostic tool[86]. Filleux-Blanchard and coworkers found this nucleus convenient, however, for determining populations and rotational barriers[87], but used proton NOEs for isomer identification.



(44)

The results, which are more trustworthy owing to the possibility of separating individual conformers at low temperature, agree in general with the principles enunciated for simple enones, such as the increase of the s-*cis* population as R is made larger. Very surprising, however, is the almost exclusively s-*cis* conformation of the gem-methylated aldehyde (entry 8). In addition, Kozerski and Dabrowski show that different N-alkyl groups have little effect on the conformational preference[84]. In their low-temperature study, these workers find that use of methanol as a solvent stabilizes the s-*trans* form; this may be due to the larger polarizability of the latter, and/or its increased tendency to form hydrogen bonds with the solvent. Filleux-Blanchard, Mabon and Martin report energy barriers for the rotation of the carbonyl group[87]. A typical value is 12.2 ± 0.2 kcal mol^{-1} for the methyl ketone (entry 2) at 255 K.

2. *Rotation barriers*

If the rotation around the N—C-β bond of a β-dimethylaminoenone is slow in the NMR time scale, two separated peaks will be observed for the methyl groups. Methyl exchange, which is chemically degenerate in the sense that it leads back to the same structure, is easily amenable to NMR lineshape analysis and values for $\Delta G^{\neq}$ at the coalescence temperature for several examples from the literature are reported in Table 4.

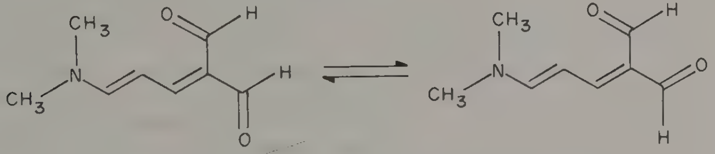
TABLE 4. =C—N Rotation barriers in β-aminoenones[a]

	Compound	$\Delta G^{\neq}$[b] (Reference)
1.	Me_2N—CHO	20.8 (88)
2.	Me_2N—CH=CH—CHO	14.6 (85), 15.6 (88)
3.	Me_2N—CH=CH—COMe	13.3 (85), 14.3 (88)
4.	Me_2N—CH=CH—CH=CH—CHO	13.0 (88)
5.	Me_2N—CH=CH—CH=CMe—CHO	12.5 (88)
6.	Me_2N—CH=C(COMe)$_2$	12.9 (89–91)
7.	Me_2N—CH=CH—CH=C(COMe)$_2$	14.5 (90, 91)

[a] The N—C=C—C=O and N—C=C—C=C—C=O systems are all-*trans*.
[b] In kcal mol^{-1}, at the coalescence temperature.

The introduction of double bonds between the carbonyl and amine function (formamide, entry 1, to entries 2 and 4) does lower the rotation barrier as expected, but the effect is far from additive; the values for the monoenone and the dienone are not that different. Methyl substitution, either to a methyl ketone or at position α (entries 3 and 5, respectively) lowers the barrier by sterically destabilizing the quasi-planar ground state. The same explanation has to apply to the surprisingly low barrier for the enedione (entry 6), which is less than that of the corresponding enone (entry 3) and dienedione (entry 7). The enedione has two bulky groups (NMe_2 and $COCH_3$) in a *cis* relationship, and the steric inhibition to resonance must be relatively severe. In polar solvents, the barriers are higher, since in the transition state the nitrogen-enone conjugation, and therefore also the charge separation, are weakened[90–92].

If the C—N bond has partial double-bond character, the olefinic bonds of enamino ketones have partial single-bond character. For the diones, rotation around the $C{=}C(COCH_3)_2$ double bond is also a chemically degenerate process, and it has been observed by NMR. For the dione (entry 6), the rate was too fast to be measured ($\Delta G^{\neq} < 10.5\ \text{kcal mol}^{-1}$)[89–91], but replacement of one of the N-methyl groups by a phenyl removes electron density from the enamino ketone system and the barrier increases to $13.9\ \text{kcal mol}^{-1}$; a *p*-nitrophenyl group has an even stronger effect ($\Delta G^{\neq} = 16.9\ \text{kcal mol}^{-1}$)[89]. For the dienone (entry 7) the corresponding value goes up to $13.0\ \text{kcal mol}^{-1}$[90,91], again showing the steric effect described above. More polar solvents lower the barriers considerably, indicating that the transition state for this process involves charge separation[90,91]. ^{13}C data for enamino diones provide information on the electron density throughout the chromophore[93].



(45a) (45b)

Recent work in these laboratories on diene dialdehyde **45** reveals that this compound gives at room temperature broad peaks in its ^1H and ^{13}C NMR spectra. At lower temperatures, the signals split into two. The species in equilibrium were proved to be **45a** and **45b**, in *ca* 3.5:1 ratio, by proton–proton coupling constants and NOEs and carbon chemical shifts. The $\Delta G^{\neq}$ for the forward process of this s-*cis*/s-*trans* rearrangement is $12.8\ \text{kcal mol}^{-1}$[94]. It is interesting to note that the more stable conformer (**45a**) is doubly s-*cis*, in contradiction to the general rule for aldehydes. Steric hindrance is probably an important factor, but electric-field effects seem to be involved as well.

V. COMPLEXED ENONES

In this section we describe systems in which a molecule of enone acts as a Lewis base and associates in solution with an electron acceptor. The latter could be a metal ion, but protonated forms of enones will also be covered.

A. Protonated Enones

Olah and coworkers looked at ^{1}H and ^{13}C NMR spectra of several α,β-unsaturated aldehydes and ketones, including some cyclic examples of the latter, in 'magic acid' solutions, at low temperature[95]. From their extensive results, they can show that, under these conditions, the organic substrates are always protonated on the carbonyl oxygen. The carbon shifts on protonation indicate that the positive charge is distributed unequally between the β carbon and the carbonyl carbon, with the former taking the largest share. No shift is seen for C-α, as might be expected from considering the possible canonic structures involved in the resonance. In the case of ketones, forms in which the added proton is *syn* or *anti* (as in oximes) can be observed in the spectrum; for aldehydes, the proton is usually exclusively *anti* to the alkyl group for steric reasons.

Similar results have been reported by Lillya and Sahatjian for $\alpha,\beta,\gamma,\delta$-unsaturated aldehydes and ketones in 'magic acid' (^{1}H NMR)[96] and by Butler for cyclohexenone in sulphuric acid[97]. Kutulya and coworkers use the chemical shift of the acidic hydrogen in trifluoroacetic acid complexes of chalcones (**8**) as a measure of the basicity of the carbonyl[98].

B. Lanthanides and Other Metals

The use of lanthanide complexes to shift NMR signals, either as a means of separating overlapping peaks in a spectrum or as an aid to assignment, is well-established. The technique applies of course also to enones, since the carbonyl oxygen is basic enough to serve as an appropriate complexing site[99–101]. As we have mentioned in the discussion of enone conformation (*vide supra*), quantitative analysis of lanthanide-induced shifts may also provide information on molecular geometry[101], but the presence of averaging conformations may make this task very difficult[102]. In any case, one is interested mainly in the through-space pseudocontact shifts. Lanthanum, which is not paramagnetic, induces only contact shifts, i.e. the changes due to the chemical effects of the complexation itself. Chadwick and coworkers show that these are relatively large for the carbonyl and the β carbon (e.g. 10.1 and 7.6 ppm, respectively, for cyclohexene), but small (usually < 1 ppm) for other carbons in the molecule[99,100,103]. The large difference between the La-induced shifts of the two olefinic carbons could in principle be employed in signal assignment.

Bose and Srinivasan show that the shifts caused by complexation with $TiCl_4$ are in the order C-$\beta >$ C$=$O $\gg$ C-α for a variety of α,β-unsaturated aldehydes and ketones[104]. They use this technique to revise the assignment of the ^{13}C shifts of α and β ionone (**34**). Lithium, sodium and magnesium ions have been shown to cause downfield shifts in the ^{13}C spectrum of mesityl oxide[105]. The shifts are largest for the carbonyl carbon, and are in the order $Mg^{++} \gg Li^+ > Na^+$.

VI. REFERENCES

1. L. H. Meyer, A. Saika and H. S. Gutowsky, *J. Am. Chem. Soc.*, **75**, 4567 (1953).
2. M. Martin and G. Martin, *Compt. Rend.*, **249**, 884 (1959).

3. A. W. Douglas and J. H. Goldstein, *J. Mol. Spectrosc.*, **16**, 1 (1965).
4. J. Kossanyi, *Bull. Soc. Chim. Fr.*, 704 (1965).
5. R. E. Klinck and J. B. Stothers, *Can. J. Chem.*, **44**, 45 (1966).
6. N. F. Chamberlain, *Anal. Chem.*, **40**, 1317 (1968).
7. J. B. Stothers and P. C. Lauterbur, *Can. J. Chem.*, **42**, 1563 (1964).
8. D. H. Marr and J. B. Stothers, *Can. J. Chem.*, **43**, 596 (1965).
9. J. B. Stothers, *Quart. Rev.*, **19**, 144 (1965).
10. R. H. Levin and L. Weingarten, *Tetrahedron Lett.*, 611 (1975).
11. M. J. Loots, L. R. Weingarten and R. H. Levin, *J. Am. Chem. Soc.*, **98**, 4571 (1976).
12. C. Delseth, T. T.-T. Nguyen and J.-P. Kintzinger, *Helv. Chim. Acta*, **63**, 498 (1980).
13. I. W. J. Still, N. Plavac, D. M. McKinnon and M. S. Chauhan, *Can. J. Chem.*, **54**, 280 (1976).
14. J. Diakur, T. T. Nakashima and J. C. Vederas, *Can. J. Chem.*, **58**, 1311 (1980).
15. O. Yamamoto, M. Watabe and O. Kikuchi, *Mol. Phys.*, **17**, 249 (1969).
16. W. Regel and W. von Philipsborn, *Helv. Chim. Acta*, **51**, 867 (1968).
17. W. Regel and W. von Philipsborn, *Helv. Chim. Acta*, **52**, 1354 (1969).
18. R. Hollenstein and W. von Philipsborn, *Helv. Chim. Acta*, **55**, 2030 (1972).
19. G. B. Savitsky, K. Namikawa and G. Zweifel, *J. Phys. Chem.*, **69**, 3105 (1965).
20. Gurudata and J. B. Stothers, *Can. J. Chem.*, **47**, 3601 (1969).
21. J. B. Stothers, J. R. Swenson and C. T. Tan, *Can. J. Chem.*, **53**, 581 (1975).
22. P. Jouve and M.-P. Simonnin, *Compt. Rend.*, **257**, 121 (1963).
23. G. A. Kalabin, A. G. Proidakov, L. D. Gavrilov and L. I. Vereshchagin, *J. Org. Chem. USSR*, **13**, 449 (1977).
24. F. Bohlmann and M. Brehm, *Org. Magn. Reson.*, **12**, 535 (1979).
25. E. Solcaniova, S. Toma and S. Gronowitz, *Org. Magn. Reson.*, **8**, 439 (1976).
26. H. E. Gottlieb, R. A. de Lima and F. delle Monache, *J. Chem. Soc., Perkin Trans. 2*, 435 (1979).
27. E. Solcaniova and S. Toma, *Org. Magn. Reson.*, **14**, 138 (1980).
28. B. Ternai and K. R. Markham, *Tetrahedron*, **32**, 565 (1976).
29. E. Wenkert and H. E. Gottlieb, *Phytochemistry*, **16**, 1811 (1977).
30. B. Unterhalt, *Arch. Pharm. (Weinheim)*, **312**, 129 (1979).
31. S. Geribaldi and M. Azzaro, *Spectrochim. Acta*, **38A**, 779 (1982).
32. D. J. Frost and J. Barzilay, *Recl. Trav. Chim. Pays-Bas*, **90**, 705 (1971).
33. N. Y. Grigor'eva, E. P. Prokof'ev and A. V. Semenovskii, *Dokl. Akad. Nauk SSR*, **245**, 366 (1979).
34. D. M. Mondeshka, *Dokl. Bolg. Akad. Nauk*, **25**, 513 (1972).
35. U. Vogeli and W. von Philipsborn, *Org. Magn. Reson.*, **7**, 617 (1975).
36. C. A. Kingsbury, D. Draney, A. Sopchik, W. Rissler and D. Durham, *J. Org. Chem.*, **41**, 3863 (1976).
37. S. Braun, *Org. Magn. Reson.*, **11**, 197 (1978).
38. B. Gregory, W. Hinz, R. A. Jones and J. S. Arques, *J. Chem. Res.*, (*S*) 311, (*M*) 2801 (1984).
39. J. Herzig, H. E. Gottlieb and A. Nudelman, *J. Chem. Res.*, (*S*), 196 (1986).
40. A. F. Kluge and C. P. Lillya, *J. Org. Chem.*, **36**, 1977 (1971).
41. R. Barlet, J. L. Pierre and P. Arnaud, *Compt. Rend.*, **262C**, 855 (1966).
42. A. Bienvenue and B. Duchatellier, *Tetrahedron*, **28**, 833 (1972).
43. I. Naito, A. Kinoshita and T. Yonemitsu, *Bull. Chem. Soc. Jpn.*, **49**, 339 (1976).
44. D. D. Faulk and A. Fry, *J. Org. Chem.*, **35**, 365 (1970).
45. M. Rouillard, S. Geribaldi and M. Azzaro, *Org. Magn. Reson.*, **16**, 94 (1981).
46. W. E. Steinmetz, J. E. Pollard, J. M. Blaney, B. K. Winker, I. K. Mun, F. J. Hickernell and S. J. Hollenberg, *J. Phys. Chem.*, **83**, 1540 (1979).
47. R. Rowan III, A. Warshel, B. D. Sykes and M. Karplus, *Biochemistry*, **13**, 970 (1974).
48. R. Rowan III and B. D. Sykes, *J. Am. Chem. Soc.*, **97**, 1023 (1975).
49. J. Ronayne and D. H. Williams, *Annu. Rev. NMR Spectrosc.*, **2**, 83 (1969).
50. C. J. Timmons, *Chem. Commun.*, 576 (1965).
51. D. H. Williams, *Tetrahedron Lett.*, 2305 (1965).
52. Y. Fujise and S. Ito, *Chem. Pharm. Bull.*, **14**, 797 (1966).
53. J. Wiemann, O. Convert, H. Danechpejouh and D. Lelandais, *Bull. Soc. Chim. Fr.*, 1760 (1966).
54. Y. Ichikawa and T. Matsuo, *Bull. Chem. Soc. Jpn.*, **40**, 2030 (1967).
55. J. Ronayne, M. V. Sargent and D. H. Williams, *J. Am. Chem. Soc.*, **88**, 5288 (1966).
56. J. D. Connolly and R. McCrindle, *J. Chem. Soc. (C)*, 1613 (1966).
57. T. M. Chau, C. Beaute, N. Thoai and J. Wiemann, *Bull. Soc. Chim. Fr.*, 4138 (1971).

58. T. M. Filippova, A. R. Bekker and B. D. Lavrukhin, *Org. Magn. Reson.*, **14**, 337 (1980).
59. G. Montaudo, V. Librando, S. Caccamese and P. Maravigna, *J. Am. Chem. Soc.*, **95**, 6353 (1973).
60. P. Finocchiaro, A. Recca, P. Maravigna and G. Montaudo, *Tetrahedron*, **30**, 4159 (1974).
61. L. I. Kruse and J. K. Cha, *Tetrahedron Lett.*, **24**, 2367 (1983).
62. F. A. L. Anet and M. Ahmad, *J. Am. Chem. Soc.*, **86**, 120 (1964).
63. T. Drakenberg, J. M. Sommer and R. Jost, *Org. Magn. Reson.*, **8**, 579 (1976).
64. P. Baas and H. Cerfontain, *Tetrahedron*, **33**, 1509 (1977).
65. H. Martens, G. Hoornaert and S. Toppet, *Tetrahedron*, **29**, 4241 (1973).
66. K. Mullen, S. Bender, E. Kotzamani, H. Schmickler, B. Frei and H. R. Wolf, *Tetrahedron Lett.*, **22**, 3513 (1981).
67. M. Sheves, A. Albeck and H. E. Gottlieb, submitted for publication.
68. A. I. Kol'tsov and G. M. Kheifets, *Russ. Chem. Rev.*, **40**, 773 (1971).
69. J. Emsley, *Struct. Bonding* (*Berlin*), **57**, 147 (1984).
70. J. Dabrowski, A. Skup and M. Sonelski, *Org. Magn. Reson.*, **1**, 341 (1969).
71. M. Azzaro, S. Geribaldi, B. Videau and M. Chastrette, *Org. Magn. Reson.*, **22**, 11 (1984).
72. A. Y. Aizikovich, K. I. Paskevich, V. V. Gorshkov, M. N. Rudaya and I. Y. Postovskii, *J. Gen. Chem. USSR*, **50**, 1523 (1980).
73. G. O. Dudek, *J. Am. Chem. Soc.*, **85**, 694 (1963).
74. G. O. Dudek and R. H. Holm, *J. Am. Chem. Soc.*, **83**, 2099 (1961).
75. G. O. Dudek and G. P. Volpp, *J. Org. Chem.*, **30**, 50 (1965).
76. G. O. Dudek, *J. Org. Chem.*, **30**, 549 (1965).
77. G. O. Dudek and E. P. Dudek, *J. Am. Chem. Soc.*, **86**, 4283 (1964).
78. G. O. Dudek and E. P. Dudek, *Tetrahedron*, **23**, 3245 (1967).
79. M. L. Filleux-Blanchard, H. Durand, M. T. Bergeon, F. Clesse, H. Quinion and G. J. Martin, *J. Mol. Struct.*, **3**, 351 (1969).
80. G. O. Dudek and G. P. Volpp, *J. Am. Chem. Soc.*, **85**, 2697 (1963).
81. C. Kashima, H. Aoyama, Y. Yamamoto, T. Nishio and K. Yamada, *J. Chem. Soc., Perkin Trans. 2*, 665 (1975).
82. L. Kozerski and J. Dabrowski, *Org. Magn. Reson.*, **5**, 459 (1973).
83. L. Kozerski, K. Kamienska-Trela and L. Kania, *Org. Magn. Reson.*, **12**, 365 (1979).
84. L. Kozerski and J. Dabrowski, *Org. Magn. Reson.*, **4**, 253 (1972).
85. J. Dabrowski and L. J. Kozerski, *Org. Magn. Reson.*, **4**, 137 (1972).
86. J. Dabrowski, K. Kamienska-Trela and L. Kozerski, *Org. Magn. Reson.*, **6**, 499 (1974).
87. M. L. Filleux-Blanchard, F. Mabon and G. J. Martin, *Tetrahedron Lett.*, 3907 (1974).
88. M. L. Blanchard, A. Chevallier and G. J. Martin, *Tetrahedron Lett.*, 5057 (1967).
89. Y. Shvo, E. C. Taylor and J. Bartulin, *Tetrahedron Lett.*, 3259 (1967).
90. E. P. Prokof'ev, Zh. A. Krasnaya and V. F. Kucherov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, **22**, 1963 (1973).
91. E. P. Prokof'ev, Zh. A. Krasnaya and V. F. Kucherov, *Org. Magn. Reson.*, **6**, 240 (1974).
92. M. L. Filleux-Blanchard, F. Clesse, J. Bignebat and G. J. Martin, *Tetrahedron Lett.*, 981 (1969).
93. E. P. Prokof'ev and Zh. A. Krasnaya, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, **27**, 1963 (1978).
94. H. E. Gottlieb, S. Braverman and S. Levinger, submitted for publication.
95. G. A. Olah, Y. Halpern, Y. K. Mo and G. Liang, *J. Am. Chem. Soc.*, **94**, 3554 (1972).
96. C. P. Lillya and R. A. Sahatjian, *J. Organomet. Chem.*, **32**, 371 (1971).
97. A. R. Butler, *J. Chem. Soc., Perkin Trans. 2*, 959 (1976).
98. L. A. Kutulya, Y. N. Durov, N. S. Pivnenko, S. V. Tsukerman and V. F. Lavrushin, *J. Gen. Chem. USSR*, **41**, 903 (1971).
99. D. J. Chadwick and D. H. Williams, *Chem. Commun.*, 128 (1974).
100. D. J. Chadwick and D. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1202 (1974).
101. Z. W. Wolkowski, *Tetrahedron Lett.*, 821 (1971).
102. G. Montaudo, S. Caccamese, V. Librando and P. Maravigna, *Gazz. Chim. Ital.*, **105**, 85 (1975).
103. R. J. Abraham, H. A. Bergen, D. J. Chadwick and F. Sancassan, *Chem. Commun.*, 998 (1982).
104. A. K. Bose and P. R. Srinivasan, *Tetrahedron Lett.*, 1571 (1975).
105. A. S. N. Murthy and A. P. Bhardwaj, *J. Chem. Soc., Perkin Trans. 2*, 727 (1984).

The Chemistry of Enones
Edited by S. Patai and Z. Rappoport

CHAPTER 6

The chemistry of ionized enones in the gas phase

FRANTIŠEK TUREČEK[†]
The J. Heyrovský Institute of Physical Chemistry and Electrochemistry, Czechoslovak Academy of Sciences, Praha, Czechoslovakia

I. INTRODUCTION

The enone group occurs frequently in organic compounds of synthetic, biological or environmental importance. In order to locate the enone group in a complex molecule by mass spectrometry it is necessary to understand the processes that lead to rupture of the carbon–carbon and carbon–hydrogen bonds pertinent to the enone functionality. The chemistry of ionized enones depends very much on the type of ions in question, that is, different decompositions are encountered with radical cations created by electron-impact (EI) ionization, with closed-shell cations produced by chemical ionization (CI), or with radical anions formed by electron attachment. The basic principles of the chemistry of

---

[†] *Present address*: Baker Laboratory, Department of Chemistry, Cornell University, Ithaca, NY 14853, USA.

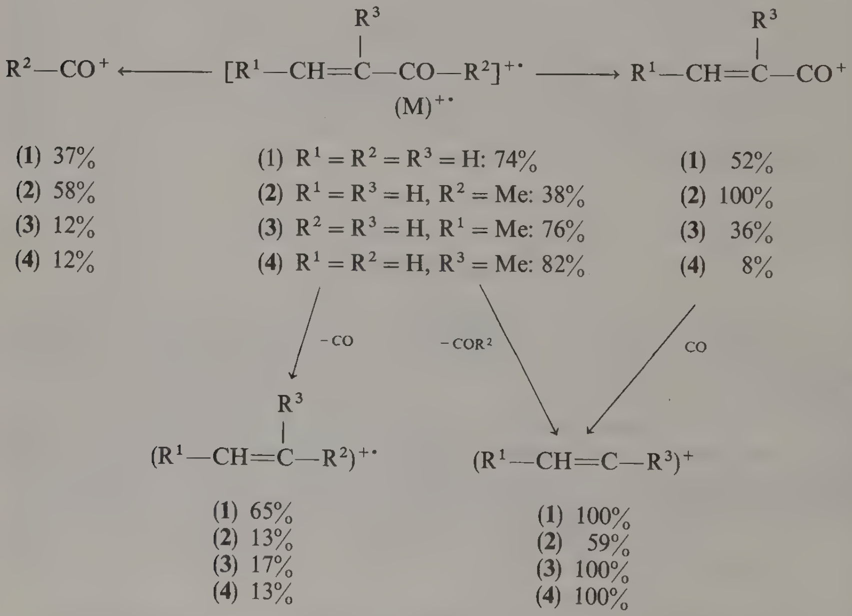
radical cations derived from unsaturated ketones have been summarized in an early paper[1]. Since then a wealth of information has been accumulated which shed more light on some of the more intricate features of enone ion chemistry in the gas phase. The EI-induced decompositions of simple aliphatic enones are now well understood owing to the efforts spent on studying ion thermochemistry and dynamics. Higher enones, both aliphatic and aromatic, undergo intricate fragmentations resulting from interactions of the enone moiety with the rest of the ion. Ion–molecule reactions of enones, namely proton transfer, have been studied and yielded fundamental thermochemical data such as gas-phase basicities and proton affinities, as well as structural information on protonated enones. Last but not least, valuable structural and energy data have been obtained from theoretical calculations of improving quality.

II. THE CHEMISTRY OF ENONE RADICAL CATIONS

A. Simple Aliphatic Enones

The EI-induced fragmentations of simple enones, e.g. propenal (**1**), 1-buten-3-one (**2**), 2-butenal (**3**) and 2-methylpropenal (**4**), provide good examples of bond-cleavage processes inherent to the ionized enone moiety (Scheme 1)[2]. The simple enones **1**–**4** afford relatively abundant molecular ions even at 70 eV (Scheme 1)[2]. The energy-rich molecular ions decompose primarily by cleavage of the CO—R^2 and $R^1CH{=}C(R^3)$—CO bonds. The facile dissociation of the carbon–carbon bonds adjacent to the carbonyl group can be accounted for by the available thermochemical data[3–15] which allow one to estimate the corresponding bond dissociation energies (BDE) in the radical cations $[\mathbf{1}]^{+\bullet}$, $[\mathbf{2}]^{+\bullet}$ and $[\mathbf{3}]^{+\bullet}$ (Table 1).

The fission of the CO—R^2 bond is evidently the lowest-energy simple cleavage



SCHEME 1

TABLE 1. Thermochemical data for $[\mathbf{1}]^{+\cdot}$, $[\mathbf{2}]^{+\cdot}$, $[\mathbf{3}]^{+\cdot}$ and their decomposition products

Precursor	ΔH_f° (kJ mol^{-1})	Products	ΔH_f°(kJ mol^{-1})	BDE (kJ mol^{-1})
$[\mathbf{1}]^{+\cdot}$	903[3,4]	$CH_2{=}CH{-}CO^+ + H^\cdot$	967[3,6]	64
		$CH_2{=}CH^+ + CHO^\cdot$	1142[6,7]	239
		$CH_2{=}CH^\cdot + CHO^+$	$\geqslant$ 1109[7–9]	$\geqslant$ 206
		$C_2H_4^{+\cdot} + CO$	955[6,10]	(52)
$[\mathbf{2}]^{+\cdot}$	818[10]	$CH_2{=}CH{-}CO^+ + CH_3^\cdot$	892[3,7]	74
		$CH_3CO^+ + CH_2{=}CH^\cdot$	$\geqslant$ 938[6,7]	$\geqslant$ 120
		$CH_2{=}CH^+ + CH_3CO^\cdot$	1090[6,7]	272
		$CH_3CH{=}CH_2^{+\cdot} + CO$	849[6,10]	(31)
$[\mathbf{3}]^{+\cdot}$	837[11,12]	$CH_3CH{=}CHCO^+ + H^\cdot$	909[6,14]	72
		$CH_3CH{=}CH_2^{+\cdot} + CO$	849[6,10]	(12)
		$CH_3CH{=}CH^+ + HCO^\cdot$	1074[7,15]	237[a]

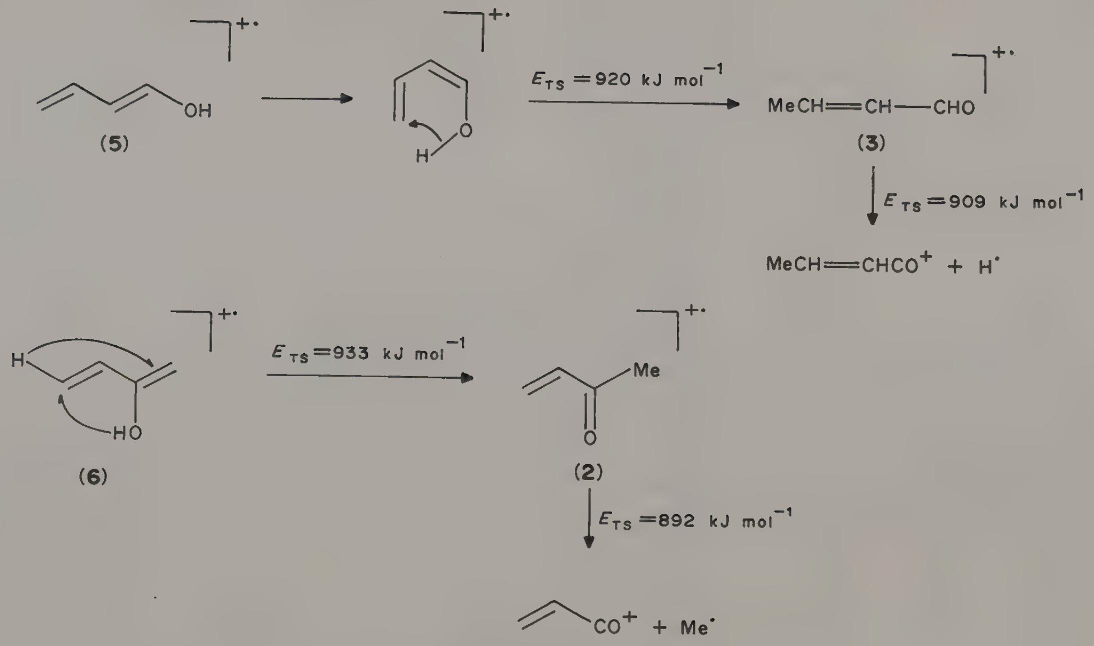
[a] The $CH_3CH{=}CH^+$ ion is calculated to be thermodynamically unstable[15].

decomposition of $[\mathbf{1}]^{+\cdot}$, $[\mathbf{2}]^{+\cdot}$ and $[\mathbf{3}]^{+\cdot}$. The acryloyl ($CH_2{=}CH{-}CO^+$) and crotonyl ($CH_3{-}CH{=}CH{-}CO^+$) ions are thermodynamically stable species[3,14], each representing the most stable structure among the corresponding isomeric ions[3,14]. The further decomposition of $CH_2{=}CH{-}CO^+$ to the vinyl cation and carbon monoxide requires an additional 250 kJ mol^{-1}[6] to proceed and is therefore energetically more demanding than the direct formation of $CH_2{=}CH^+$ from both $[\mathbf{1}]^{+\cdot}$ and $[\mathbf{2}]^{+\cdot}$ (Table 1). Nevertheless, the loss of carbon monoxide from $CH_2{=}CH{-}CO^+$ does occur[2,3] and contributes significantly to the overall abundance of the vinylic species[2].

The dissociations of the $CO{-}CH_3$ and $CO{-}H$ bonds in $[\mathbf{2}]^{+\cdot}$ and $[\mathbf{3}]^{+\cdot}$, respectively, are typical simple-cleavage processes, as confirmed by metastable ion studies[3,14]. In these experiments, the parent ions are first selected by mass in a tandem mass spectrometer[16] and delayed decompositions of metastable ions occurring some 10–20 μs after ion formation are then monitored[17]. The amounts of kinetic energy released in the fragmentations of metastable $[\mathbf{2}]^{+\cdot} \rightarrow CH_2{=}CH{-}CO^+ + CH_3^\cdot$ and $[\mathbf{3}]^{+\cdot} \rightarrow CH_3{-}CH{=}CH{-}CO^+ + H^\cdot$ are small (1.9 and 2.8 kJ mol^{-1}, respectively)[3,14], which shows that the corresponding transition states involve little excess energy above the thermochemical thresholds. The transition states are located on the product sides of the reactions, a typical feature of simple cleavage decompositions[3].

The thermochemical data further reveal (Table 1) that the simple cleavage reactions, although predominating in the fast decompositions observed in the conventional mass spectra of **1**–**3**, are not the energetically most favourable processes. In each case the lowest energy of the threshold belongs to expulsion of carbon monoxide from the molecular ion. The latter decomposition necessitates a more extensive bond reorganization in the transition state than does the simple cleavage reaction. Therefore, the loss of carbon monoxide is more pronounced in slowly decomposing metastable $[\mathbf{2}]^{+\cdot}$ and $[\mathbf{3}]^{+\cdot}$ in whose spectra the $[M - CO]^+$ ions represent the most abundant products[3,14].

The enone ions $[\mathbf{2}]^{+\cdot}$ and $[\mathbf{3}]^{+\cdot}$ appear to be important intermediates in the decompositions of the more stable dienol ions $[\mathbf{6}]^{+\cdot}$ and $[\mathbf{5}]^{+\cdot}$, respectively (Scheme 2)[18,19]. For both $[\mathbf{2}]^{+\cdot}$ and $[\mathbf{3}]^{+\cdot}$, the energy barriers to isomerization to the corresponding dienol ions, $[\mathbf{3}]^{+\cdot} \rightarrow [\mathbf{5}]^{+\cdot}$ and $[\mathbf{2}]^{+\cdot} \rightarrow [\mathbf{6}]^{+\cdot}$, are higher than the critical energies[20] for decompositions to the acylium ions. This explains why $[\mathbf{2}]^{+\cdot}$ and $[\mathbf{3}]^{+\cdot}$


(5)
$E_{TS}=920$ kJ mol^{-1}
MeCH=CH—CHO
(3)
$E_{TS}=909$ kJ mol^{-1}
MeCH=CHCO$^+$ + H$^\cdot$
(6)
$E_{TS}=933$ kJ mol^{-1}
Me
(2)
$E_{TS}=892$ kJ mol^{-1}
CO$^+$ + Me$^\cdot$

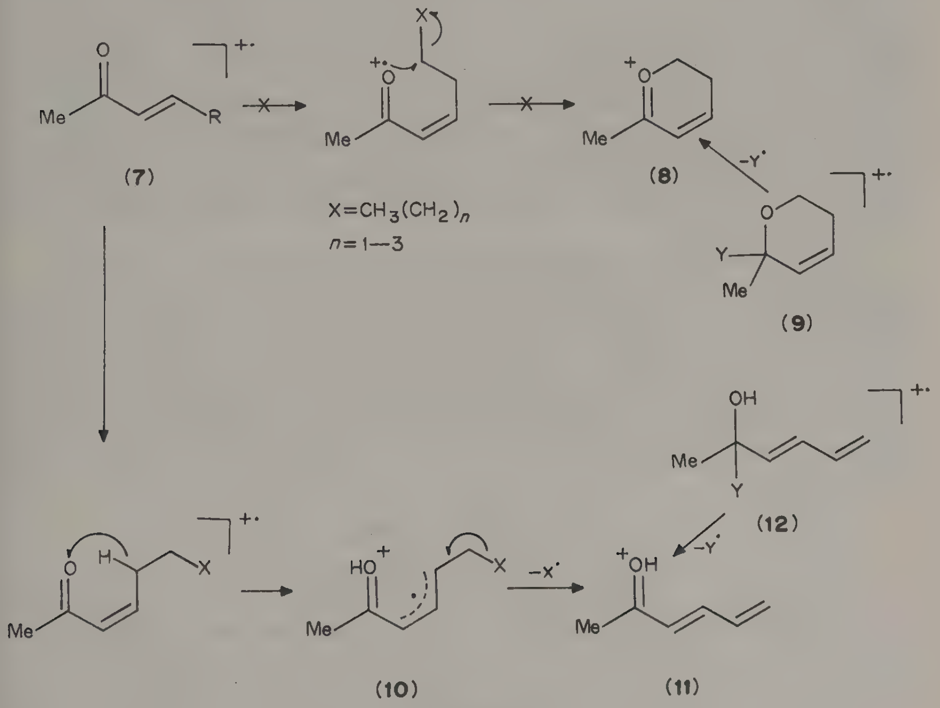
SCHEME 2

preserve their structural identity and display different fragmentation patterns than do the more stable [**5**]$^{+\cdot}$ and [**6**]$^{+\cdot}$[18,19].

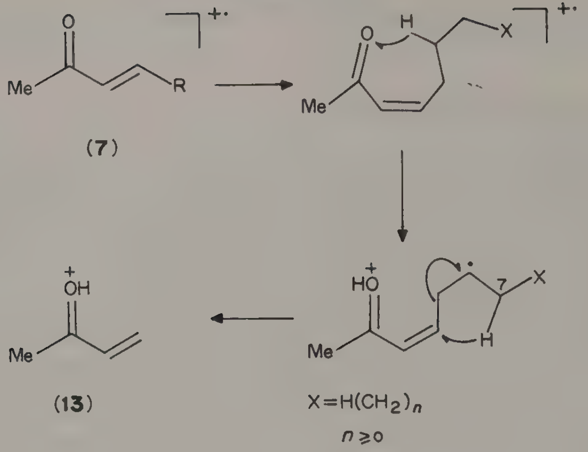
B. Rearrangements in Higher Enones

The fairly simple fragmentation patterns of the radical cations derived from the lowest enones become more complicated with higher linear and branched enones. It should be noted that the simple cleavage reactions, as outlined above, still represent the major, and diagnostically most valuable, decomposition pathways. However, when lengthening the aliphatic chain in enone ions, other fragmentations appear owing to intra-ionic, bond-making interactions of the enone part with the side-chains[1].

A typical feature of the EI mass spectra of enones of the $CH_3—CO—CH=CH—R$ type (**7**, R = n-C_4H_9, n-C_5H_{11} and n-C_6H_{13}, Scheme 3) is the presence of a $C_6H_9O^+$ ion at m/z 97. The $C_6H_9O^+$ ion was originally formulated[1] as having the cyclic structure **8**, formed by a radical S_Ni mechanism[21]. However, structure **8** was later disproved in a study[22] that made use of the collisionally activated decomposition (CAD)[23] spectra to identify isomeric $C_6H_9O^+$ ions. Ions **8** and **11** were generated by unambiguous fragmentations of the corresponding precursors **9** and **12**, respectively, and shown to afford distinct CAD spectra. Based on its CAD spectrum, the $C_6H_9O^+$ ion from **7** was identified to have the linear structure **11**[22]. The mechanistic explanation[22] for the formation of **11** from **7** invoked a hidden transfer[24] of the activated allylic hydrogen atom from C-5 onto the carbonyl oxygen (intermediate **10**, Scheme 3), followed by cleavage of the weak allylic C-6—C-7 bond.



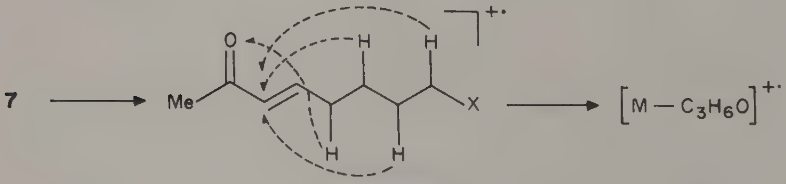
SCHEME 3



SCHEME 4

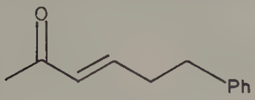
Hydrogen migrations, both hidden and directly observable, play an important role in the decompositions of ionized enones of type 7. For instance, double hydrogen migration accounts for the formation of $C_4H_7O^+$ ions (13) from enones 7 having R larger than n-C_3H_7 (Scheme 4)[1]. As established by deuterium labelling, the migration of hydrogen atoms from C-6 and C-7 is not totally regiospecific (Scheme 4), since positions more remote from the enone group are also involved to a significant extent[1]. By contrast, the allylic hydrogen atoms from C-5 do not appear in ions **13** which shows that the decompositions leading to **11** (Scheme 3) and **13** (Scheme 4) are competitive processes that do not share common intermediates. Another interesting rearrangement in ionized **7** involves non-specific migration of hydrogen atoms from C-5, C-6, C-7 and even more remote positions onto the enone group, eventually resulting in the elimination of a C_3H_6O molecule. As shown in Scheme 5, the final carbon–carbon bond cleavage dissects the original double bond in 7[1].

Enones 7 that contain a terminal phenyl group, e.g. 6-phenylhex-3-en-2-one (**7a**), 7-phenylhept-3-en-2-one (**7b**) and 8-phenyloct-3-en-2-one (**7c**), show some specific features depending on the length of the chain separating the aromatic ring from the enone moiety[25]. The $[M-C_3H_6O]^{+\cdot}$ ions dominate the 12 eV mass spectra of **7a**–**7c**. Metastable ion studies revealed that these $[M-C_3H_6O]^{+\cdot}$ ions are formed by two processes, i.e. by direct elimination of the C_3H_6O neutral from the molecular ion and by loss of a methyl from $[M-CH_3CO]^+$ fragments[25]. Both these reactions involve extensive hydrogen migrations whose specificity depends on the position of the phenyl group. In **7a**

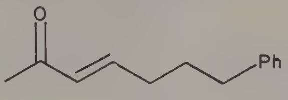


SCHEME 5

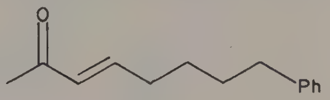
the two hydrogen atoms being transferred onto the enone group originate specifically from the benzylic (C-6) and vinylic (C-4) positions, respectively. In **7b** the benzylic methylene group (C-7) remains the major source for one hydrogen atom to be transferred, while the other comes largely from the phenyl group[25].



(7a)



(7b)

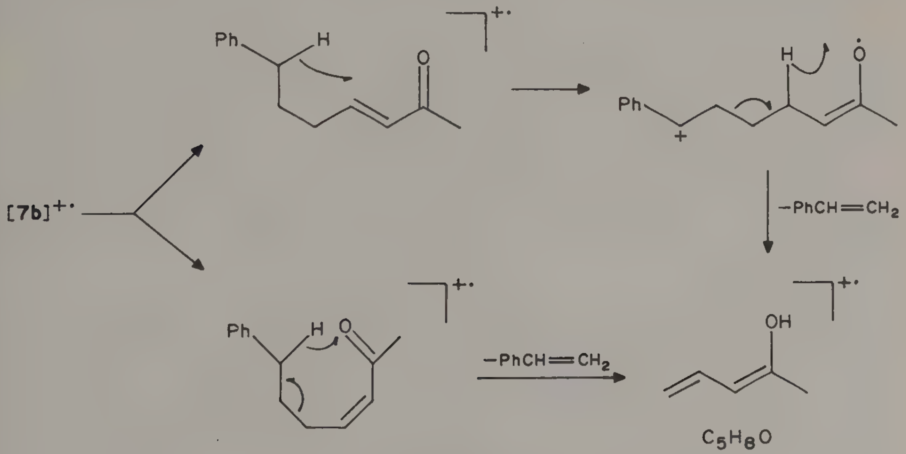


(7c)

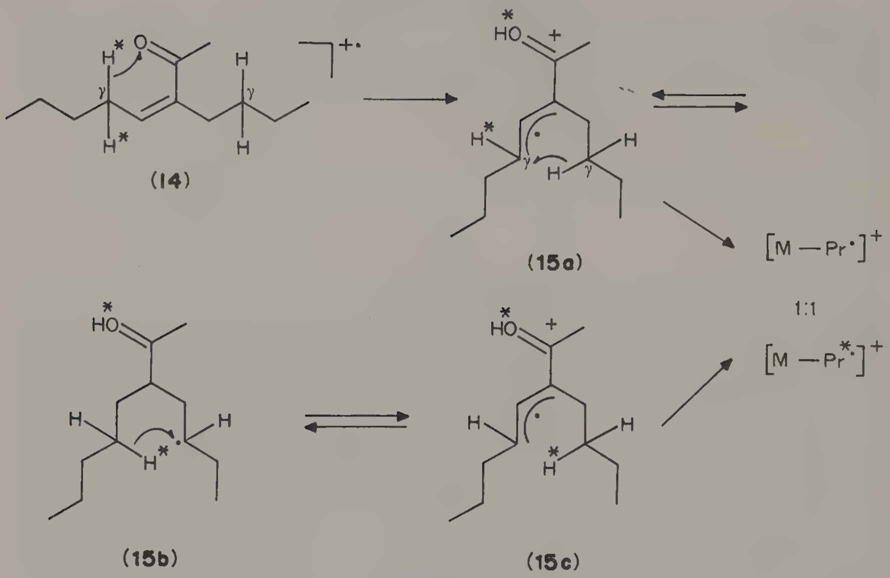
The molecular ion of **7b** undergoes yet another fragmentation which leads to complementary (by both labelling and elemental composition) $[C_5H_8O]^{+\cdot}$ and $[C_8H_8]^{+\cdot}$ ions. The possible mechanistic paths leading to the former ion are shown in Scheme 6. Deuterium labelling in **7b** revealed that the formation of both ions involved clean transfer of one benzylic hydrogen atom onto the oxygen-containing fragment[25]. The $[C_5H_8O]^{+\cdot}$ ion probably has the dienol structure shown in Scheme 6 (for detailed discussion see Reference 25). The hydrogen atom being transferred may either jump directly to the oxygen atom via an eight-membered transition state[25], or the reaction may proceed via two consecutive 1,4-hydrogen transfers, first from C-7 to C-4 and then from the latter position to the oxygen atom (Scheme 6).

Fragmentations by alkyl loss of branched-chain enones (e.g. **14**, Scheme 7) mostly include hidden or directly observable hydrogen migrations[1]. As determined by specific deuterium labelling[1], in *ca* 80% of ionized **14** the γ-hydrogen atoms in both hydrocarbon chains are interchanged prior to the loss of a propyl radical, which eventually takes place from the saturated chain. The hydrogen migration may be mediated by the carbonyl oxygen atom as suggested originally, or one can envisage a direct interchange of the γ-hydrogen atoms proceeding between the hydrocarbon chains in the intermediates **15** (Scheme 7). Mass spectra of other branched enones have recently been reported[26].

In the absence of saturated hydrocarbon chains, ionized enones undergo different isomerizations in which new carbon–carbon or carbon–oxygen bonds are formed before decomposition. Enone **16** (Scheme 8) loses mainly (67%) the remote methyl group (C-6)



SCHEME 6

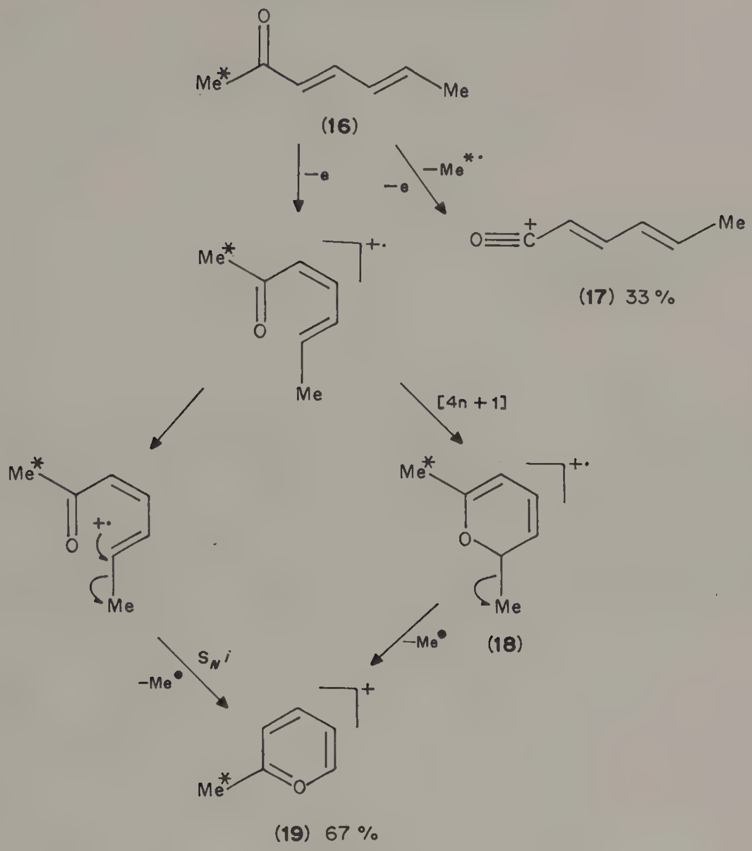


SCHEME 7

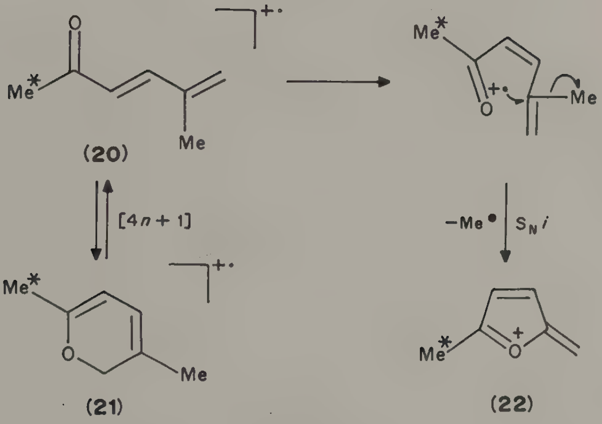
despite a stable acylium ion (**17**) being accessible directly by conventional loss of the C-1 methyl[27]. The unusual reactivity of **16** was explained by assuming two competing mechanisms for the methyl loss. Following a *trans*-to-*cis* isomerization in ionized **16**, the molecular ion can undergo electrocyclic ring closure to give the pyran **18** in which the C-5—C-6 bond becomes weak and splits rapidly. Alternatively, the reaction may be viewed as an S_Ni substitution[21] of the C-6 methyl with the carbonyl oxygen atom in a 6-endo-Trig ring-forming process[28], affording the stable pyrylium ion **19** (Scheme 8). The loss of the C-6-terminal methyl is even more preferred at lower electron energies and, especially, in unimolecular decompositions of metastable $[\mathbf{16}]^{+\cdot}$. The S_Ni mechanism gains support from the finding that a loss of the vinylic methyl from **20** is observed, too (Scheme 9). In this case the electrocyclic ring closure $\mathbf{20} \rightarrow \mathbf{21}$ does not result in activation of the CH_3—C bond which remains vinylic in the cyclic intermediate **21**. By contrast, the S_Ni substitution by the carbonyl oxygen at C-5 can proceed as a favoured 5-exo-Trig ring-forming process to give **22** or an isomeric ion formed by a subsequent rearrangement[27].

Competing ring closures can take place in ionized trienal **23**, in which both the carbonyl and the α,β-enone double bond can enter the electrocyclic reaction (Scheme 10). The bonds to the allylic substituents in the heterocyclic (**24**) or carbocyclic (**25**) rings are weak, and their dissociation gives rise to stable pyrylium ions (**26**) or protonated aromatic ions **27** and **28** respectively[27].

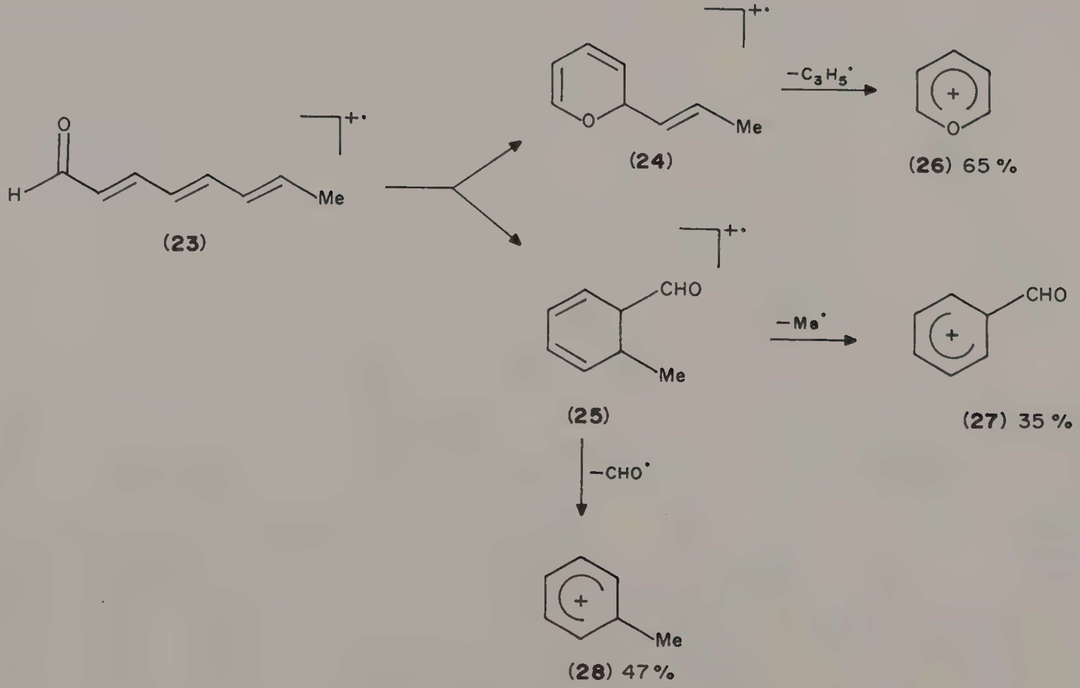
Skeletal rearrangements and hydrogen migrations evidently play a role in the as yet unexplained, complex loss of a methyl from ionized 5-hexen-2-one (**29**, Scheme 11)[29]. While the molecular ion of **29** decomposing in the ion source eliminates cleanly the original methyl group, metastable ions $[\mathbf{29}]^{+\cdot}$ lose methyls incorporating carbon and hydrogen atoms from various parts of the parent ion. Two, as yet unspecified reaction paths for the loss of methyl from metastable $[\mathbf{29}]^{+\cdot}$ have been distinguished by metastable peak shape analysis, after having partially disentangled the spectra by means of deuterium and ^{13}C labelling (Scheme 11)[29].



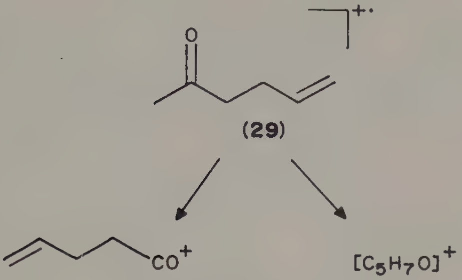
SCHEME 8



SCHEME 9



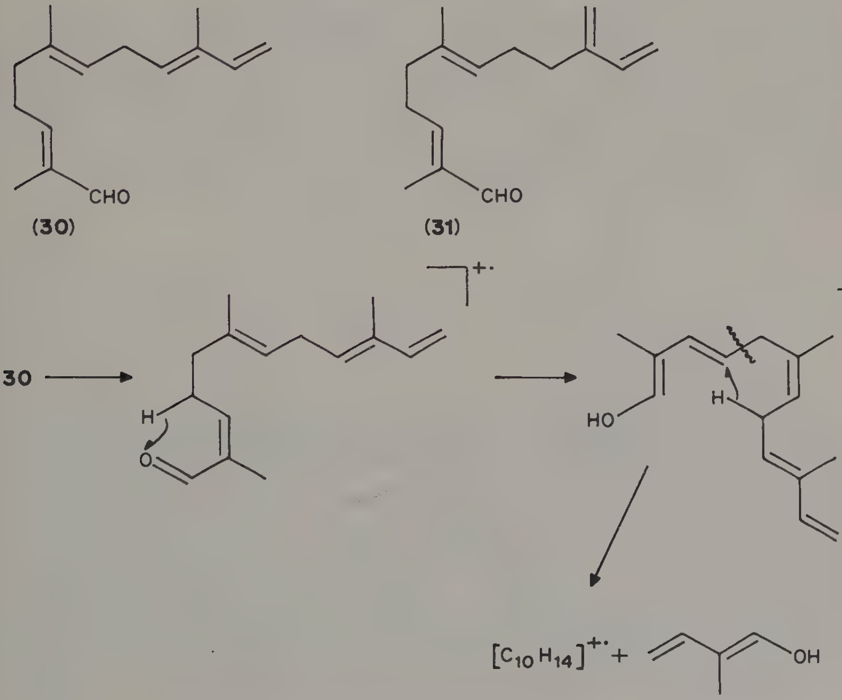
SCHEME 10



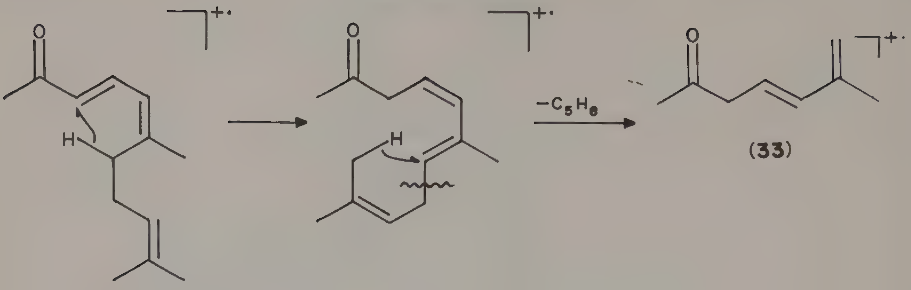
SCHEME 11

Other non-conjugated unsaturated ketones with longer chains and terminal or remote double bonds have been scrutinized in some detail[30].

The complex chemistry of ionized enones may further be documented by rearrangements in the EI mass spectra of naturally occurring enals and enones, e.g. α- and β-sinensal (**30**, **31**, Scheme 12) and pseudoionone (**32**, Scheme 13)[31]. The 70 eV mass spectra of **30** and **31** differ strikingly in the relative abundances of $[M - C_5H_8O]^{+\cdot}$ ions and other second-generation fragments derived therefrom. The differences in the spectra of **30** and **31** are remarkable indeed for isomeric olefins, and they point to some specific mechanism by which the C_5H_8O molecule is eliminated from **30**, but almost not from **31**. The mechanism



SCHEME 12



(32)

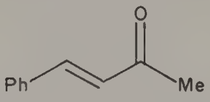
(33)

SCHEME 13

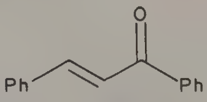
suggested in the original work[31] invoked the familiar γ-hydrogen rearrangement in the first step (Scheme 12), followed by transfer of a second hydrogen atom and terminated by elimination of neutral 2-methyl-1,3-butadien-1-ol. A similar rationalization was put forward to account for the elimination of C_5H_8 from the molecular ion of pseudoionone (**32**, Scheme 13). Although the structure of **33** remained tentative, the elimination of the terminal C_5H_8 moiety was unambiguously established by deuterium labelling[31].

C. Cyclizations, *ortho*-Effects and Related Phenomena

Valence-bond rearrangements[32] preceding simple-cleavage decompositions are important processes in the mass spectra of aromatic enones. The 70 eV EI mass spectra of benzalacetone (**34**) and chalcone (**35**) display abundant $[M-H]^+$ ions which constitute the base peak of the spectrum of the latter enone[33]. The loss of the hydrogen atom from ionized **34** and **35** is by no means trivial, since strong carbon–hydrogen bonds should have been broken were the decompositions to proceed from the intact enone structures. By comparison, saturated analogues, e.g. 4-phenylbutan-2-one[34] and 1,3-diphenylpropan-1-one[35], show very weak $[M-H]^+$ ions in their mass spectra.



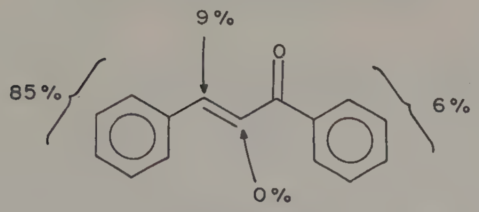
(34)



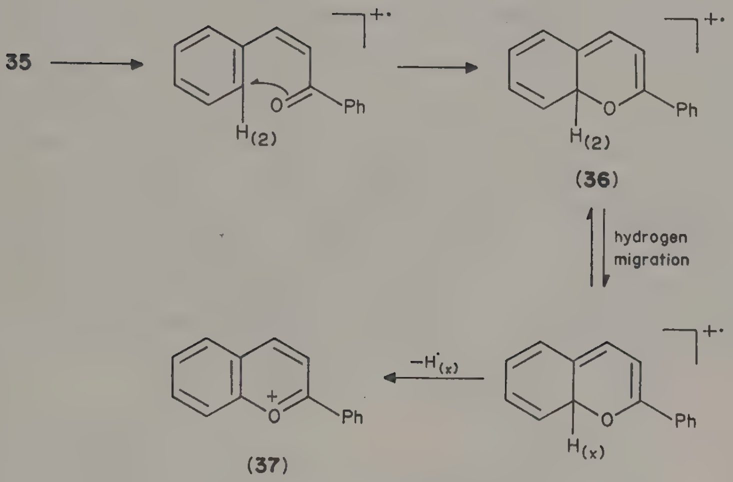
(35)

The mechanism leading to the loss of the hydrogen atom from **34** and **35** was elucidated in the classical study of Williams and coworkers[33]. Extensive deuterium labelling in **35** allowed the authors to identify the hydrogen atoms having been eliminated from the molecular ion (Scheme 14). The styryl ring accounts for most of the hydrogen atoms eliminated. Regiospecific labelling within the styryl ring revealed further that the five aromatic hydrogen atoms were lost in a statistical manner. This and the facile loss of hydrogen were rationalized by assuming a cyclization in the *cis* isomer of **35** to yield the intermediate **36** (Scheme 15). Before losing the angular hydrogen atom ($H_{(2)}$ in **36**), the intermediate undergoes several hydrogen migrations that effectively randomize the ring hydrogens. The eventual loss of $H_{(x)}$ from the bridgehead position creates the stable benzopyrylium ion **37**[33].

The loss of various groups from substituted benzalacetones **38** (R = 2-, 3- and 4-CH_3,

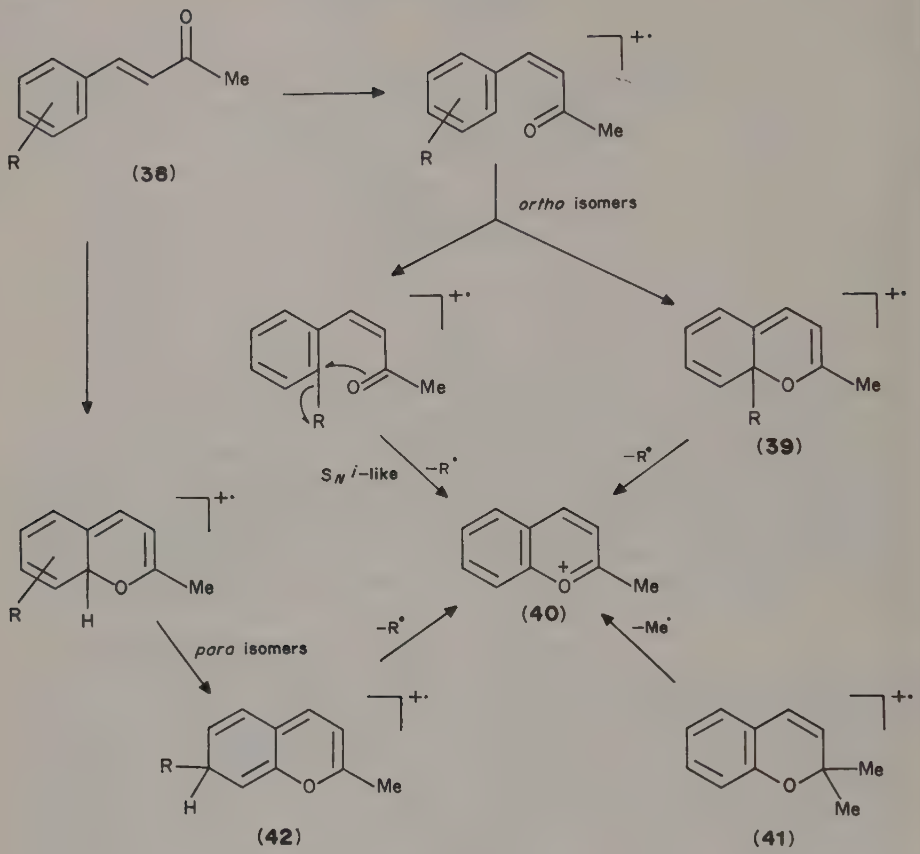


SCHEME 14



SCHEME 15

OCH_3, F, Cl, Br, I, NO_2, CF_3) has been investigated in detail[36–38]. The fragmentation exerts several interesting features. First, the loss of $R^{\bullet}$ occurs from all positional isomers with similar critical energies (50–80 kJ mol^{-1}), while the relative abundances of the $[M-R]^+$ ions $[C_{10}H_9O]^+$ show a decreasing trend in the series *ortho* > *meta* > *para*. Second, the dissociations of the C—R bonds are made substantially easier by assistance of the enone group, regardless of the position of R in the ring. Third, the resulting $C_{10}H_9O^+$ ion has been identified as having the benzopyrylium structure **40**, by comparing its mass-analyzed kinetic energy (MIKE) spectrum and kinetic energy release values with those of a standard generated from the straightforward precursor **41** (Scheme 16)[37]. This rendered strong support to the suggested benzopyran intermediate **39**. Moreover, thorough analysis of the critical energies and kinetic energy release data for the loss of $R^{\bullet}$ from **38** provided detailed information on the probable locations of the transition states, which were found to depend on the nature of the leaving group $R^{\bullet}$. For all the groups R the transition state energies have been assessed to lie above the corresponding thermochemical thresholds, defined by $\Delta H_f[C_{10}H_9O^+] + \Delta H_f(R^{\bullet})$. The enthalpy changes in these reactions ranged from slight endoergicity ($\Delta H_r = 50$ kJ mol^{-1} for R = 2-F) up to substantial exoergicity ($\Delta H_r = -180$ kJ mol^{-1} for R = 2-NO_2)[38]. The cyclization **38** → **39** has been assumed to have the highest transition-state energy in each case. However, for



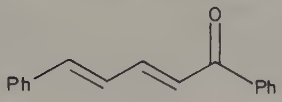
SCHEME 16

weakly bound substituents, e.g. Br, I and NO$_2$, the intermediates **39** may be unstable, such that the overall reaction resembles a S$_N$i substitution rather than a two-step process (Scheme 16)[36]. The loss of R$^\cdot$ from positions other than *ortho* has been rationalized by isomerization via hydrogen jumps to create the isomeric intermediates **42** (Scheme 16).

An important point to be noted in these fundamental studies is their analytical utility, for the loss of R$^\cdot$ is diagnostically valuable in distinguishing the position of the substituent in the ring[36].

A large number of related chalcones, both aromatic and heterocyclic which showed analogous losses of substituents from the styryl or heterostyryl rings, have been investigated[35,39].

Compared with chalcone **35**, the loss of hydrogen is much less abundant in the mass spectrum of the vinylogous 1,5-diphenylpenta-2,4-dien-1-one (**43**)[40]. The fraction for the loss of deuterium from [4-^{2}H]-**43** (24% of the [M − (H,D)] total) was attributed to complete scrambling of the vinylic hydrogen atoms in the diene chain[40].

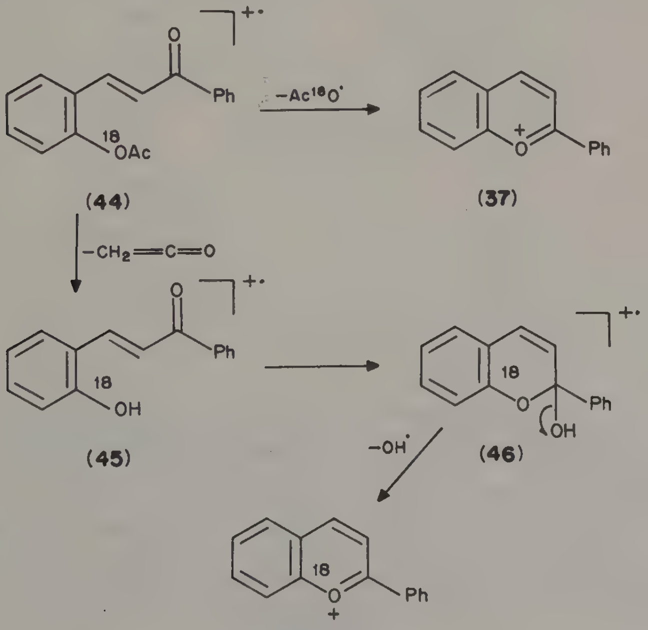


(43)

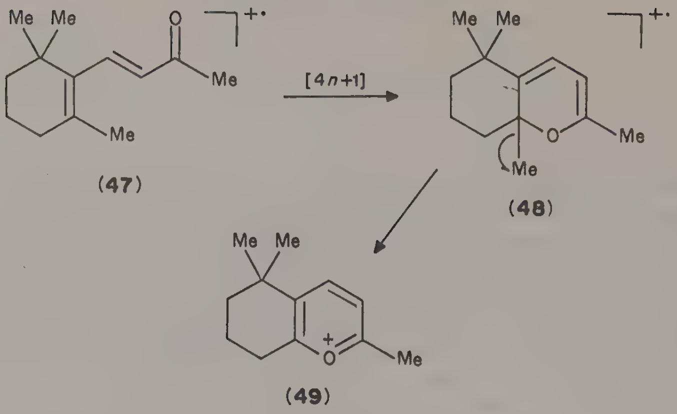
In an interesting ^{18}O-labelling study[41], different mechanisms were distinguished for the loss of the acetoxy and hydroxy group from substituted chalcones **44** and **45**, respectively (Scheme 17). The ^{18}O-labelled acetate **44** cleanly eliminates the acetoxy group to give ion **37** (Scheme 17). In contrast, the labelled ion **45**, generated by EI-induced elimination of ketene from **44**, decomposes via a different route consisting of intra-ionic acetalization to **46** followed by loss of the newly formed, unlabelled hydroxy group (Scheme 17). The loss of acetoxyl has been found to be a common decomposition pathway of 2-acetylchalcones of various complexity and it has been helpful in structure elucidation of the red cell wall pigments of some peat mosses[41].

Cyclizations preceding the loss of ring substituents are not restricted to occur in aromatic enones only. An unusual loss of a ring methyl group takes place in the molecular ion of β-ionone (**47**) whose EI mass spectrum is dominated by the $[M-CH_3]^+$ fragment[31]. Careful labelling of the acetyl and the geminal methyl groups in **47** disproved the earlier intuitive claim that one of the latter methyls is lost[42]. Instead, the labelling data were consistent with a mechanism in which the molecular ion first isomerized via a $(4n+1)$ cyclization to intermediate **48** (Scheme 18) in which the original vinylic methyl group became activated and was lost in the elimination[31].

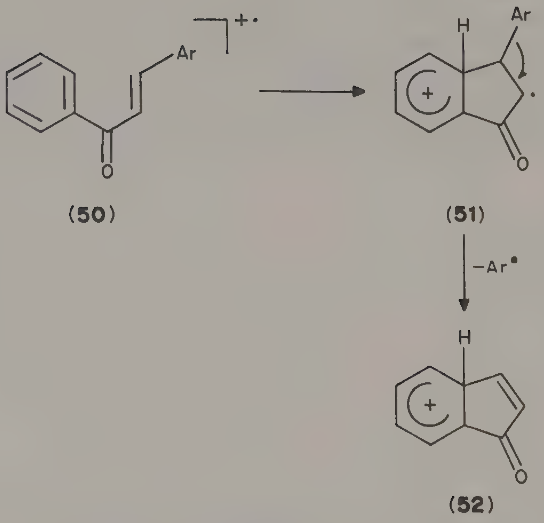
Ionized chalcones undergo another rearrangement which resembles the Nazarov cyclization known from solution chemistry[43,44], and leads to loss of the styryl aromatic



SCHEME 17



SCHEME 18



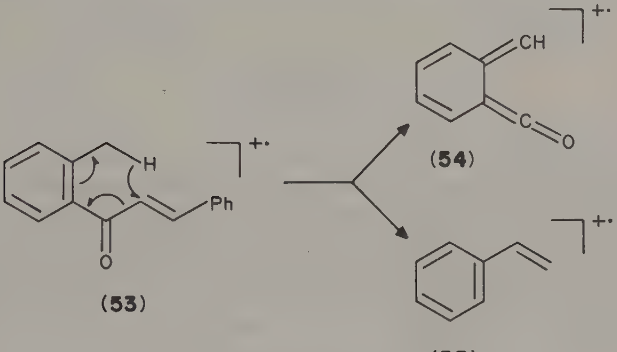
SCHEME 19

ring (Scheme 19)[45]. The fragmentation commences with electrophilic attack of the enone *β*-carbon atom at the *ortho* position of the benzoyl ring to give intermediate **51**. The latter eliminates the aryl group to afford the protonated benzocyclopentenone **52**. It is noteworthy that a competing loss of the angular hydrogen atom from **51** does not take place[45] as it would produce a biradical ion or an unstable α-carbonyl carbenium ion[46].

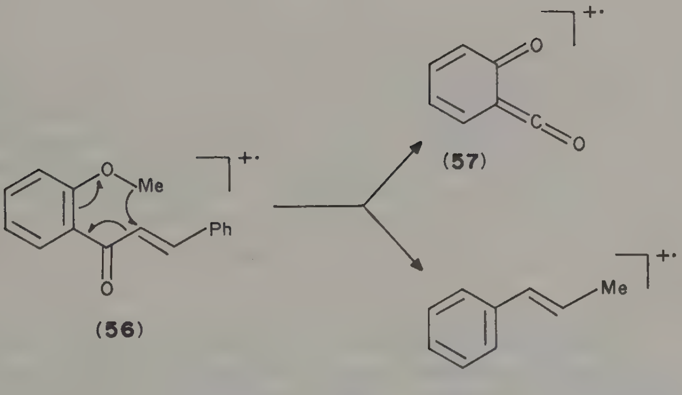
Beside reacting as an electrophile, the enone group can also function as an acceptor for radicals being transferred from the *ortho* positions of the benzoyl ring. This *ortho* effect, which is a general phenomenon in the mass spectra of *ortho*-disubstituted aromatic compounds[47,48], takes up different forms depending on the nature of substituents in the ionized chalcone.

In the *ortho*-methyl substituted chalcone **53** (Scheme 20), the transfer onto the enone double bond of one of the methyl hydrogens triggers a fragmentation leading to complementary ions **54** and **55**. The transfer of the methyl group from the methoxyl in chalcone **56** is even more pronounced and gives rise to complementary ions **57** and **58** (Scheme 21)[45].

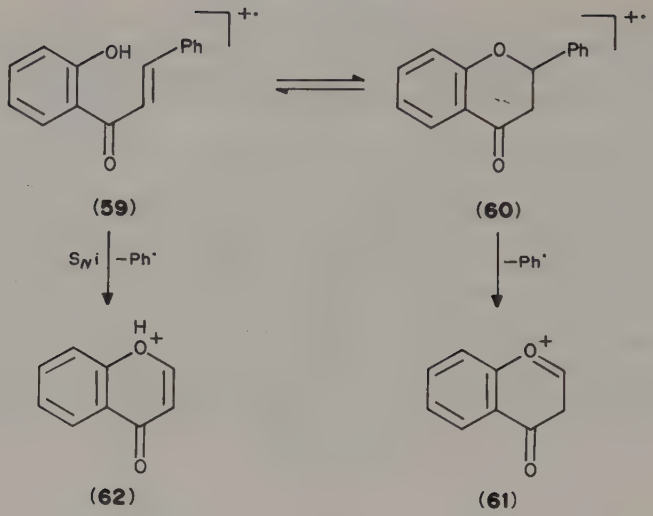
The *ortho*-hydroxy group in ionized chalcone **59** can attack the β-carbon atom of the enone group in an intramolecular Michael addition (Scheme 22), yielding the isomeric flavanone **60**[45,49]. The isomers **59** and **60** give similar mass spectra which indicate that the corresponding molecular ions may interconvert[49]. Deuterium labelling in **59** and **60** showed that the equilibration $[\mathbf{59}]^{+\cdot} \rightleftarrows [\mathbf{60}]^{+\cdot}$ precedes the loss of the hydrogen atom from both isomers, but is slower than the loss of the hydroxyphenyl group, as far as rapid decompositions in the ion source are concerned[45,49]. It should be noted that the loss of the vinylic phenyl group (Scheme 22) can also be regarded as an S_Ni substitution by the *ortho*-hydroxy group in $[\mathbf{59}]^{+\cdot}$. The carbon- and oxygen-protonated benzpyrones (**61** and **62**, respectively) can be expected not to interconvert via the symmetry-forbidden 1,3-proton shift, and hence they might be distinguishable through their CAD spectra.



SCHEME 20

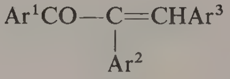


SCHEME 21



SCHEME 22

1, 2, 3-Triarylpropenones (**63**) behave in many respects similarly to the simpler chalcones, though some quantitative differences have been observed[50]. The additional aryl group at C-2 considerably weakens the CO—C-2 bond in the molecular ions of **63**, while stabilizing the Ar^2—$\dot{C}$=CH—Ar^3 radicals and Ar^2—$\overset{+}{C}$=CH—Ar^3 ion being formed. Consequently, the Ar^1CO^+ and Ar^2—$\overset{+}{C}$=CH—Ar^3 species become the most abundant fragment ions in the spectra of enones **63**. The formation of the latter ions predominates in the presence of electron-donating groups (OH, OMe, $OSiMe_3$) in Ar^3 and, especially, Ar^2.



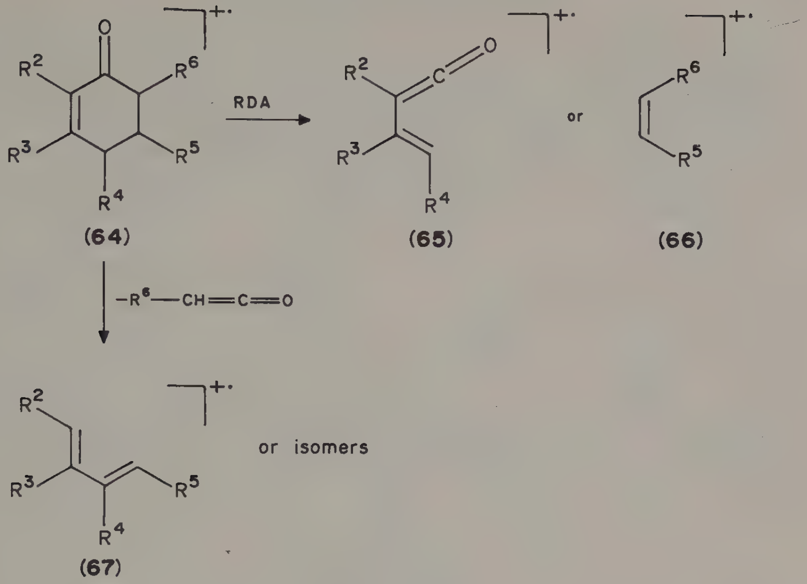
$$\underset{\displaystyle Ar^2}{\mathrm{Ar^1CO{-}\underset{|}{C}{=}CHAr^3}}$$

(63)

Another interesting feature of the ion chemistry of enones **63** is the enhanced elimination of arene molecules (Ar^2H or Ar^3H) from the molecular ions. This rearrangement is especially promoted if Ar^2 or Ar^3 carry hydroxy, methoxy or trimethylsilyloxy groups in *ortho* or *para* positions. Also, unimolecular decomposition spectra of metastable **63** ($Ar^1 = Ar^2 = Ar^3 = Ph$) are dominated by $(M - PhH)^{+\cdot}$ ions[50]. Mechanistic details of this interesting rearrangement have not been revealed, though the scarce labelling data indicate that the olefinic hydrogen atom from C-3 is involved in a part of the ArH molecules eliminated[50].

D. Cyclic Enones

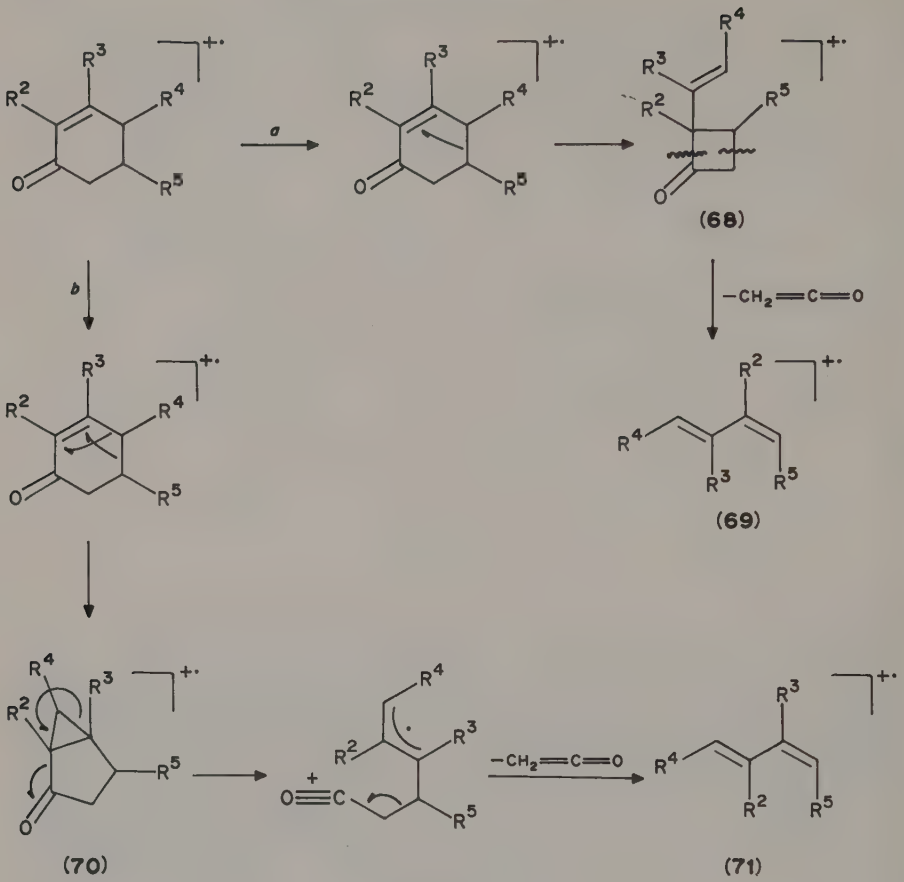
Compounds containing a cyclohexenone or a cyclopentenone ring are often of great biological importance (e.g. steroid hormones, phorbol esters, etc.), and the need for their analytical determination has prompted detailed mass spectral studies of model cyclic enones[51–59]. Under electron impact, cyclohexenone derivatives undergo two competing fragmentations, i.e. the loss of ketene and the retro-Diels–Alder (RDA) cleavage



SCHEME 23

(Scheme 23). The relative intensities of fragment ions **65**, **66** and **67** strongly depend on the substitution pattern of the cyclohexenone ring, which makes the above fragmentations diagnostically important.

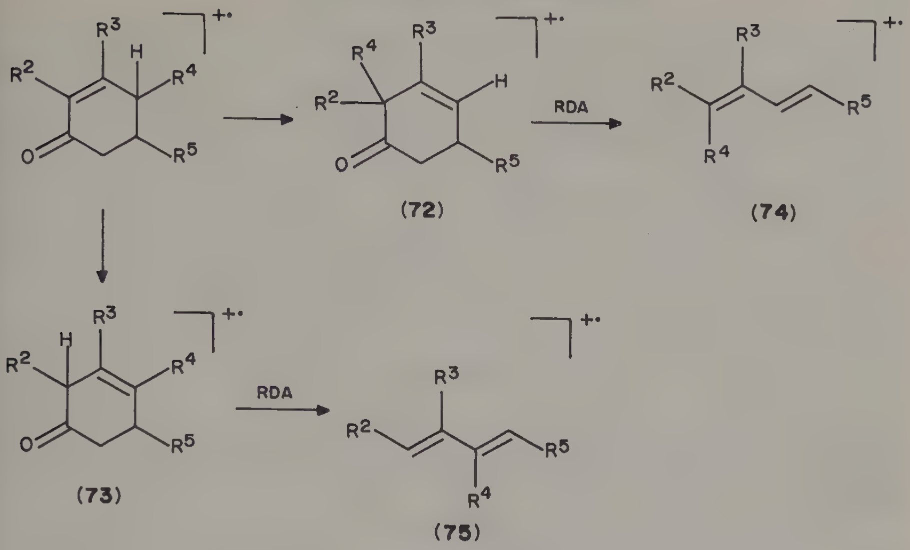
The elimination of ketene occurs for $R^6 = H$ and necessitates the presence of an alkyl or an aryl group at C-4 of the cyclohexenone ring[51,52]. The identity of the ketene molecule has been established beyond any doubt by deuterium labelling in various cyclohexenone derivatives[51,53]. On the other hand, the mechanism of ketene elimination has remained speculative because of lack of thermochemical and structural data on the $(M - CH_2CO)^{+\cdot}$ ions. The large effect of substitution at the remote C-4 center points to a hidden rearrangement preceding the loss of ketene[51,55]. Based on chemical intuition that a simple cleavage of a bond between two sp^2 carbon atoms would be an unfavourable process[51,54], two mechanisms have been put forward to explain the loss of ketene. The first mechanism (Scheme 24, *a*)[51] assumes migration of the cyclohexenone C-4—C-5 bond onto C-2 to form a cyclobutane intermediate (**68**) which eventually eliminates ketene to afford a stable diene ion (**69**)[51,54]. The second mechanism (Scheme 24, *b*)[55] is analogous to the photochemical lumirearrangement of cyclic enones, involving the intermediacy of cyclopropyl ketone **70**, and yielding the isomeric diene **71**. There is a third plausible mechanism[55] which comprises migration of the C-4 substituent (or the hydrogen atom) onto C-2, producing isomeric ions **72** and **73**, respectively (Scheme 25). Both these β,γ-enone radical ions can undergo facile retro-Diels–Alder fragmentation[57] to give isomeric diene ions **74** and **75**, respectively. The last mechanism explains well the observed stereochemistry in ketene elimination from stereoisomeric 5α-H and 5β-H androst-1-ene-17β-ol-3-ones (**76**, **77**) of which only the 5α-isomer affords abundant $[M - CH_2CO]^{+\cdot}$ ions[58]. In **76** the *trans* junction of the AB rings secures an axial orientation of the 10-methyl group with respect to the cyclohexenone ring, which is essential for a stereoelectronically facilitated migration[59]. In the 5β-isomer **77** the same methyl is equatorial with respect to



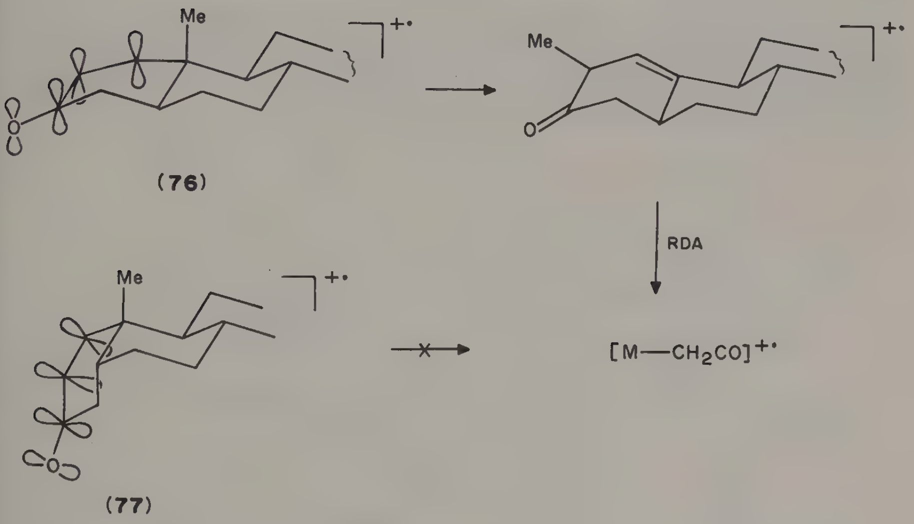
SCHEME 24

the A ring, and its migration onto C-2 would require conformational excitation of the AB ring system in order to become stereoelectronically assisted (Scheme 26).

The retro-Diels–Alder (RDA) decomposition takes place in ionized cyclohexenones of various types and often gives rise to abundant 'diene' or 'ene' fragment ions[54,60]. The $[C_4H_4O]^{+\cdot}$ ion formed upon RDA decomposition of ionized cyclohexenone was originally formulated as having the cyclic cyclobutenone structure **78** (Scheme 27)[60]. In the light of the more recent studies of the properties of $[C_4H_4O]^{+\cdot}$ isomers[61–65] it now appears more probable that the $[C_4H_4O]^{+\cdot}$ species from cyclohexenone is the more stable vinylketene ion **79** (Scheme 27). The $[C_4H_4O]^{+\cdot}$ ion from cyclohexenone and that prepared by ionization of neutral vinylketene gave identical CAD spectra[61] and were found to have nearly identical heats of formation (812 and 816 kJ mol^{-1}, respectively)[61,62]. Hence, at least near the threshold of decomposition, the formation of **79** from cyclohexenone appears to be very likely. The $[C_4H_4O]^{+\cdot}$ ions generated from cyclohexenone at 70 eV may contain a small fraction of the less stable **78**, as judged by the kinetic energy release in the further decomposition of metastable $[C_4H_4O]^{+\cdot}$ by loss of carbon

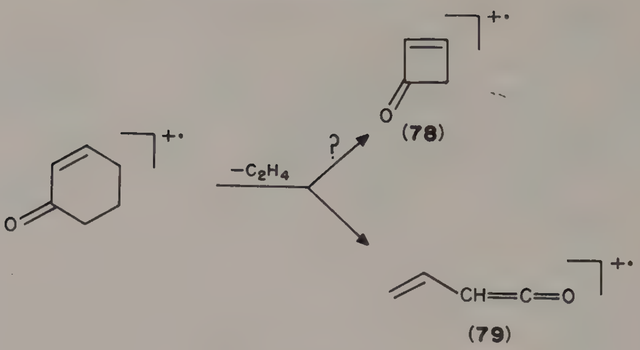


SCHEME 25



SCHEME 26

monoxide[61]. The cyclobutenone ions, prepared by loss of carbon monoxide from 4-cyclopenten-1,3-dione[63], provide indistinguishable CAD spectra from those of the more stable **79**[63]. The isomers can be differentiated only by the kinetic energy release values (T_{av}) in unimolecular loss of carbon monoxide (7.4 and 5.8 kJ mol^{-1} for **78** and **79**, respectively). Metastable $[C_4H_4O]^{+\bullet}$ from cyclohexenone release on average 6.6 kJ mol^{-1} during the

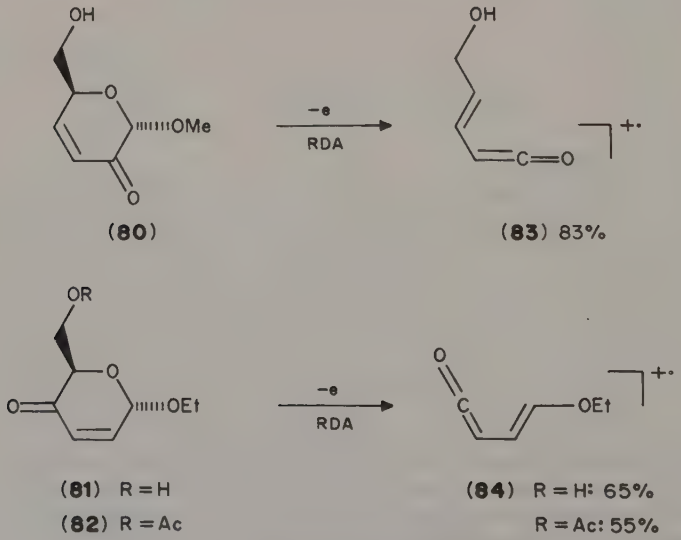


SCHEME 27

loss of carbon monoxide, so an admixture of an isomer other than **79** is not excluded. The existence of a stable ion **78** is remarkable in view of the facile thermal and photochemical electrocyclic ring cleavage in neutral cyclobutenone[66].

A retro-Diels–Alder reaction in cyclohexenones of general formula **64** does not result in immediate fragmentation, if the substituents R^3 and R^4 are part of a ring. This topological property has been utilized for establishing the positions of double bonds in polycyclic enones, e.g. α, β-unsaturated steroid ketones (for comprehensive treatment of this topic cf. References 67 and 68).

Even highly substituted cyclic enones, e.g. the carbohydrate derivatives **80–82** (Scheme 28), undergo facile retro-Diels–Alder fragmentation yielding abundant ketene ions **83** and **84**, respectively[69]. Since the ketene fragments retain the γ-substituent (CH_2OH and OEt for **83** and **84**, respectively), the position of the enone group in the sugar molecule can be unambiguously allocated from the mass spectrum[69].

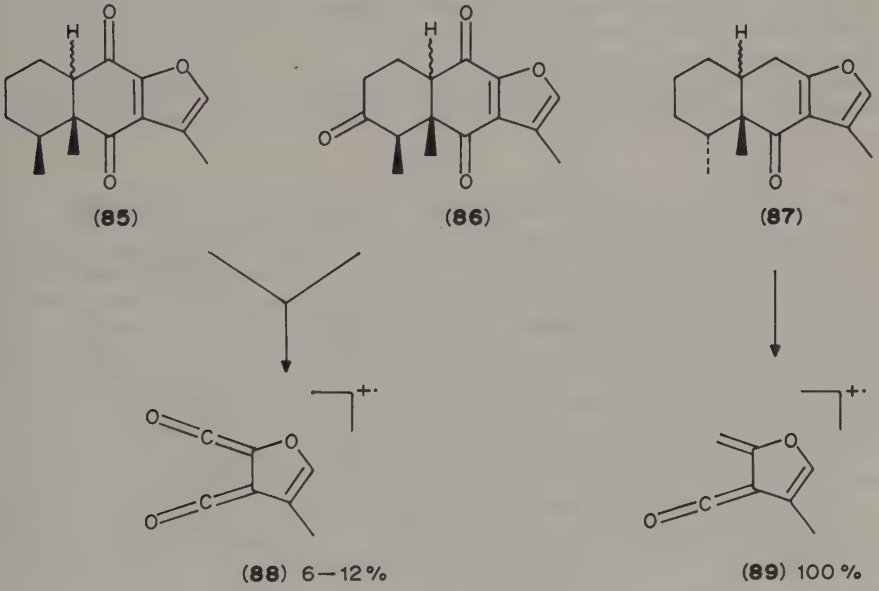


SCHEME 28

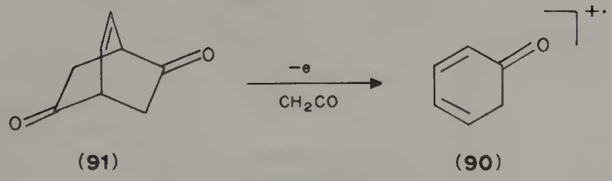
Stereochemistry of the retro-Diels–Alder reaction has been investigated with tricyclic enones **85–87** (Scheme 29), but only weak effects of ring annulation on the relative intensities of the RDA fragments have been found[70]. Of interest is the much greater relative abundance of the ketene ions **89** from **87**, compared with that of the oxa-analogues **88** (Scheme 29). Vinylketene radical cations are remarkably stable species[61,63] which may explain the facile formation of **89** from **87**.

It should finally be noted that the ease with which the cyclohexenone-derived radical cations undergo the RDA cleavage conforms to the rules that have been formulated to account for the behaviour of ionized cyclohexene derivatives in general[57].

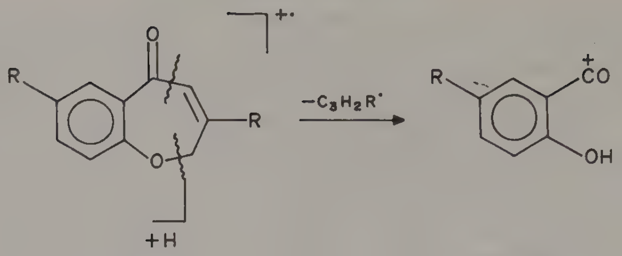
The 2,4-cyclohexadienone radical cation (**90**) has been the subject of numerous mass spectral studies owing to its role in decompositions of ionized phenyl ethers and phenyl esters[71] (for more recent accounts of the earlier work cf. References 72 and 73). Ion **90** is readily generated by the electron-impact-induced retro-Diels–Alder decomposition of bicyclo[2.2.2]oct-7-en-2,5-dione (**91**, Scheme 30)[74]. Although the dienone ion **90** is less stable than the tautomeric phenol ion (the destabilization has been estimated as 110 kJ mol^{-1})[72], there is a high-energy barrier separating both isomers, such that the less



SCHEME 29



SCHEME 30



(92) **(93)**

R=CH$_2$OH, CHO

SCHEME 31

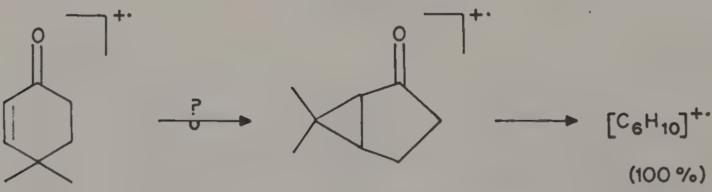
stable dienone ion behaves as a unique species[72,74,75]. Both unimolecular and collision-induced decompositions of **90** are dominated by expulsion of carbon monoxide to give a $[C_5H_6]^{+\cdot}$ ion[72,75]. The kinetic energy release accompanying the loss of carbon monoxide from metastable $[\mathbf{90}]^{+\cdot}$ is rather high ($T_{0.5} = 42\ \text{kJ mol}^{-1}$)[75], suggesting a substantial energy barrier to the reverse reaction.

Mass spectra of some medium-ring enones have been reported[76]. Substituted benzoxepinones **92** undergo cleavage of the enone ring which results in the formation of stable acylium ions **93** (Scheme 31)[76].

E. Analogies Between Enone Photochemistry and Gas-phase Ion Chemistry

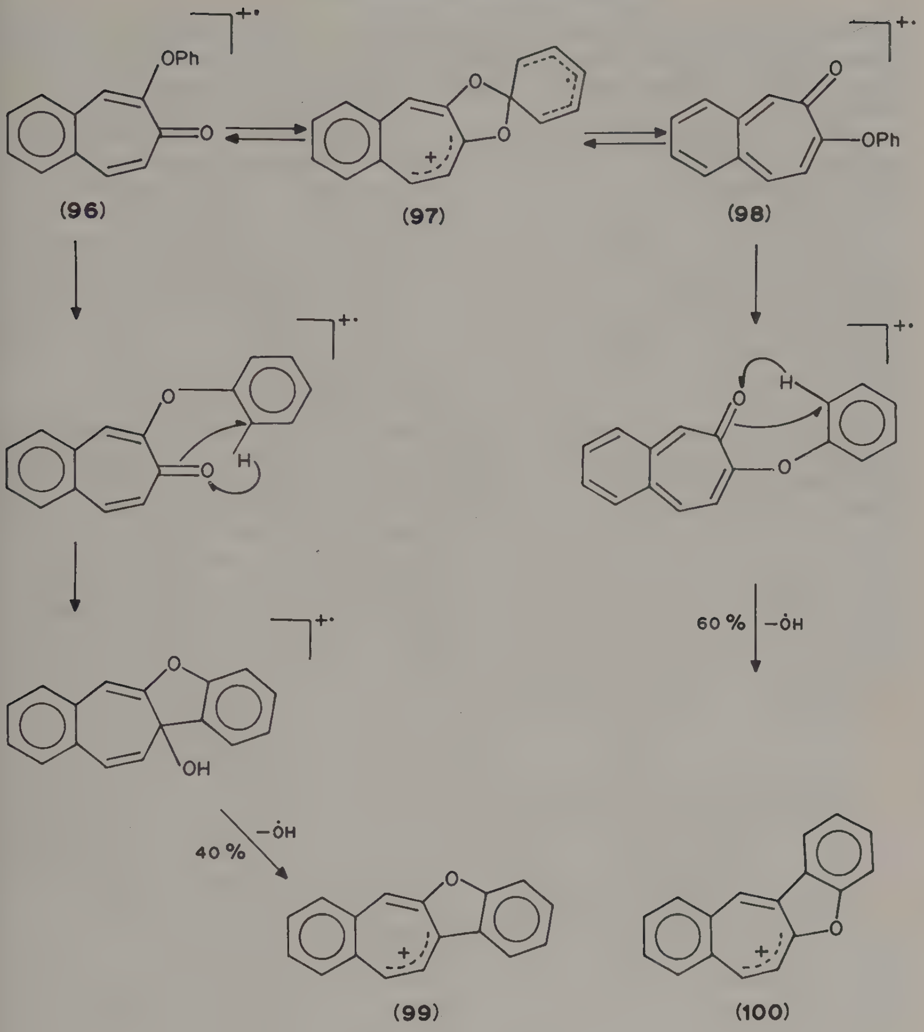
The chemistry of gaseous radical cations shares some common features with the chemistries of other open-shell species, e.g. radicals[77] and photoexcited molecules[55,78–80]. As mentioned earlier in this chapter, one of the ways to explain the loss of ketene from the 4,4-dimethylcyclohexenone molecular ion (**94**) comprises a lumirearrangement in which the 'photoisomer' **95** plays the role of a reactive intermediate (Scheme 32)[55]. As a matter of fact, the ionized ketone **95** itself eliminates ketene very readily giving rise to a $C_6H_{10}^{+\cdot}$ ion as the base peak of the spectrum[55]. While more convincing evidence based on modern mass-spectrometric techniques is still to be gathered to support the suggested interconversion $[\mathbf{94}]^{+\cdot} \rightleftarrows [\mathbf{95}]^{+\cdot}$, there are other systems that do show close similarities between the reactions of radical cations and those of the corresponding photoexcited molecules.

Under electron impact, 2-phenoxy-4, 5-benztropone (**96**) undergoes an unusual loss of a hydroxy group, the mechanism of which was elucidated by extensive ^{2}H, ^{13}C and ^{18}O labelling (Scheme 33)[80]. The hydroxyl eliminated involves both the carbonyl and the ether



(94) **(95)**

SCHEME 32

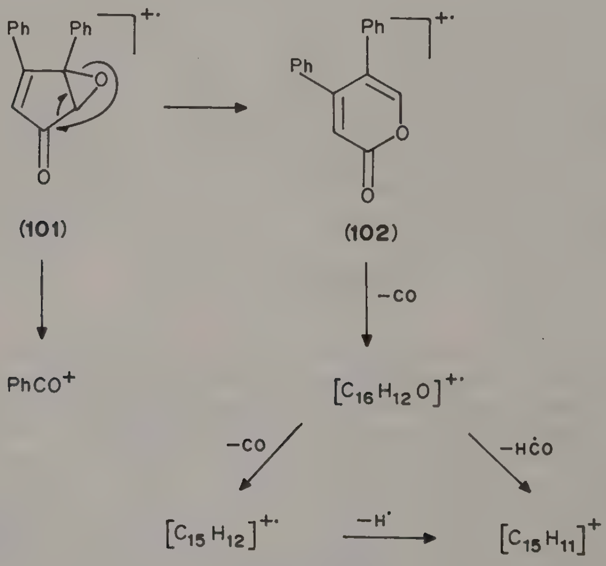


SCHEME 33

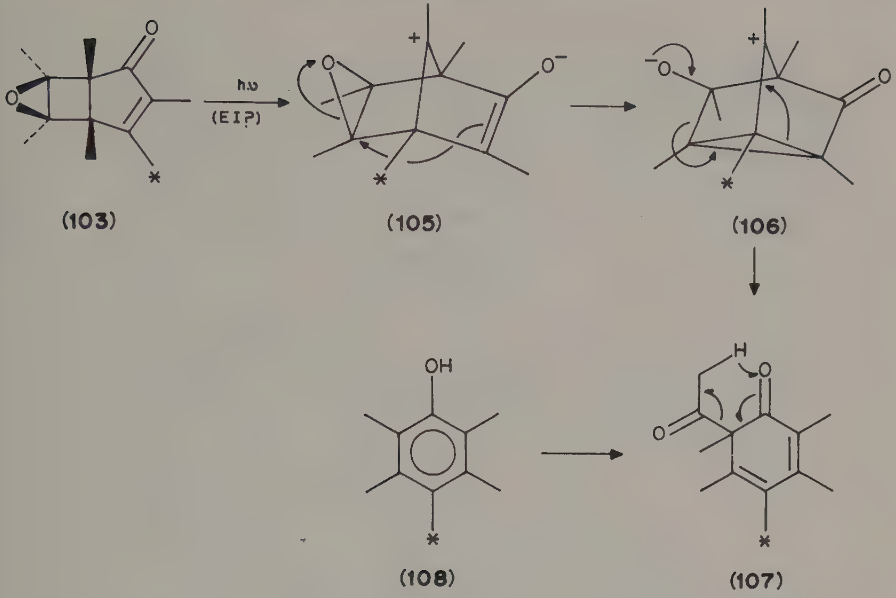
oxygen atoms in a 60:40 ratio which shows that a rapid equilibrium has been established between the isomeric ions **96** and **98**[80]. A related phenyl migration in **96** can be brought about by photochemical n–π* excitation of the enone carbonyl group[81], which points to formal analogy between the photochemistry and ion chemistry of this system[80]. However, in a molecular-orbital description the photochemical and electron-impact-induced reactions differ, because different electronic states are involved in each. In the light-induced rearrangement the reactivity is centred at the enone chromophore whose electrophilic, singly occupied n orbital attacks the electron-rich π system of the neighbouring phenoxy group[82]. By contrast, the electron-impact ionization of **96** produces ions whose ground electronic state encompasses electron vacancy in the phenoxy group which is the subunit of the lowest ionization energy[10]. The bond formation in ionized **96** to give the intermediate **97** (Scheme 33) can thus be regarded as a nucleophilic attack by the enone oxygen atom at the electron-deficient centre of the ionized phenoxy group.

Analogies between light- and electron-impact-induced reactivity have been found for some epoxy enones[83,85]. 3,4-Diphenyl-4,5-epoxy-2-cyclopentene-1-one (**101**) affords a mass spectrum which is very similar to that of 4,5-diphenyl-2-pyrone (**102**, Scheme 34)[83]. Both these compounds are photochemically related, as irradiation of the former with light of wavelength longer than 280 nm affords the latter pyrone[84]. The similarity between **101** and **102** is especially salient in decompositions of long-lived metastable ions which display indistinguishable spectra and peak shapes[83]. The fast decompositions in the ion source show some distinctions between **101** and **102**, namely the former affords more abundant $PhCO^+$ ions than does the latter, which reflects the presence of the Ph—C—O structural subunit in the epoxy enone **101**, but not in the pyrone **102**[83].

Isomeric epoxides **103** and **104** derived from hexamethylbicyclo[3.2.0]hepta-3,6-dien-2-one differ remarkably in their mass spectral fragmentation patterns[85]. Under electron impact the 6,7-epoxide **103** eliminates ketene to produce an ion at *m/z* 164 as the base peak of the spectrum. The latter ion corresponds by mass to pentamethyl phenol (**108**) which is formed as the major isolable product upon photolysis of **103** (Scheme 35)[85]. The mechanism suggested for the photo-induced elimination of ketene from **103** involved the subsequent migration of the allylic carbon–carbon bond, cleavage of the oxirane ring (**105**) and cyclopropane ring opening (**106**) to give the transient cyclohexadienone **107** which would finally undergo the Norrish II fragmentation yielding pentamethylphenol (**108**)[85]. As established unequivocally by deuterium labelling, the original 3-methyl from **103** ends up in the *para* position (C-4) in **108**[85]. Each of the reaction steps involved in the photochemical transformation **103**→**108** has an analogy in the chemistry of gaseous



SCHEME 34

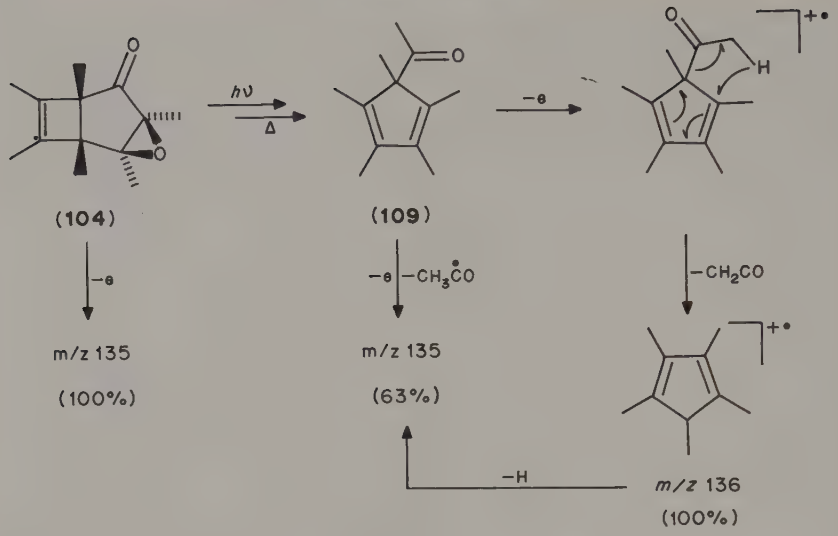


SCHEME 35

radical cations and so, at least formally, the above mechanism may be plausible for the electron-impact-induced loss of ketene, too. However, it should be emphasized that the information provided by the published low-resolution mass spectrum of **103** is too rudimentary to substantiate the ionic intermediates **105**–**107**, and that alternative mechanisms can be drawn to account for the mass spectral fragmentation.

The electron-impact mass spectrum of epoxy enone **104** displays the base peak at m/z 135 due to loss of a fragment of 71 daltons from the molecular ion[85]. It was suggested that this fragmentation could proceed via initial elimination of carbon monoxide to give the 1-acetyl-1,2,3,4,5-pentamethylcyclopentadiene ion which would lose the acetyl group to give $C_{10}H_{15}^{+}$ at m/z 135[85]. Upon photolysis at room temperature the epoxy ketone **104** yielded **109** which was regarded as an analogy between the photochemical and electron-impact-induced behaviour of **104**[85]. However, the 70 eV mass spectrum of **109** is dominated by fragments due to elimination of ketene (m/z 136)[85], while the direct loss of the acetyl group is less abundant (Scheme 36). This makes the suggested intermediacy of **109** doubtful, since the vibrationally cooler acetylcyclopentadiene ions $[\mathbf{109}]^{+\cdot}$ produced upon loss of carbon monoxide from **104** would be expected to prefer eliminating ketene even more than do the high-energy $[\mathbf{109}]^{+\cdot}$ prepared by direct ionization.

The 70 eV electron-impact mass spectra of 4,5-epoxy-6,6-dimethyl-2-cyclohexen-1-one (**110**) and its primary and secondary photoproducts **111**–**115** are quantitatively very different[86], though some qualitative similarities can be traced down (Scheme 37). The spectrum of **110** is dominated by a fragment at m/z 82 due to loss of a molecule of 56 daltons[86]. The latter ion is very weak or absent in the spectra of the photoproducts **111**–**115**. The unique behaviour of **110** under electron impact suggests that the majority of molecular ions $(\mathbf{110})^{+\cdot}$ decompose via non-photochemical pathways, that is, without isomerizing to **111**–**115**. On the other hand, the spectra of the valence-bond isomers

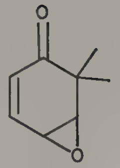
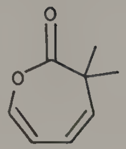
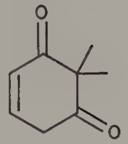
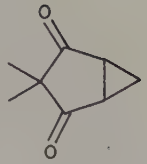
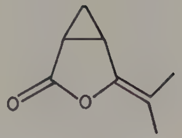
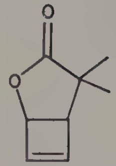


SCHEME 36

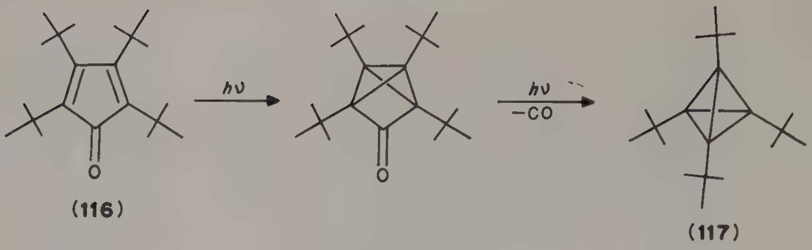
112–114 are similar, each showing the base peak at *m/z* 70, presumably due to $[(CH_3)_2C{=}C{=}O]^{+\cdot}$ ions. Hence it can be inferred that a large part of decomposing $[\mathbf{113}]^{+\cdot}$ and $[\mathbf{114}]^{+\cdot}$ undergo isomerization to $[\mathbf{112}]^{+\cdot}$ which then fragments via RDA cleavage. The differences in the spectra of **112–114** (Scheme 37) are probably due to fast decompositions that precede the isomerization. A metastable ion study would be useful here to show whether the ionized **112–114** are completely equilibrated on the microsecond time scale. The enedione **112** represents an interesting case of hidden degeneracy, as shifting the double bond interchanges the keto groups, but does not alter the overall structure. Hence, either keto group can appear in the $[(CH_3)_2C{=}C{=}O]^{+\cdot}$ ion provided the double-bond shift is rapid enough to compete with the RDA decomposition.

Loss of carbon monoxide from substituted cyclopentadienones is another reaction which can be induced both photochemically[87] and by electron impact[89]. Irradiation of 2,3,4,5-tetratert-butylcyclopentadienone (**116**) in matrix yields tetratert-butyltetrahedrane (**117**, Scheme 38) which, though being remarkably stable, can be isomerized thermally to tetratert-butylcyclobutadiene[88]. The intermediacy of tetrahedrane species had already been suggested earlier for the electron-impact-induced decompositions of tetraarylcyclones (**118**)[89–91], benzoquinones **119**[92], cyclopentenols **120**[91] and thiophene-*S*,*S*-dioxides **121**[93]. These compounds were shown to undergo facile cheletropic decompositions under electron impact to yield $[C_4Ar_4]^{+\cdot}$ ions which further decomposed to $[Ar_2C_2]^{+\cdot}$ fragments[89–93]. Careful labelling of the aryl groups with both deuterium and fluorine revealed[89–93] that nearly complete (*ca* 80%) scrambling of all four aryl groups had occurred in metastable $[C_4Ar_4]^{+\cdot}$, such that the $[C_2Ar_2]^{+\cdot}$ secondary fragments were produced in nearly statistic ratios (Scheme 39). Thence came a suggestion that the scrambling of the aryl groups proceeded via valence-bond isomerization in the central ring, involving the tetrahedrane ion **122** as the key intermediate[89]. The intermediate **122** was regarded either as a stable structure[89,90] or as a low-energy saddle point interconnecting the more stable cyclobutadiene $[C_4Ar_4]^{+\cdot}$ isomers **123** and **124**[94].

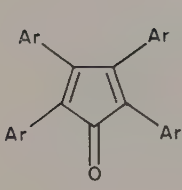
The intermediacy of tetrahedral structures in decompositions of $[C_4Ar_4]^{+\cdot}$ ions was definitely disproved by Schwarz and coworkers[95] who used the central-ring labelled

m/z	 (110)	 (111)	 (112)	 (113)	 (114)	 (115)
138	7	12	42	47	50	1.5
123	10	—	1	9	18	2
122	29	—	—	—	—	—
110	—	—	12	21	15	15
109	45	2	—	16	20	36
95	44	100	22	70	80	100
82	100	—	—	10	—	—
81	—	5	—	15	—	—
79	60	6	—	24	35	66
77	30	4	4	8	25	35
70	20	—	100	100	100	—

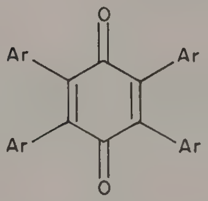
SCHEME 37



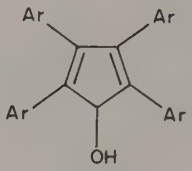
SCHEME 38



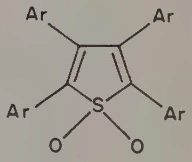
(118)



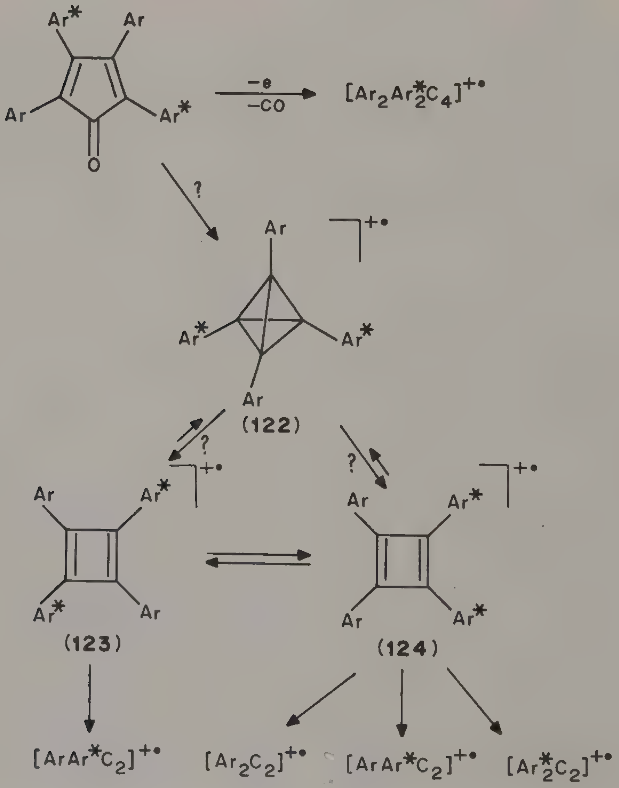
(119)



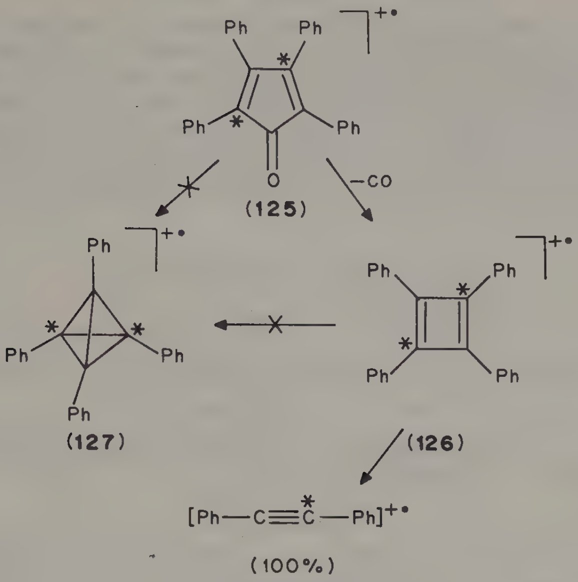
(120)



(121)



SCHEME 39



SCHEME 40

cyclone **125** as a precursor (Scheme 40). The collision-activated decomposition of stable ions **126** afforded exclusively singly labelled $[C_2Ph_2]^{+\bullet}$ which excluded any intermediates (e.g. tetrahedrane **127**) in which the two labelled or unlabelled positions, respectively, would have become connected. It follows that the positional scrambling observed by Bursey and coworkers[89–94] was due to aryl group migrations in metastable **123** and **124** (Scheme 39) and, to some extent, also in the molecular ions of **118** and **119**, but not **121**[94]. Label interchange between the aryl groups has not been observed[91]. The high symmetry of the **123**/**124** system allows for simple kinetic analysis. The calculation shows that on average it is sufficient that the aryl group migration in **123**, **124** be five times faster than the ring cleavage to obtain a fit with the reported relative intensities of the labelled $[C_2Ar_2]^{+\bullet}$ ions.

It can be concluded that direct analogy between the photochemical and the electron-impact-induced behaviour of cyclic enones is not a general phenomenon. This is not very surprising if one takes into consideration the different nature of the species involved. Enone photochemistry in solution deals mostly with triplet states produced upon intersystem crossing following initial n–π^* or π–π^* excitation[96]. Triplet reactivity includes often intramolecular [2 + 2] cycloadditions or [1, 2] bond shifts closing small rings[96]. This state-selective reactivity contrasts the fundamental assumptions of the chemistry of gaseous ions[97]. Ionization of complex organic molecules produces radical cations in a variety of available excited states which undergo rapid radiationless transitions to vibrationally excited doublet ground electronic state prior to decomposition. Under these conditions strained structures containing small rings, both cyclopropane and oxirane, are disfavoured as intermediates or transition states, because often the ion has other reaction paths that require less energy.

III. THE CHEMISTRY OF EVEN-ELECTRON CATIONS

Even-electron ions derived from enones, e.g. the $C_nH_{2n-1}O^+$ species from aliphatic enones, have been of considerable recent interest owing to their role in ion chemistry of cyclic and unsaturated alcohols and aliphatic aldehydes and ketones[98–109]. The most direct way to $C_nH_{2n-1}O^+$ ions is the gas-phase protonation of neutral enones with Brønsted acids of sufficient strength. Proton transfer under equilibrium conditions (equation 1) makes it possible to determine the gas-phase basicity (GB) of the enone, whence its proton affinity (PA) and the heat of formation of the $(MH)^+$ ion can be calculated[111]. The gas-phase basicity of the enone is determined from the change of the free enthalpy in reaction 1, $\Delta G_r = -RT \ln K_{eq}$, and the GB of the conjugated base **B** according to equation 2:

$$\text{Enone} + \text{BH}^+ \overset{K_{eq}}{\rightleftharpoons} [\text{Enone} + \text{H}]^+ + \text{B} \tag{1}$$

$$\text{GB(Enone)} = \text{GB(B)} - \Delta G_r(1) \tag{2}$$

The proton affinity is defined as the negative enthalpy change in reaction 3:

$$\text{Enone} + \text{H}^+ \longrightarrow [\text{Enone} + \text{H}]^+ \tag{3}$$

i.e. $\text{PA(Enone)} = -\Delta H_r(3) = \Delta H_f^\circ(\text{Enone}) + \Delta H_f^\circ(\text{H}^+) - \Delta H_f^\circ([\text{Enone} + \text{H}]^+)$. The GB and PA quantities are interrelated by equation 4:

$$\text{PA} = \text{GB} - T\Delta S_r(3) \tag{4}$$

Protonation of the enone group raises several questions as to the site of proton attachment, geometries and relative stabilities of isomeric $(MH)^+$ ions, barriers to their interconversions and, last but not least, the energetics and dynamics of unimolecular decompositions. Most of these questions have been addressed by experiment or theory.

A. Structure and Energetics

Proton affinities of the four simplest enones, propenal (**1**), 1-buten-3-one (**2**), (E)-2-butenal (**3**) and 2-methylpropenal (**4**), have been determined using the ion-trapping method[110]. As the proton affinities of **1–4** (Table 2) were invariably higher than those of comparable olefins, e.g. PA(**1**) = 811 kJ mol^{-1} vs. PA(propene) = 733–751 kJ mol^{-1} [111], it was concluded that, under equilibrium conditions, the protonation occurs at the oxygen atom[110]. This suggestion has gained support from several experimental and theoretical studies and is now generally accepted.

The proton affinities of **1–4** were shown to correlate with the oxygen core (1s) ionization energies[110], rendering support to oxygen protonation[110].

TABLE 2. Energy data (kJ mol^{-1}) for enones **1–4**, **128–137**

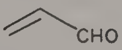
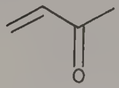
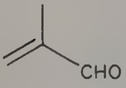
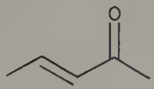
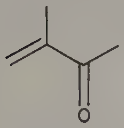
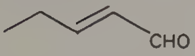
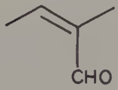
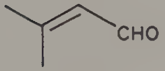
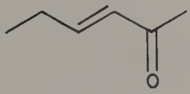
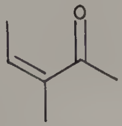
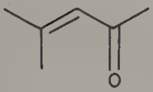
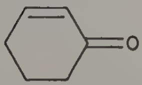
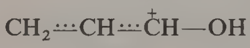
Compound	$\Delta H^\circ_{f,298}$(M)	PA	GB	$\Delta H^\circ_f(MH)^+$	IE_{vert}
(1) 	−74[a]	811[b]	778[c]	645	978[d]
(2) 	−124[a]	838[b]	805[c]	568	931[e]
(3) 	−104[f]	836[b]	803[c]	590	946[g]
(4) 	−109[a]	817[b]	784[c]	604	957[h]

TABLE 2. (*continued*)

Compound	$\Delta H^\circ_{f,298}(M)$	PA	GB	$\Delta H^\circ_f(MH)^+$	IE_{vert}
(128) 	-157^a	867^i	834^i	506	906^h
(129) 	-157^a	851^i	819^i	522	917^h
(130) 	-127^a	848^j	815^j	555	936^h
(131) 	-137^a	853^j	819^j	539	926^h
(132) 	-137^a	861^j	828^j	531	
(133) 	-177^a	867^j	834^j	486	
(134) 	-188^a	870^j	837^j	473	902^h
(135) 	-187^a	880^j	847^j	463	879^h
(136) 	-63^a	861^k	828^k	606	900^l
(137) 	-114^a	869^k	835^k	547	889^m

[a] By additivity[4], for details see text.
[b] From Reference 110 as recalculated by Lias and coworkers[126]. All values are based on $GB(NH_3) = 822\,kJ\,mol^{-1}$.
[c] Calculated from the PA values[115,126]
[d] Average value from References 5 and 139.
[e] Average value from References 13, 140 and 141.
[f] Reference 12.
[g] Average value from References 13 and 117.
[h] From Reference 13.
[i] From Reference 119.
[j] From Reference 115.
[k] From Reference 142.
[l] Average value from References 139 and 141.
[m] Average value from References 62, 139 and 141.

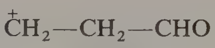
Ab initio calculations of the geometries and relative energies of twelve $C_3H_5O^+$ isomers, performed at the 4-31G/CIPSI level of theory, supplied data which agreed well with the experimental results[112]. The oxygen-protonated structure **138** was calculated to be 189 and 193 kJ mol^{-1} more stable than the carbon-protonated structures **139** and **140**, respectively[112]. The existence of **139** and, especially, **140** as equilibrium structures is somewhat questionable and may well be due to the size of the basis set used in the calculations[112]. Analogous $\overset{+}{C}H_2CHO$, $CH_3CH_2^+$ and $CH_3CH_2CH_2^+$ ions which are also obtained as local minima in calculations with the 4-31G basis set cease to exist when larger basis sets are employed and when the calculated energy minima are complemented with zero-point vibrational energies[113,114]. Nevertheless, structures **139** and **140** can possibly play a role in decompositions of **138** (*vide infra*).


$CH_2{\cdots}CH{\cdots}\overset{+}{C}H{-}OH$

(138)

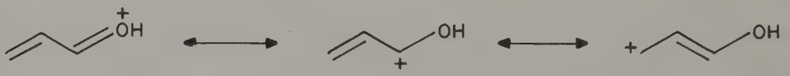

$Me{-}\overset{+}{C}H{-}CHO$

(139)


$\overset{+}{C}H_2{-}CH_2{-}CHO$

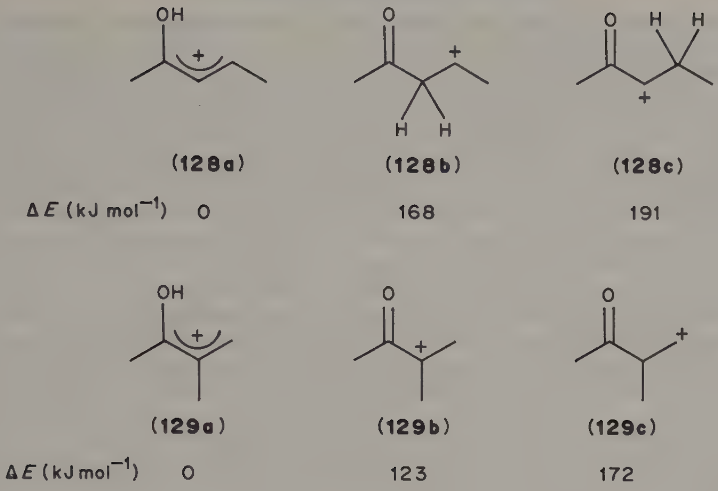
(140)

Of the $C_3H_5O^+$ isomers investigated[112], **138** was calculated to be the second most stable structure being only 57 kJ mol^{-1} higher in energy than the absolute minimum corresponding to $CH_3CH_2CO^+$ (**141**). The calculated difference in the ΔH_f° (without zero-point corrections) is in excellent agreement with the most recent experimental data that give $\Delta H_f^\circ(\mathbf{138}) - \Delta H_f^\circ(\mathbf{141}) = 54$ kJ mol^{-1} [115,116]. The calculated equilibrium geometry of **138** shows that the most stable structure assumes all-planar s-*trans* conformation whereas the s-*cis* conformer is slightly less stable ($\Delta E \approx 6$ kJ mol^{-1})[112]. The planar geometry of **138** corresponds to an in-plane attachment of proton to the oxygen *n*-orbital which is HOMO in **1**[117] and is largely localized at the oxygen atom[118]. The protonation has a marked effect on the lengths of bonds between the heavy atoms in **138**. The carbon–oxygen bond is prolonged while the C-1—C-2 bond is shortened relative to the same bonds in **1**[112]. The calculated lengths of the C-1—O, C-1—C-2 and C-2—C-3 bonds in **138** are intermediate between those of the corresponding single and double bonds, such that structure **138** can be depicted by the canonical formulae:



Gas-phase basicities of a series of aliphatic and cyclic enones have been determined from measurements of proton-transfer equilibrium constants in ion-cyclotron resonance experiments (Table 2)[115,119,120]. The thermochemical data show again that the protonation in higher aliphatic and cyclic enones is likely to occur at the enone oxygen atom, notwithstanding the substitution pattern of the double bond. For instance, the proton affinities of **131** and **135**, which contain an isobutylene-like double bond, are substantially higher than the PA of isobutylene itself (820–824 kJ mol^{-1})[111], which would not have been expected had the protonation occurred at the enone double bond. This was corroborated by semiempirical MNDO calculations of structures and heats of formation for protonated **128** and **129**[119]. The calculated relative energies (Scheme 41) of isomeric ions **128a-c** and **129a-c** show that the oxygen-protonated structures **128a** and **129a** are the most stable ones[119]. Protonation of the double bonds in **128** and **129** would require substantially stronger acids and is therefore unfeasible under conditions of equilibrium proton transfer.

The order of relative stabilities of the carbon-protonated ions seems to be predicted reasonably well by the MNDO calculations[119]. The proximity of the carbonyl group and a carbocation centre, as in the acylcarbenium ion **128c**, is a destabilizing factor[146] which accounts for the lower stability of the latter compared with the secondary carbocation



SCHEME 41

128b. Stable secondary α-acylcarbenium ions are still a matter of dispute since the only evidence for their existence comes from MNDO calculations[121], while higher-quality computational or experimental data have been lacking.

The order of stability is reversed with **129b** and **129c** where the latter represents an unstable primary carbocation[113,114], while the cationic centre in the former gains stabilization from the two methyl substituents. Ion **129b** has been generated in the gas phase by loss of one of the quaternary-carbon bound methyls in ionized pinacone[122]. Metastable **129b** and the isomeric pivaloyl ion, Me_3CO^+, have been distinguished through the kinetic energy release in the elimination of carbon monoxide, with the former giving a substantially higher value ($T_{0.5} = 35.2$ kJ mol^{-1}) than the latter (1.5 kJ mol^{-1}). The heat of formation of **129b** was estimated to be comparable to that of Me_3CO^+ (517 kJ mol^{-1})[123], based on the relative abundances of these ions formed from metastable pinacone[122] which, however, is in conflict with the MNDO calculations[119].

The thermochemical data summarized in Table 2 reveal several useful correlations, but also deserve a critical comment. The gas-phase basicities and the ionization energies are directly accessible by experiment and hence the uncertainties in these values are given by the accuracy of the technique employed. The proton affinities are calculated from the GB data by correcting for the translational entropy of free proton ($-T\Delta S = 33$ kJ mol^{-1} at 298 K). Save for a few exceptions[120] the changes in the vibrational and rotational partition functions when passing from M to MH^+ are neglected as their contributions to ΔS are considered small. The $\Delta H^\circ_{f,298}$ of neutral enones have been mostly estimated from Benson's additivity scheme[4], which unfortunately rests on the single experimental value for ΔH°_f(**3**). The term for CO—(C_d)(C) has been missing while various, often rather arbitrary, values have been used throughout the literature[3,110,115]. In order to put the data on a consistent basis we here approximate CO—(C_d)(C) = CO—$(C)_2$ + [CO—(C_d)(H)—CO—(C)(H)] giving -141 kJ mol^{-1} for the required term. Ring and *cis*-alkene corrections[4] have been implemented to calculate the ΔH°_f(M) where appropriate. The uncertainties in the ΔH°_f are transmitted to the calculated $\Delta H^\circ_f(MH)^+$ and further amplified by uncertainties in the *PA* values (*vide supra*) and the $\Delta H^\circ_f(H^+)$ (here taken as

1530 kJ mol^{-1})[115]. Hence the $\Delta H_f^\circ(\mathrm{MH})^+$ values should be regarded as the least accurate ones.

The effects of methyl substituents on the $\Delta H_f^\circ(\mathrm{MH})^+$ and proton affinities of aliphatic enones have been evaluated[115]. The former values have been shown to fit the linear relationship where n is the total number of atoms in the ion. In the same sense the $\Delta H_f^\circ(\mathrm{MH})^+$ correlate with the number of carbon atoms in **1–3**, **128**, **132** and **135** as shown in Figure 1. The linear correlation 5, which is also typical of homologous allylic ions[124,125], points to homologous structures for the protonated enones, thus providing additional support for the oxygen protonation in the higher members of the series.

$$\Delta H_f^\circ(\mathrm{MH})^+ = \alpha - \beta \ln n \tag{5}$$

The proton affinities of **1–4**, **128–137** tend to increase with increasing number of alkyl substituents at the enone moiety[115]. Upon placing a methyl at C-1 the proton affinity increases by 17–31 kJ mol^{-1} which is similar in magnitude to a C-3 substitution giving an increment of 19–25 kJ mol^{-1} [115]. Methyl substituents at C-2 provide on average a smaller increase in PA with the increments showing a larger dispersion (3–17 kJ mol^{-1})[115]. The magnitude of these increments roughly follows the positive charge densities at the enone carbon atoms as calculated for **1**, C-1 > C-3 > C-2[118].

The PA-increasing effect of the methyl at C-1 is probably due to combined σ and π donation that both increase the electron density at the oxygen atom. Very similar PA increments upon introducing a methyl have been encountered with saturated aliphatic aldehydes and ketones, e.g. $\Delta\mathrm{PA} = 33$ kJ mol^{-1} when going from propanal to 2-butanone[111].

The effect of the alkyl at C-3 is largely due to π donation. The electron flow from the alkyl group is transmitted by the enone π system to increase the negative charge density at

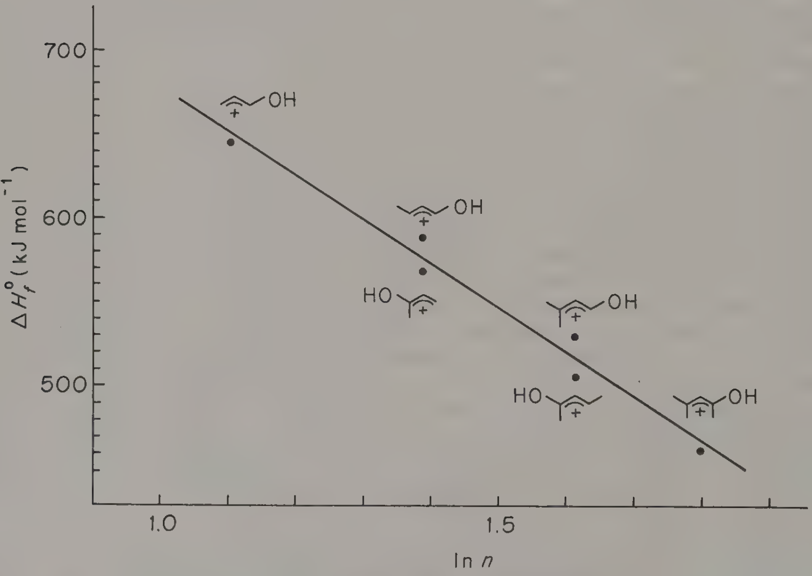


FIGURE 1. Correlation between the heats of formation of protonated enones and the number of carbon atoms in the ions

the oxygen atom. As the oxygen n-orbital does not mix much with the enone π orbitals due to their different symmetry[118], the increased energy of the former can be attributed to Coulombic repulsion. The π-donation effect of the alkyl substituents at C-3 becomes more apparent if one compares the proton affinities of enones with those of their saturated counterparts. In the absence of the C-3 alkyl (e.g. in **2** and **4**) the enones are only marginally more basic than their saturated analogues [PA(2-butanone) = 836 kJ mol^{-1}, PA(isobutyraldehyde) = 811 kJ mol^{-1}][126]. With a C-3 substituent being present the differences increase dramatically, ranging from 19 kJ mol^{-1} for the system cyclohexenone-cyclohexanone[120,127] up to 28 kJ mol^{-1} for the system 2-butenal-butanal[126,111].

σ-Donation by the C-3 substituent is observable in aldehydes [PA(**130**) > PA(**3**)], but is barely visible in ketones [PA(**128**) = PA(**133**) ≈ PA(**137**)]. In ketones the electron tug through the enone σ-bond framework is largely compensated by σ donation of the methyl at C-1. The combined σ- and π-donation effects of the alkyl substituents introduce non-linearity in the PA increments attributable to the given methyl in the given position. In fact the PA increments slightly decrease with the number of substituents attached to the enone system.

Enone proton affinities further show a linear correlation with enone vertical ionization energies (Table 2, Figure 2). The first ionization potential in enones corresponds to abstraction of electron from the oxygen n-orbital which is the HOMO[117] and whose energy is expected to rise with increasing electron density at oxygen due to methyl σ and π donation[117]. The correlation between the IE$_{\text{vert}}$ and PA values shows that the latter also

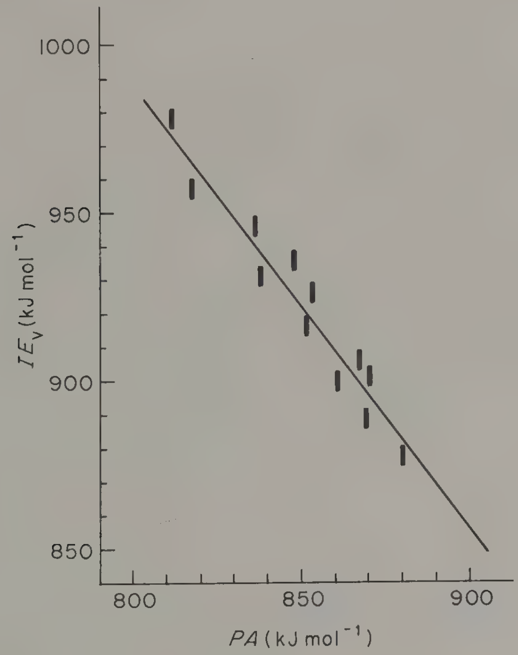


FIGURE 2. Correlation between proton affinities and vertical ionization energies in **1–4**, **128–131** and **134–137**

depend on the electron density at the oxygen atom, consistent with the presumed site of protonation. Conversely, IE and PA values do not correlate in systems where small structural alterations result in changing the protonation sites[128].

The data in Table 2 allow for assessment of bond dissociation energies (BDE) pertinent to oxygen–hydrogen bonds in protonated enones. While heterolytic BDE are given directly by the PA values, homolytic BDE can be calculated according to equation 6:

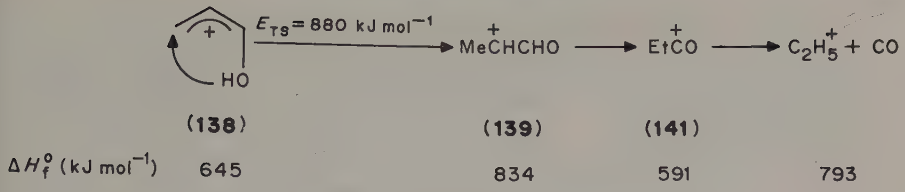
$$\begin{aligned}\mathrm{BDE(O{-}H)} &= \Delta H_f^\circ(\mathrm{M})^{+\bullet} + \Delta H_f^\circ(\mathrm{H}^\bullet) - \Delta H_f^\circ(\mathrm{MH})^+ \\ &= \mathrm{IE(M)} + \mathrm{PA(M)} - \mathrm{IE}(\mathrm{H}^\bullet)\end{aligned} \tag{6}$$

The BDE obtained in this way correspond to thermochemical thresholds and neglect reverse activation energies for the attachment of hydrogen atom to the molecular cation radicals. It should be noted that the BDE calculated according to equation 6 are free of the uncertainties in the $\Delta H_f^\circ(\mathrm{M})$ since the latter term is used to construct both $\Delta H_f^\circ(\mathrm{MH})^+$ and $\Delta H_f^\circ(\mathrm{M})^{+\bullet}$ and so it cancels out. The O—H bond dissociation energies range between 446–477 kJ mol^{-1}, showing that the O—H bond in protonated enones is extremely strong, in fact stronger than any aliphatic C—H bond and comparable to olefinic and aromatic C—H bonds in neutral molecules[7]. This provides a clue to understanding the hydrogen transfer rearrangements that dominate the chemistry of enone radical cations (see Section II.B). Transfer of any carbon-bound hydrogen atom onto the enone oxygen is expected to be exoergic, such that the enone radical cations are metastable with respect to the corresponding distonic isomers and they can exist only if separated by a significant energy barrier. The high exoergicity of the C—H→O—H transfer explains the low regiospecificity of some hydrogen transfer rearrangements, as frequently observed for aliphatic enones (cf. Section II.B).

B. Unimolecular and Collision-induced Decompositions

Protonated propenal **138** is formed upon electron-impact-induced fragmentation of unsaturated and cyclic alcohols where it frequently gives rise to the base peak of the 70 eV mass spectra[34,54]. Metastable **138** decomposes chiefly by losing carbon monoxide and ethylene in a 4:1 ratio, as distinguished by deuterium labelling[98] and high-resolution measurements[99]. A third, minor, decomposition of metastable **138** is due to loss of a fragment of 16 daltons[98] identified as oxygen atom[99]. The losses of ethylene and oxygen distinguish metastable **138** from the thermodynamically more stable propanoyl ion (**141**) which eliminates only carbon monoxide[98]. The transition state energy (E_{TS}) for the loss of carbon monoxide from metastable **138** was determined[100] as $E_{TS} = 880$ kJ mol^{-1} on the ΔH_f° scale, which is in considerable excess over the thermochemical threshold corresponding to $[\mathrm{C_2H_5^+} + \mathrm{CO}]$ (793 kJ mol^{-1})[103,129]. Consistent with this the average kinetic-energy release ($T_{av} = 11 \pm 2$ kJ mol^{-1})[100] in the latter decomposition was found to be substantially higher than with **141** losing carbon monoxide ($T_{av} = 1.2$ kJ mol^{-1}). Ion **141** decomposes to $[\mathrm{C_2H_5^+} + \mathrm{CO}]$ with E_{TS} close to the thermochemical threshold[100].

The loss of carbon monoxide from **138** has been suggested to proceed via a rate-determining isomerization to **141** which would then rapidly decompose to the products[100]. The transition state of highest energy is very likely to belong to hydrogen migration from the oxygen atom onto one of the carbons, by analogy with the behaviour of other oxygen-containing even-electron ions[130]. The possible reaction sequence (Scheme 42) involves 1,4-hydrogen migration in **138** to yield **139** which then undergoes facile isomerization[113,130] to **141**. The latter is formed with large excess of vibrational energy $\varepsilon^* \approx 288$ kJ mol^{-1}) and can be expected to decompose very rapidly to the products[100]. The existence of a reverse activation energy in the decarbonylation of **138** also follows from the breakdown curves for $\mathrm{C_3H_5O^+}$ and $\mathrm{C_2H_5^+}$ investigated in a



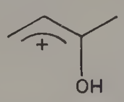
SCHEME 42

photoelectron–photoion study of cyclopropanol and 2-propen-1-ol[103]. Both these C_3H_6O isomers have independently been shown to produce mainly **138** at higher excitation energies[131]. The breaks on the high-energy portions of the curves[103] indicate that the decarbonylation of **138** starts *ca* 3.3 eV above ΔH_f°(cyclopropanol)$^{+\bullet}$, giving $E_{TS} = 868\,\text{kJ mol}^{-1}$ in fair agreement with the value obtained from appearance energy measurements[100]. The experimental T_{av} (*vide supra*) is only slightly higher than the one calculated for $\varepsilon^* = E_{TS} - \Delta H_f^\circ(C_2H_5^+ + CO) = 75$ to $87\,\text{kJ mol}^{-1}$ using the Haney-Franklin formula[132] which gives $T_{av} = 8$–$9\,\text{kJ mol}^{-1}$. This means that the excess vibrational energy in the intermediate **141** is distributed statistically among the internal degrees of freedom, consistent with the rate-determining barrier occurring in the early stage of the isomerization (Scheme 42).

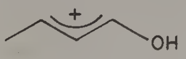
Ion–molecule reactions of **138** have not been studied. There is some indirect evidence, based on critical energy measurements[103,131], showing that attachment of a hydrogen atom to **138** would proceed with non-negligible activation energy.

Collisional activation of stable **138** opens new, higher-energy, decomposition channels in addition to those encountered with metastable **138**. Of particular importance are the dehydrogenation, **138** $\rightarrow C_3H_3O^+$, followed by decarbonylation, $C_3H_3O^+ \rightarrow C_2H_3^+$, and the formation of $C_3H_3^+$ and CH_2OH^+ which all distinguish **138** from other $C_3H_5O^+$ isomers[104,105,108,133].

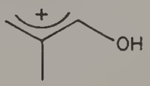
The chemistry in the gas phase of protonated **2**, **3** and **4** (ions **142**, **143** and **144**) has been scrutinized in connection with the role these $C_4H_7O^+$ ions play in decompositions of isomeric $C_5H_{10}O$ radical cations[134–136]. Ions **142**–**144** can clearly be distinguished from each other through their fast decompositions in the ion source following highly exothermic protonation with H_3^+[134]. Ion **142** eliminates methane by analogy with alkane eliminations from protonated saturated ketones[137], while the protonated aldehydes **143** and **144** lose a molecule of dihydrogen. Further differences are observed in the relative abundances of fragments due to eliminations of water, carbon monoxide, ethylene and formaldehyde (Scheme 43). The molecule of ethylene eliminated from **142** contains the proton added by the ionizing medium as established by deuterium labelling[134].



(142)

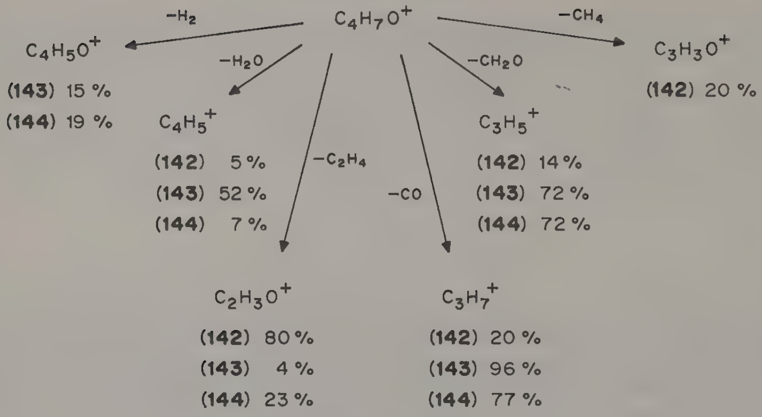


(143)



(144)

Unimolecular decompositions of metastable **142**–**144** proceed via losses of water, ethylene and carbon monoxide[134,135]. Curiously, the loss of water which is a minor fragmentation of unstable **142** becomes more prominent with metastable **142**, whereas with metastable **143** the relative abundance of $[MH - H_2O]^+$ decreases. The elimination

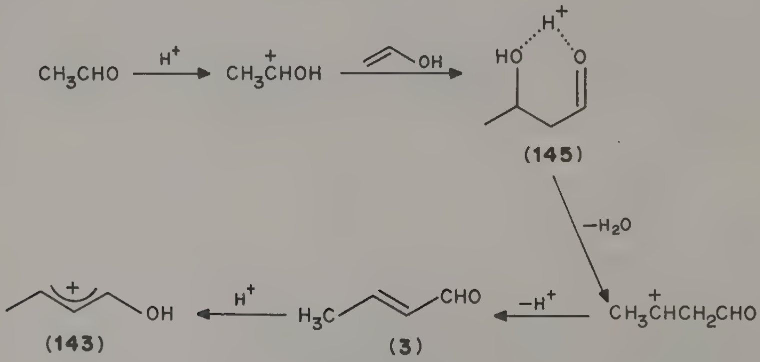


SCHEME 43

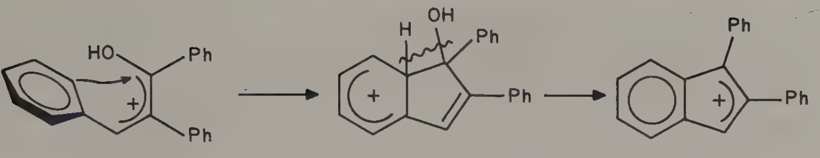
of CO vs. C_2H_4 from metastable **142–144** follows the same line as with decompositions in the ion source[99,134,135].

Protonated butenal **143** has been identified as a product of the gas-phase aldol condensation of acetaldehyde occurring under CI conditions[138]. The condensation was postulated to commence with protonated acetaldehyde attacking a molecule of acetaldehyde enol to give an adduct ion (**145**, Scheme 44). The latter undergoes dehydration and deprotonation yielding 2-butenal **3** which is reprotonated by the acidic medium to give eventually **143**. The yield of this gas-phase aldolization is very low as the relative abundance of **143** amounts to only 0.4% that of CH_3CHOH^+ [138]. As the methane plasma used as acid in this case contained several other reactive ions, it would be interesting to establish whether the C_2 fragment incorporated in **143** comes exclusively from acetaldehyde or from the ionizing medium, too.

Protonated triarylpropenones **63** (see Section II.C) are very stable and show only little fragmentation under conditions of methane CI[50]. The main decompositions are the elimination of Ar^1H, analogous to arene loss from other aryl ketones[143], and the loss of water. The latter fragmentation probably commences with intra-ionic Friedel–Crafts cyclization in **146** followed by proton transfer and heterolysis of the carbon–oxygen bond



SCHEME 44



(146) **(147)**

SCHEME 45

yielding the diphenylindene ion **147** (Scheme 45)[50]. The loss of water from **146** has been observed regardless of the original configuration at the enone double bond, indicating that (*E*, *Z*)-isomerization has taken place prior to the fragmentation.

Gas-phase ion–molecule reactions of **63** with NH_4^+ in ammonia CI involve two competing equilibria due to adduct formation (equation 7) and proton transfer (equation 8)[144]. The $[M + NH_4]^+/[MH]^+$ abundance ratios which are determined by K_a/K_p under a given constant pressure of ammonia were clearly different for the (*E*)- and (*Z*)-isomers of series **63**, with the latter affording higher values[144]. This stereochemical effect was interpreted as being due to higher basicities of (*E*)-**63** compared with (*Z*)-**63**, e.g. $K_p(E) > K_p(Z)$, while tacitly assuming that there was no discrimination in the adduct formation, $K_a(E) \approx K_a(Z)$. The gas-phase basicities of (*E*)- and (*Z*)-1,2,3-triphenylpropenones, though not determined explicitly, have been postulated to be higher than that of ammonia, since no NH_4^+ could be detected after CID of $[M + NH_4]^+$ from both isomers[144]. The latter argument should be accepted with caution in this case. CID of 8 keV $[M + NH_4]^+$ ions of *m/z* 302 would produce NH_4^+ of only *ca* 600 eV kinetic energy, so these slow light ions would be heavily discriminated against protonated **63** (*m/z* 285) due to increased scattering and low transmission and detection efficiency[16], and they might well have escaped detection. The reported $[M + NH_4]^+/[MH]^+$ ratios[144] in fact indicate that (*E*)-1,2,3-triphenylpropenone may be marginally more basic than ammonia[145] while the (*Z*)-isomer is probably less basic.

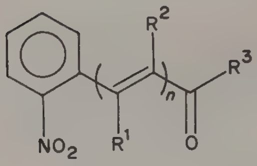
$$M + NH_4^+ \overset{K_a}{\rightleftharpoons} [M + NH_4]^+ \tag{7}$$

$$M + NH_4^+ \overset{K_p}{\rightleftharpoons} [MH]^+ + NH_3 \tag{8}$$

IV. THE CHEMISTRY OF ENONE ANIONS

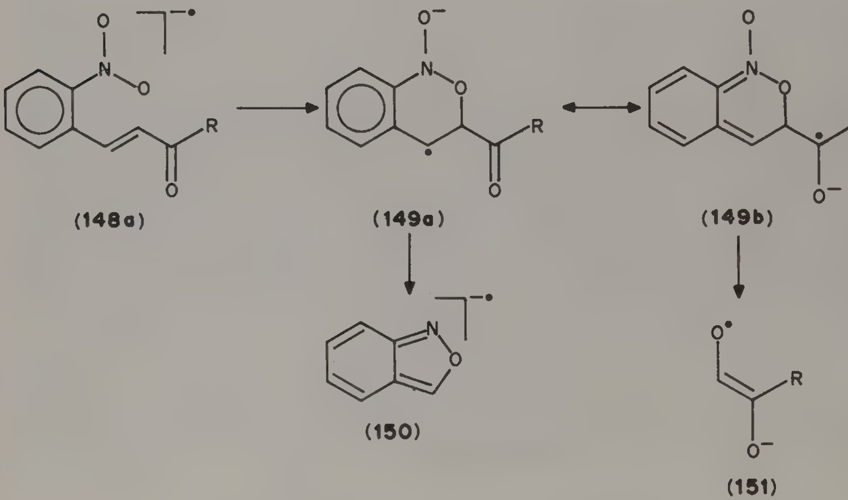
While the gas-phase chemistry of enone positive ions has been studied in depth, its anionic counterpart resembles a terra incognita awaiting exploration[147,148]. Formation of an observable radical anion $[M]^{-\bullet}$ from an organic molecule requires that the latter possess a low-lying LUMO which can accept a thermal electron and keep it until $[M]^{-\bullet}$ is stabilized by collisions with the residual gas[147]. The LUMOs in aliphatic enones are antibonding [e.g. $\varepsilon(3a'') = 1.9$ eV in **1**][118], so rapid decomposition of molecular radical anions can be anticipated, as also observed for saturated aldehydes and ketones[147]. Aryl groups at the enone group provide stabilization to molecular radical anions, such that $[M]^{-\bullet}$ derived from triarylpropenones **63** do not fragment at all under conditions of resonance electron capture[144].

By contrast, complex decompositions have been observed for radical anions of *o*-nitrophenylenones of the type **148**, induced mostly by interactions of the nitro group with the enone functionality[149].

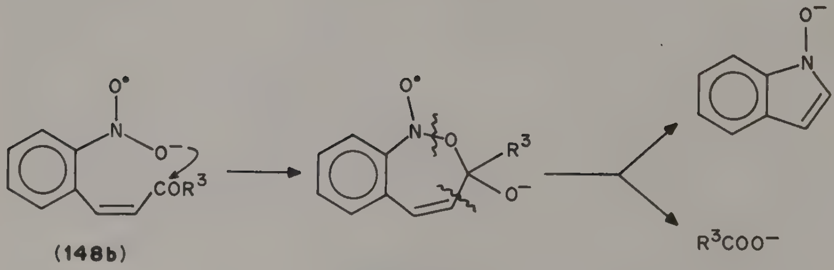


(148)

The nitro group in **148a** attacks the enone α-carbon atom to form the oxazine ring in the intermediate **149** which decomposes by cycloreversion affording the complementary radical anions **150** and **151** (Scheme 46)[149]. The resonance-stabilized[150] radical anions **151** become more abundant with increasing number of double bonds separating the oxygen atoms (trienone > dienone > enone)[149]. Attack by the nitro group oxygen atom at the enone carbonyl group results in the formation of stable carboxylate and hydroxylamine anions (Scheme 47)[149].



SCHEME 46



SCHEME 47

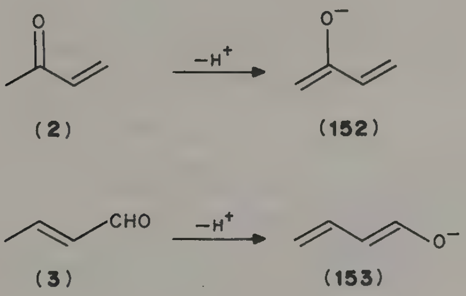
Even-electron anions, $[M-H]^-$, are formed readily from cyclic enones under conditions of CH_4/H_2O negative chemical ionization (NCI) which uses gaseous hydroxyl anion as the base[151]. Steroid enones, e.g. cholest-4-en-3-one, cholesta-3,5-dien-7-one and cholest-4-ene-3,6-dione, give mostly $[M-H]^-$ ions accompanied by low-abundance dehydrogenation products $[M-H-H_2]^-$ and $[M-H-2H_2]^-$ [151]. Interestingly, the non-conjugated cholest-7-en-3-one affords an additional ionic product $[M-H+O-H_2]^-$ at *m/z* 397 which is absent in the NCI mass spectra of the former enones[151].

Monoterpene enones, e.g. pulegone, carvone and perillaldehyde, show only $[M-H]^-$ ions in NCI[152].

Nucleophilic additions to enone systems, e.g. the 1,2- and the Michael addition, are commonplace and synthetically useful reactions in organic chemistry in solution. Analogous ion–molecule reactions in the gas phase of propenal (**1**) with F^- and MeO^- have been examined by theory and experiment[153]. *Ab initio* calculations predicted that **1** should react exothermically with F^- to give products of both 1,2- and 1,4-conjugate addition. The products were calculated to be of comparable stabilities. Due to the exothermicity of the additions the products and the reactants can be expected to exist in equilibrium unless the excessive energy is carried away by collisional deactivation[153]. Ion-cyclotron-resonance experiments using CF_3O^- and $[F^- \cdots HOMe]$ as fluoride anion sources confirmed that stable $[M+F^-]$ adduct ions can be detected[153]. Ion–molecule reactions of **1** with MeO^- and $[MeO^- \cdots HOMe]$ also afforded stable $[M+MeO]^-$ anions beside other products[153].

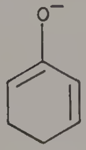
Halide anions (Cl^- and Br^-) add to triarylpropenones **63** under conditions of NCI[144]. The formation of $[M+Cl]^-$ and $[M+Br]^-$ relative to $[M]^{-\bullet}$ was shown to differentiate (*E*)- and (*Z*)-isomers of **63**, with the later affording the adduct ions in higher abundance[144]. Substituent effects on the relative rates of halide addition in **63** were in line with the nucleophilic character of the reaction[144].

Although the gas-phase chemistry of enone anions is still in its infancy, some future trends and developments can be envisaged or proposed. The facile formation of enone $[M—H]^-$ ions opens access to isomeric dienolates **152** and **153** (Scheme 48) which are direct analogues of the much studied electron-rich dienes[154]. Several questions immediately arise concerning the gas-phase chemistry of **152** and **153**. Will these anions undergo cycloadditions with suitable dienophiles in the gas phase[155]? What decompositions do they undergo following collisional activation[156]? What is the reactivity of the radicals prepared from these anions upon neutralization[157,158], if compared with the corresponding radical cations[18,19]? Further, can cyclic dienolates **154** and **155** be

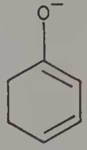


SCHEME 48

prepared separately and distinguished in the gas phase? All these questions, and many others, can be answered with the help of the present state-of-the-art mass-spectrometry techniques.



(154)



(155)

V. ACKNOWLEDGEMENTS

This chapter would not have been completed without the help and support of friends and colleagues to whom I feel deeply indebted. Special thanks are due to Dr R. Houriet of Ecole Polytechnique Fédérale, Lausanne, and Dr G. Bouchoux of Ecole Polytechnique, Palaiseau, for supplying me with unpublished data on protonation as well as critically revised data from other sources. I am very grateful to Dr I. S. Doležal of EMPA, Zürich, and Dr T. Kovář of the University of Erlangen for sending the literature unavailable to me at the time of writing this work. The support and encouragement provided by Professors H. Schwarz and F. W. McLafferty is also gratefully acknowledged.

VI. REFERENCES

1. Y. S. Sheikh, A. M. Duffield and C. Djerassi, *Org. Mass Spectrom.*, **4**, 273 (1970).
2. A. L. Bowles, E. F. H. Brittain and W. O. George, *Org. Mass Spectrom.*, **2**, 809 (1969).
3. J. L. Holmes, J. K. Terlouw and P. C. Burgers, *Org. Mass Spectrom.*, **15**, 140 (1980).
4. 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.*, **69**, 279 (1969).
5. A. Katrib and J. W. Rabalais, *J. Phys. Chem.*, **77**, 2358 (1973).
6. H. M. Rosenstock, K. Draxl, B. W. Steiner and J. T. Herron, *J. Phys. Chem. Reference Data*, **6** (1977), Suppl. No 1.
7. D. M. Golden and S. W. Benson, *Chem. Rev.*, **69**, 125 (1969).
8. R. Krässig, D. Reinke and H. Baumgärtel, *Ber. Bunsenges. Phys. Chem.*, **78**, 425 (1974).
9. H. W. Jochims, W. Lohr and H. Baumgärtel, *Chem. Phys. Lett.*, **54**, 594 (1978).
10. R. D. Levin and S. G. Lias, Ionization Potential and Appearance Potential Measurements, 1971–1981, NSRDS, U.S. Department of Commerce, National Bureau of Standards (1982).
11. J. K. Terlouw, W. Heerma, J. L. Holmes and P. C. Burgers, *Org. Mass Spectrom.*, **15**, 582 (1980).
12. J. B. Pedley and J. Rylance, *Sussex N.P.L Computer Analyzed Thermochemical Data; Organic and Organometallic Compounds*, University of Sussex, Sussex, 1977.
13. P. Masclet and G. Mouvier, *J. Electron Spectrosc. Relat. Phenom.*, **14**, 77 (1978).
14. H. Hommes and J. K. Terlouw, *Org. Mass. Spectrom*, **14**, 51 (1979).
15. L. Radom, P. C. Hariharan, J. A. Pople and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **95**, 6531 (1973).
16. F. W. McLafferty (Ed.), *Tandem Mass Spectrometry*, Wiley, New York; 1983.
17. R. G. Cooks, J. H. Beynon, R. M. Caprioli and G. R. Lester, *Metastable Ions*, Elsevier, Amsterdam, 1973.
18. F. Tureček, Z. Havlas, F. Maquin, N. Hill and T. Gäumann, *J. Org. Chem.*, **51**, 4061 (1986).
19. F. Tureček, F. Maquin, N. Hill, D. Stahl and T. Gäumann, *Org. Mass. Spectrom.*, **23**, 91 (1988).
20. A. Maccoll, *Org. Mass Spectrom.*, **15**, 109 (1980).
21. H. Bosshardt and M. Hesse, *Angew. Chem.*, **86**, 256 (1974).
22. C. C. Van de Sande, C. De Meyer and A. Maquestiau, *Bull. Soc. Chim. Belg.*, **85**, 79 (1976).
23. F. W. McLafferty, R. Kornfeld, W. F. Haddon, K. Levsen, I. Sakai, P. F. Bente III, S.-C. Tsai and H. D. R. Schuddemage, *J. Am. Chem. Soc.*, **95**, 3886 (1973).
24. H. Schwarz, *Top. Curr. Chem.*, **97**, 1 (1981).

25. R. J. Liedtke, A. F. Gerrard, J. Diekman and C. Djerassi, *J. Org. Chem.*, **37**, 776 (1972).
26. K. Ogura, T. Iihama, S. Kiuchi, T. Kajiki, O. Koshikawa, K. Takahashi and H. Iida, *J. Org. Chem.*, **51**, 700 (1986).
27. H. Schwarz, B. Richter and F. Bohlmann, *Org. Mass Spectrom.*, **10**, 1125 (1975).
28. J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 734, 736, 738 (1976).
29. G. G. Attardo and R. T. B. Rye, *Org. Mass Spectrom.*, **19**, 241 (1984).
30. J. R. Dias, Y. M. Sheikh and C. Djerassi, *J. Am. Chem. Soc.*, **94**, 473 (1972).
31. A. F. Thomas, B. Willhalm and R. Müller, *Org. Mass Spectrom.*, **2**, 223 (1969).
32. R. G. Cooks, *Org. Mass Spectrom.*, **2**, 481 (1969).
33. J. Ronayne, D. H. Williams and J. H. Bowie, *J. Am. Chem. Soc.*, **88**, 4980 (1966).
34. E. Stenhagen, S. Abrahamsson and F. W. McLafferty, *Registry of Mass Spectral Data*, Vol. 2, Wiley, New York, 1974.
35. E. Rouvier, H. Medina and A. Cambon, *Org. Mass Spectrom.*, **11**, 800 (1976).
36. B. Schaldach, B. Grotemeyer, J. Grotemeyer and H.-F. Grützmacher, *Org. Mass Spectrom.*, **16**, 410 (1981).
37. B. Schaldach and H.-F. Grützmacher, *Int. J. Mass Spectrom. Ion Phys.*, **31**, 257 (1979).
38. B. Schaldach and H.-F. Grützmacher, *Int. J. Mass Spectrom. Ion Phys.*, **31**, 271 (1979).
39. A. Arcoria, F. P. Ballisteri, G. Musumarra and S. Occhipinti, *Org. Mass. Spectrom.*, **16**, 54 (1981).
40. M. Ricard and M. Simalty, *Org. Mass Spectrom.*, **17**, 397 (1982).
41. R. Mentlein and E. Vowinkel, *Org. Mass Spectrom.*, **19**, 330 (1984).
42. K. Biemann, *Mass Spectrometry*, McGraw-Hill, New York, 1962.
43. I. N. Nazarov, *Usp. Khim.*, **18**, 377 (1949); *Chem. Abstr.*, **45**, 6572 (1951).
44. C. Santelli-Rouvier and M. Santelli, *Synthesis*, 429 (1983).
45. C. Van de Sande, J. W. Serum and M. Vandewalle, *Org. Mass Spectrom.*, **6**, 1333 (1972).
46. R. H. Nobes, W. J. Bouma and L. Radom, *J. Am. Chem. Soc.*, **105**, 309 (1983).
47. H. Schwarz, *Top. Curr. Chem.*, **73**, 232 (1978).
48. R. A. W. Johnstone, Senior Reporter, *Specialist Periodical Report-Mass Spectrometry*, Vol. 5, The Chemical Society, London, 1979.
49. C. C. Van de Sande and M. Vandewalle, *Bull. Soc. Chim. Belg.*, **82**, 775 (1973).
50. K. P. Madhusudanan, S. Mittal, S. Durani and R. S. Kapil, *Org. Mass Spectrom.*, **20**, 215 (1985).
51. R. L. N. Harris, F. Komitsky and C. Djerassi, *J. Am. Chem. Soc.*, **89**, 4765 (1967).
52. A. L. Burlingame, C. Fenselau, W. J. Richter, W. G. Dauben, G. W. Shaffer and N. D. Vietmeyer, *J. Am. Chem. Soc.*, **89**, 3346 (1967).
53. R. H. Shapiro, J. M. Wilson and C. Djerassi, *Steroids*, **1**, 1 (1963).
54. H. Budzikiewicz, C. Djerassi and D. H. Williams, *Mass Spectrometry of Organic Compounds*, Holden-Day, San Francisco, 1967, pp. 151–155.
55. C. Fenselau, W. G. Dauben, G. W. Shaffer and N. D. Vietmeyer, *J. Am. Chem. Soc.*, **91**, 112 (1969).
56. W. G. Dauben, G. W. Shaffer and N. D. Vietmeyer, *J. Org. Chem.*, **33**, 4060 (1968).
57. F. Tureček and V. Hanuš, *Mass Spectrom. Rev.*, **3**, 85 (1984).
58. H. Egger, *Monatsh. Chem.*, **97**, 1290 (1966).
59. F. Tureček and V. Hanuš, in *Advances in Mass Spectrometry 1985* (Ed. J. F. J. Todd), Wiley, New York, 1986, p. 215.
60. J. H. Bowie, *Aust. J. Chem.*, **19**, 1619 (1966).
61. J. K. Terlouw, P. C. Burgers and J. L. Holmes, *J. Am. Chem. Soc.*, **101**, 225 (1979).
62. J. L. Holmes, J. K. Terlouw, P. C. Vijfhuizen and C. A'Campo, *Org. Mass Spectrom.*, **14**, 204 (1979).
63. P. C. Burgers, J. L. Holmes, F. P. Lossing, A. A. Mommers, F. R. Povel and J. K. Terlouw, *Can. J. Chem.*, **60**, 2246 (1982).
64. A. Maquestiau, P. Pauwels, R. Flammang, P. Lorenczak and C. Wentrup, *Spectroscopy Int. J.*, **3**, 173 (1984).
65. F. Tureček, Z. Havlas, F. Maquin and T. Gäumann, *Helv. Chim. Acta*, **69**, 683 (1986).
66. J. E. Baldwin and M. C. McDaniel, *J. Am. Chem. Soc.*, **90**, 6118 (1968).
67. Z. V. Zaretskii, *Mass Spectrometry of Steroids*, Wiley, New York, 1976, p. 26.
68. H. Budzikiewicz, C. Djerassi and D. H. Williams, *Structure Elucidation of Natural Products by Mass Spectrometry*, Vol. 2, Holden-Day, San Francisco, 1964.
69. N. L. Holder and B. Fraser-Reid, *Tetrahedron*, **29**, 4077 (1973).

70. F. Bohlmann, C.-H. Fischer, J. Förster, W. Mathar and H. Schwarz, *Org. Mass Spectrom.*, **10**, 1141 (1975).
71. J. K. MacLeod and C. Djerassi, *J. Am. Chem. Soc.*, **88**, 1840 (1966).
72. F. Borchers, K. Levsen, C. B. Theissling and N. M. M. Nibbering, *Org. Mass Spectrom.*, **12**, 746 (1977).
73. A. Maquestiau, R. Flammang, P. Pauwels, P. Vallet and P. Meyrant, *Org. Mass Spectrom.*, **17**, 643 (1982).
74. K. B. Tomer and C. Djerassi, *Tetrahedron*, **29**, 3491 (1973).
75. M. K. Hoffman, M. D. Friesen and G. Richmond, *Org. Mass Spectrom.*, **12**, 150 (1977).
76. J. K. Holroyde, A. F. Orr and V. Thaler, *J. Chem. Soc., Perkin Trans. 1*, 1490 (1978).
77. M. M. Green, *Tetrahedron*, **36**, 2687 (1980).
78. F. W. McLafferty, *Anal. Chem.*, **31**, 82 (1959).
79. S. Meyerson, I. Puskas and E. K. Fields, *J. Am. Chem. Soc.*, **88**, 4974 (1966).
80. T. H. Kinstle, O. L. Chapman and M.-T. Sung, *J. Am. Chem. Soc.*, **90**, 1227 (1968).
81. O. L. Chapman, H. G. Smith, R. W. King, D. J. Pasto and M. R. Stoner, *J. Am. Chem. Soc.*, **85**, 2031 (1963).
82. J. Mattay, *Angew. Chem.*, **99**, 849 (1987).
83. M. M. Bursey, L. R. Dusold and A. Padwa, *Tetrahedron Lett.*, 2649 (1967).
84. A. Padwa and R. Hartman, *J. Am. Chem. Soc.*, **88**, 1518 (1966).
85. See footnote 17 in: H. Hart, S.-M. Chen, S. Lee, D. L. Ward and W.-J. H. Kung, *J. Org. Chem.*, **45**, 2091 (1980).
86. H. Hart, C.-T. Peng and E.-M. Shih, *J. Org. Chem.*, **42**, 3635 (1977).
87. G. Maier, S. Pfrien, U. Schäfer and R. Matusch, *Angew. Chem.*, **90**, 552 (1978).
88. H. Bock, B. Roth and G. Maier, *Angew. Chem.*, **92**, 213 (1980).
89. M. M. Bursey, R. D. Rieke, T. A. Elwood and L. R. Dusold, *J. Am. Chem. Soc.*, **90**, 1557 (1968).
90. M. M. Bursey and T. A. Elwood, *Org. Mass Spectrom.*, **1**, 531 (1968).
91. M. M. Bursey and T. A. Elwood, *J. Am. Chem. Soc.*, **91**, 3812 (1969).
92. T. A. Elwood and M. M. Bursey, *Org. Mass Spectrom.*, **1**, 537 (1968).
93. M. M. Bursey, T. A. Elwood and P. F. Rogerson, *Tetrahedron*, **25**, 605 (1969).
94. M. K. Hoffman, T. A. Elwood, P. F. Rogerson, J. M. Tesarek, M. M. Bursey and D. Rosenthal, *Org. Mass Spectrom.*, **3**, 891 (1970).
95. W. Blum, H. Kurreck, W. J. Richter, H. Schwarz and H. Thies, *Angew. Chem.*, **95**, 59 (1983).
96. N. J. Turro, *Modern Molecular Photochemistry*. The Benjamin/Cummings Publ. Co., Menlo Park, 1978, pp. 473–525.
97. H. M. Rosenstock, M. B. Wallenstein, A. L. Wahrhaftig and H. Eyring, *Proc. Natl. Acad. Sci. U.S.A.*, **38**, 667 (1952).
98. T. J. Mead and D. H. Williams, *J. Chem. Soc.* (*B*), 1654 (1971).
99. P. Krenmayr, *Monatsh. Chem.*, **106**, 925 (1975).
100. R. D. Bowen and D. H. Williams, *J. Chem. Res.* (*S*), 482 (1978).
101. D. G. I. Kingston and H. P. Tannenbaum, *Org. Mass Spectrom.*, **10**, 263 (1975).
102. G. Bouchoux and Y. Hoppilliard, *Int. J. Mass Spectrom. Ion Phys.*, **43**, 63 (1982).
103. R. Bombach, J. Dannacher, E. Honegger and J.-P. Stadelman, *Chem. Phys.*, **82**, 459 (1983).
104. C. E. Hudson and D. J. McAdoo, *Org. Mass Spectrom.*, **17**, 366 (1982).
105. G. Bouchoux, Y. Hopilliard, R. Flammang, A. Maquestiau and P. Meyrant, *Org. Mass Spectrom.*, **18**, 340 (1983).
106. D. J. McAdoo and C. E. Hudson, *Org. Mass Spectrom.*, **18**, 466 (1983).
107. D. J. McAdoo, C. E. Hudson and D. N. Witiak, *Org. Mass Spectrom.*, **14**, 350 (1979).
108. J. J. Zwinselman and A. G. Harrison, *Org. Mass Spectrom.*, **19**, 573 (1984).
109. J. C. Traeger and D. J. McAdoo, *Int. J. Mass Spectrom. Ion Processes*, **68**, 35 (1986).
110. J. Hegedüs-Vajda and A. G. Harrison, *Int. J. Mass Spectrom. Ion Phys.*, **30**, 293 (1979).
111. D. H. Aue and M. T. Bowers, in *Gas Phase Ion Chemistry*, Vol. 2, Chapter 9, Academic Press, New York, 1979.
112. G. Bouchoux, J. P. Flament and Y. Hoppilliard, *Nouv. J. Chim.*, **7**, 385 (1983).
113. G. Bouchoux and Y. Hoppiliard, *J. Mol. Struct.* (*Theochem*), **104**, 365 (1983).
114. K. Raghavachari, R. A. Whiteside, J. A. Pople and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **103**, 5649 (1981).
115. G. Bouchoux, F. Djazi, R. Houriet and E. Rolli, *Org. Mass Spectrom.*, submitted.

116. J. C. Traeger, *Org. Mass Spectrom.*, **20**, 223 (1983).
117. M. Klessinger and E. Gunkel, *Tetrahedron*, **34**, 3591 (1978).
118. C. E. Dykstra, *J. Am. Chem. Soc.*, **98**, 7182 (1976).
119. G. Bouchoux, Y. Hoppilliard, P. Jaudon and R. Houriet, *Org. Mass Spectrom.*, **19**, 394 (1984).
120. G. Bouchoux, Y. Hoppilliard and R. Houriet, *Nouv. J. Chim.*, **11**, 225 (1987).
121. A.-M. Dommröse and H.-F. Grützmacher, *Int. J. Mass Spectrom. Ion Processes*, **76**, 95 (1987).
122. H.-F. Grützmacher, A.-M. Dommröse and U. Neuert, *Org. Mass Spectrom.*, **16**, 279 (1981).
123. A. Maccoll, *Org. Mass Spectrom.*, **16**, 297 (1981).
124. J. L. Holmes, M. Fingas and F. P. Lossing, *Can. J. Chem.*, **59**, 80 (1981).
125. J. L. Holmes and F. P. Lossing, *Can. J. Chem.*, **60**, 2365 (1982).
126. S. G. Lias, J. F. Liebman and R. D. Levin, *J. Phys. Chem. Ref. Data*, **13**, 695 (1984).
127. G. Bouchoux and R. Houriet, *Tetrahedron Lett.*, **25**, 5755 (1984).
128. R. Houriet, J. Vogt and E. Haselbach, *Chimia*, **34**, 277 (1980).
129. H. M. Rosenstock, R. Buff, M. A. Almoster-Ferreira, S. G. Lias, A. C. Parr, R. L. Stockbauer and J. L. Holmes, *J. Am. Chem. Soc.*, **104**, 2337 (1982).
130. R. H. Nobes and L. Radom, *Org. Mass Spectrom.*, **21**, 407 (1986).
131. F. Tureček, V. Hanuš and T. Gäumann, *Int. J. Mass Spectrom. Ion Processes*, **69**, 217 (1986).
132. M. A. Haney and J. L. Franklin, *J. Chem. Phys.*, **48**, 4093 (1968).
133. F. W. McLafferty, T. Wachs, C. Köppel, P. P. Dymerski and F. M. Bockhoff, *Adv. Mass Spectrom.*, **7**, 1231 (1978).
134. K. R. Laderoute, J. J. Zwinselman and A. G. Harrison, *Org. Mass Spectrom.*, **20**, 25 (1985).
135. A. G. Harrison, N. E. Middlemiss and J. Hegedüs-Vajda, *Adv. Mass Spectrom.*, **8**, 853 (1980).
136. J. J. Zwinselman, N. M. M. Nibbering, N. E. Middlemiss, J. Hegedüs-Vajda and A. G. Harrison, *Int. J. Mass Spectrom. Ion Phys.*, **38**, 163 (1981).
137. A. G. Harrison, *Chemical Ionization Mass Spectrometry*, CRC Press, Boca Raton, 1979.
138. C. Wesdemiotis and F. W. McLafferty, *Org. Mass Spectrom.*, **16**, 381 (1981).
139. A. Schweig, H. Vermeer and U. Weidner, *Chem. Phys. Lett.*, **26**, 229 (1974).
140. W.-C. Tam, D. Yee and C. E. Brion, *J. Electron Spectrosc. Relat. Phenom.*, **4**, 77 (1974).
141. G. Hentrich, E. Gunkel and M. Klessinger, *J. Mol. Struct.*, **21**, 231 (1974).
142. G. Bouchoux, private communication, October 1987.
143. J. Michnowicz and B. Munson, *Org. Mass Spectrom.*, **6**, 283 (1972).
144. K. P. Madhusudanan, S. Mittal, S. Durani and R. S. Kapil, *Org. Mass Spectrom.*, **20**, 323 (1985).
145. C. Guenat, R. Houriet, D. Stahl and F. J. Winkler, *Helv. Chim. Acta*, **68**, 1647 (1985).
146. T. T. Tidwell, *Angew. Chem.*, **96**, 16 (1984).
147. H. Budzikiewicz, *Angew. Chem.*, **93**, 635 (1981).
148. J. H. Bowie, *Mass Spectrom. Rev.*, **3**, 161 (1984).
149. J. H. Bowie and S. Janposri, *J. Chem. Soc., Perkin Trans. 2*, 1656 (1976).
150. A. Hadjiantoniou, L. G. Christophorou and J. G. Carter, *J. Chem. Soc., Faraday Trans. 2*, 1691, 1704, 1713 (1973).
151. T. A. Roy, F. H. Field, Y. Y. Lin and L. L. Smith, *Anal. Chem.*, **51**, 272 (1979).
152. A. P. Bruins, *Anal. Chem.*, **51**, 967 (1979).
153. G. Klass, J. C. Sheldon and J. H. Bowie, *J. Chem. Soc., Perkin Trans. 2*, 1337 (1983).
154. S. Danishefsky, T. Kitahara, P. F. Schude and S. J. Etheredge, *J. Am. Chem. Soc.*, **98**, 3027 (1976).
155. G. S. Groenewold and M. L. Gross, *J. Am. Chem. Soc.*, **106**, 6569 (1984).
156. J.-C. Tabet, I. Hanna and M. Fétizon, *Org. Mass Spectrom.*, **20**, 61 (1985).
157. C. Wesdemiotis and F. W. McLafferty, *Chem. Rev.*, **87**, 485 (1987).
158. H. Schwarz, *Angew. Chem.*, **99**, 829 (1987).

The Chemistry of Enones
Edited by S. Patai and Z. Rappoport

CHAPTER 7

Synthesis of enones

CHACHANAT THEBTARANONTH and YODHATHAI THEBTARANONTH
Department of Chemistry, Faculty of Science, Mahidol University, Rama 6 Road, Bangkok 10400, Thailand

---

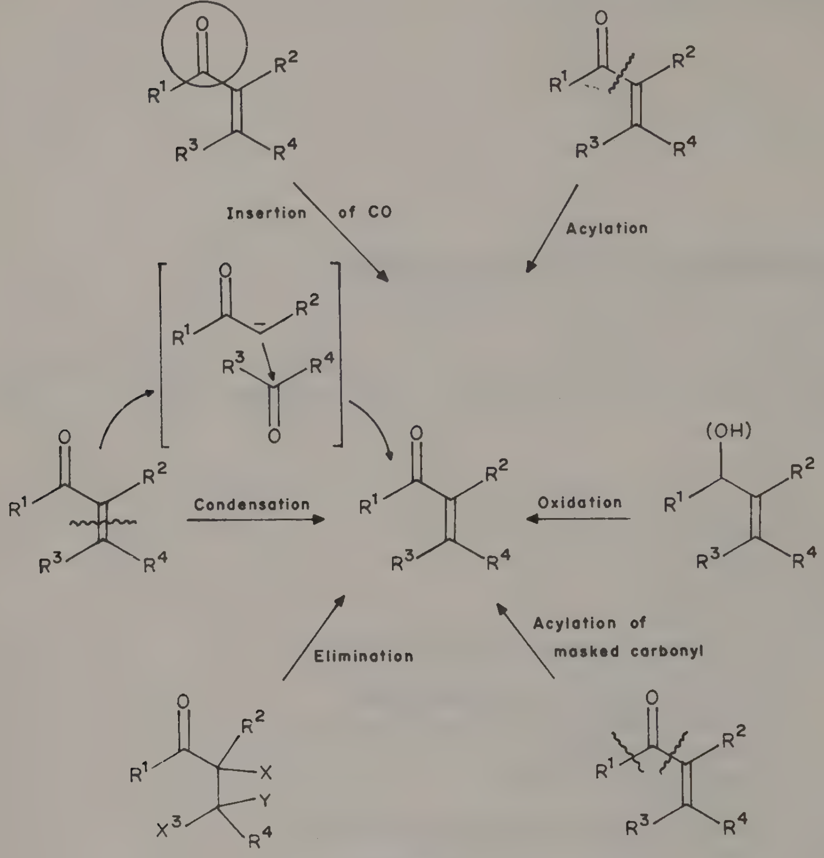
I. INTRODUCTION

The rapid development of enone synthesis in the last decade has resulted from intensive efforts to synthesize biologically important natural products and their derivatives, many of which contain the enone functionality. Scheme 1 summarizes the major routes to the enone system. These are discussed consecutively in Sections II–VI, while methods that fall outside these routes are treated in Section VII and the synthesis of optically active enones in Section VIII of the chapter.

II. CONDENSATION

The most common route to enones is certainly via the aldol condensation. Although discovered a long time ago, the reaction continues to be successfully employed today, frequently in the annelation process to form five- or six-membered cycloalkenones of which there are several good reviews[1–3].

The first report of the 'classical' annelation reaction was by Rapson and Robinson[4] (hence the name 'Robinson annelation') and involves base-catalyzed Michael addition of

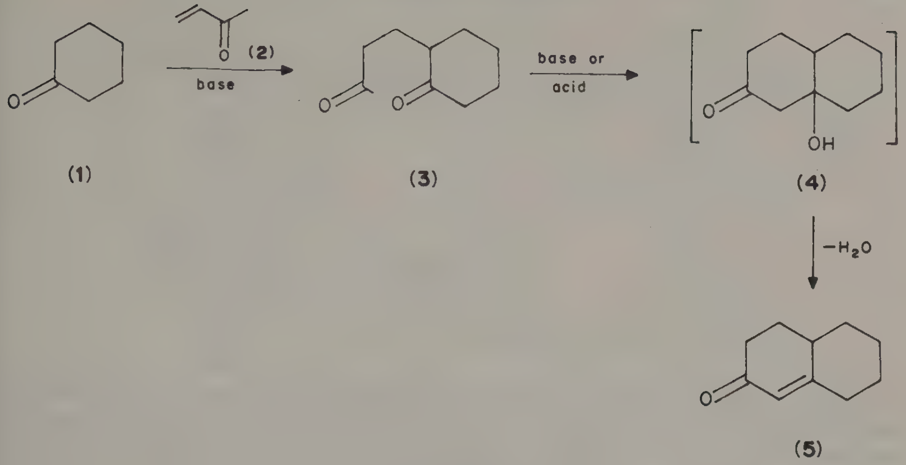


SCHEME 1

an active methylene group of ketone **1** to methyl vinyl ketone **2**, followed by the base- or acid-catalyzed aldol condensation of **3**. The sequence is represented in Scheme 2.

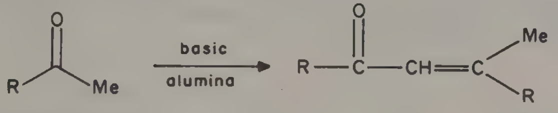
This sequence, however, is not without problems in many cases, especially low yields because of polymerization of the Michael acceptor (e.g. **2**), and lack of control of the direction of enolate formation in unsymmetrical ketones. Hence the sequence has been the target of constant development which has greatly improved the use of this 'classical' reaction today. Modifications of the Robinson annelation range from *in situ* generation of the alkyl vinyl ketone[5–7] to asymmetric Michael addition leading to optically active products[8].

Besides development of the Robinson annelation, which is an intramolecular aldol condensation, much attention has also been paid to the synthesis of enones by intermolecular aldol condensation, self-condensation and cross-condensation inclusive. Although the self-condensation of ketones is well known[9], the device discovered by Muzart[10], using basic alumina as the catalyst, offers a novel alternative. By simply absorbing the liquid ketones (ketones which are liquid at room temperature) on basic

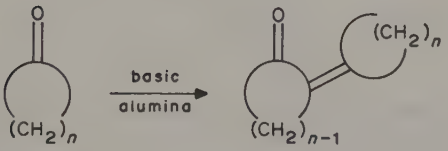


SCHEME 2

alumina for a few days, the corresponding enones can be obtained, while solid ketones require heating at 80 °C for one or two days.



(6) (7)

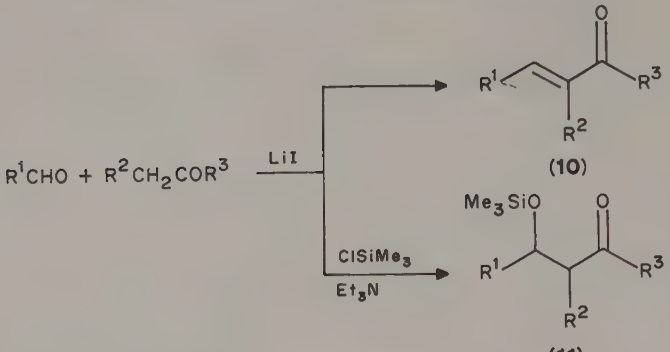


(8) (9)

The method, however, has certain disadvantages: first, although product yields are reasonable, the percentage of conversion is rather low, and a large amount of starting material is recovered (although it can be recycled); second, the reaction is very slow or completely fails when hindered ketones are employed. For example, the self-condensations of benzyl methyl ketone and phenyl propyl ketone are very slow.

Apart from the growing use of Lewis acids, especially titanium(IV) chloride, for promoting aldol condensation[11], there is available a technique based on the use of anhydrous lithium iodide, an extremely mild reagent for effecting cross aldol condensation between alkyl ketones and a variety of enolizable and non-enolizable aldehydes. The method employs lithium iodide in ether, tetrahydrofuran or benzene, and gives α,β-unsaturated ketones in yields of 70–90% according to the following equations[12].

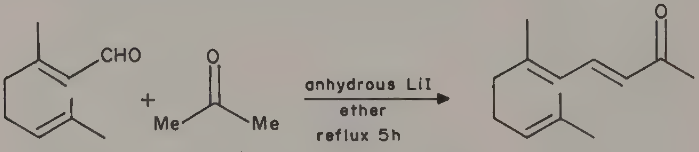
Several important facts about this reaction, described by McKervey and coworkers[12], are as follows: (i) if carried out in the presence of chlorotrimethylsilane and triethylamine, the reaction gives ketol trimethylsilyl ether **11**; (ii) acyclic methyl ketones react almost



(10)

(11)

exclusively at the methyl carbon, for example, 2-butanone condenses with benzaldehyde almost exclusively at the terminal carbon, and competition experiments between equimolar amounts of 2-butanone and 3-pentanone result in more than 90% of the product from 2-butanone; (iii) yields of condensation products from methyl ketones and enolizable aldehydes (or enolizable α,β-unsaturated aldehydes) are superior to those obtained from conventional acid- or base-catalyzed reactions; citral **12** and acetone, for example, give pseudoionone **13** in 85% yield; (iv) the role of LiI as catalyst is unique, the use of LiCl, LiBr, NaI or KI as substitutes having all failed. Furthermore, the addition of crown ether which can complex with the lithium ion also destroys the catalytic effect. Hence the lithium ion is apparently vital for the success of the condensation, and its role will be discussed later in more detail.



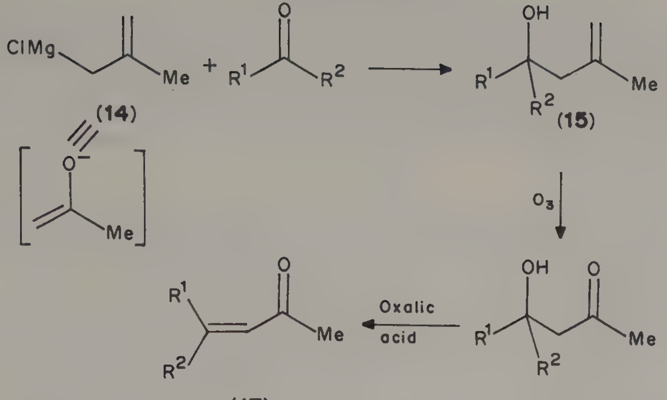
(12)

(13)

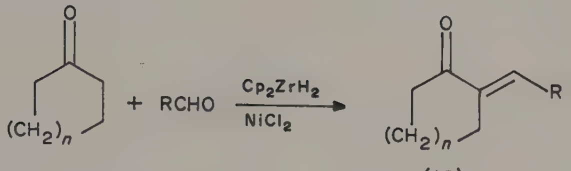
It is common knowledge that enolate addition to hindered ketones is difficult to achieve, presumably due to unfavourable equilibria for these reversible reactions. Likewise, addition to readily enolizable ketones also often fails, due to competitive kinetically-preferred proton transfer. One solution to these problems is provided by the use of methallyl magnesium chloride **14** as the acetone enolate synthon. This reagent cleanly overcomes the above difficulties and adds efficiently to ketones to give **15** in high yield, regardless of the nature of R^1 and R^2, which can be any alkyl substituent, even hindered groups such as *i*-Pr and *t*-Bu[13].

A recent discovery is that dicyclopentadienylzirconium dihydride ($Cp_2ZrH_2, Cp = C_5H_5$), first prepared by Wailes and Weigold[14], catalyzes hydrogen transfer from alcohol to carbonyl compound, i.e. simultaneously oxidizes the alcohol and reduces the carbonyl compound[15]. The same group of workers[16] then found that the zirconocene dihydride also effectively catalyzes the cross aldol condensation of ketones when used in conjunction with nickel chloride in equal amounts of 0.02 equivalents at 130 °C without solvent, giving the cross condensation product **18** in fair to substantial yields.

This catalyst system is also able to effect condensation between ketones and alcohols to give 2-substituted cycloalkenones **19**. Therefore, by using commercially available 3-methylcyclopentanone **20** and pentanol as starting materials, dihydrojasmone **21** can be synthesized in one step in 35% yield, albeit accompanied by 8% of the regioisomer **22**.

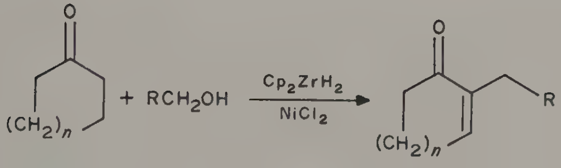


(14) (15) (16) (17)

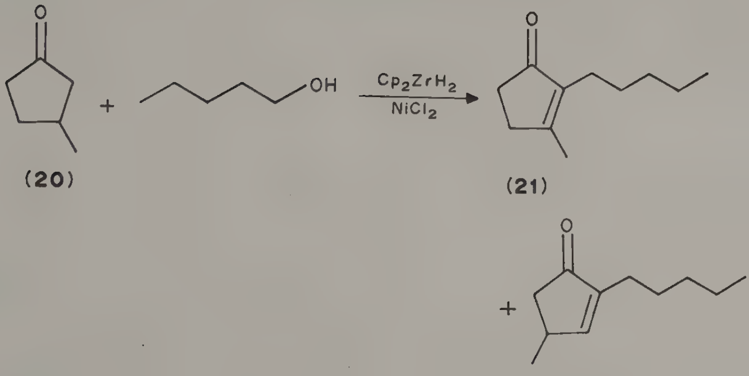


(18)

$n = 1, 2$ R=H, alkyl

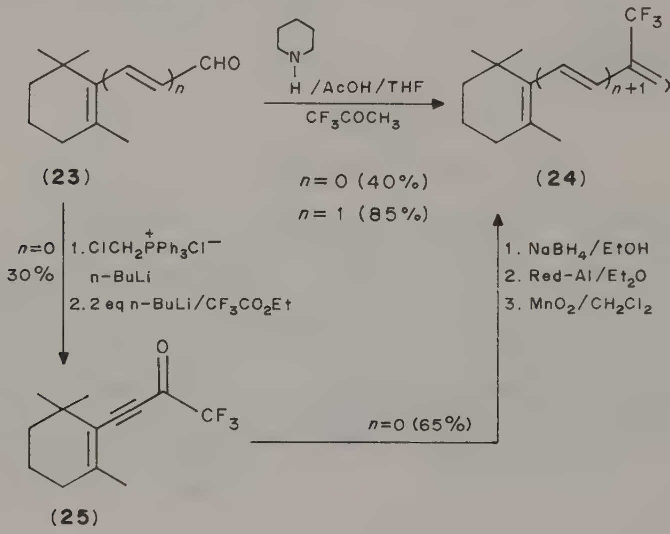


(19)

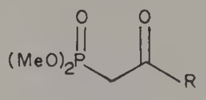


(20) (21) (22)

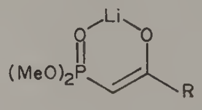
In recent years fluorine has not only found common usage in NMR spectroscopy, but is increasingly utilized as a label for probing structural information and mechanistic details of bioorganic molecules and their processes. Isoprenoid enones such as **24** with trifluoromethyl labels can be synthesized directly by piperidine–acetic acid catalyzed aldol condensation between the corresponding aldehyde **23** and trifluoroacetone[17], or, alternatively, via manipulation of a preformed trifluoromethyl acetylenic ketone **25**[18,19].



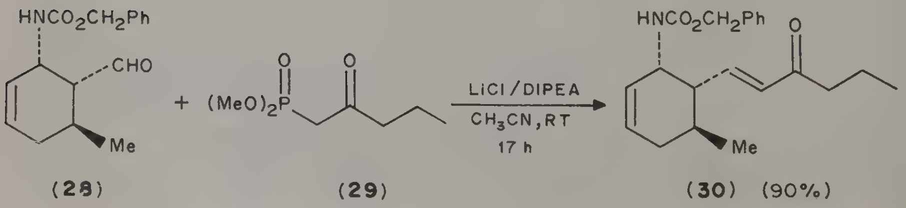
Condensations between carbonyl compounds and phosphonates (Horner–Wadsworth–Emmons reaction) provide another good method for the preparation of enones, as is evident from several reports[20–22]. Moreover, the method is further enhanced by the subsequent discovery[23] that, in the presence of a lithium salt, the phosphonate **26** can be easily deprotonated by an amine such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or diisopropylethylamine (DIPEA), most likely because Li$^+$ forms a tight complex with the carbanion derived from **26** as shown in **27**, thereby enhancing the acidity of **26**. The use of base-sensitive substrates and reagents in the Horner–Wadsworth–Emmons reaction is thus made possible; for example, aldehyde **28** can be smoothly condensed with **29** in the presence of LiCl/DIPEA (1.2:1) in acetonitrile at room temperature for 17 h to give **30** in 90% yield without epimerization, in contrast to an earlier report[24] using sodium hydride as base.



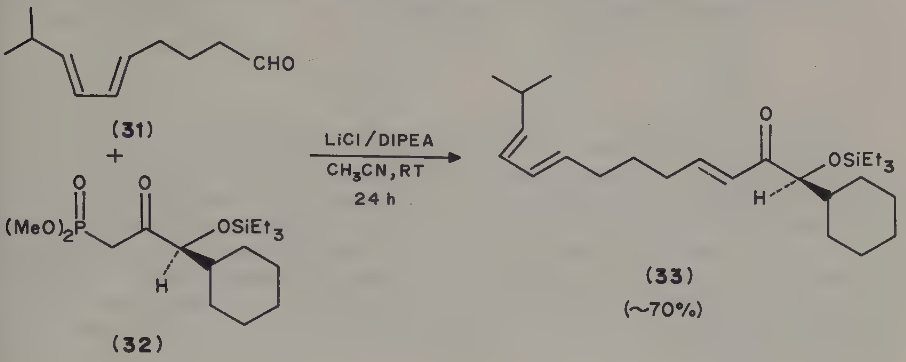
(26)

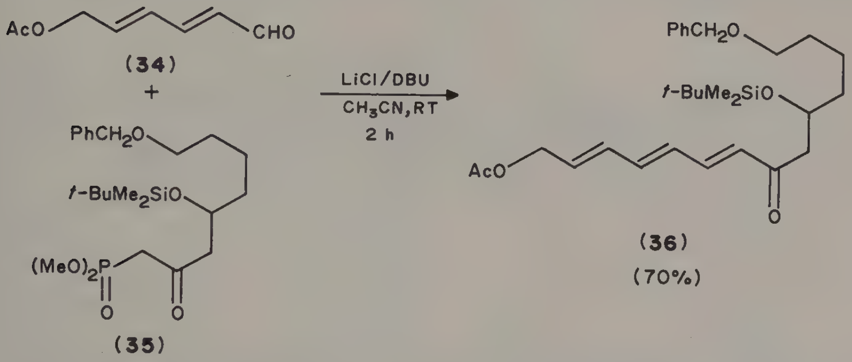


(27)

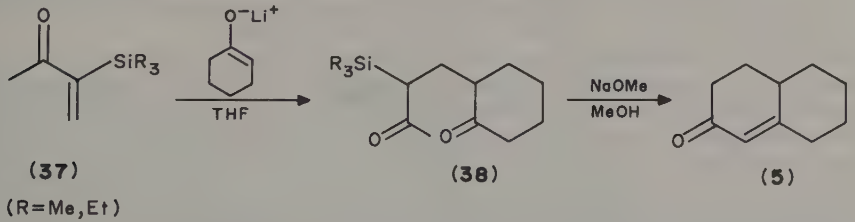


Similarly, phosphonates such as **32** that contain epimerizable centres, or such as **35** that are prone to undergo elimination, can also undergo the condensation under these conditions, without much danger of epimerization, elimination or self-condensation.

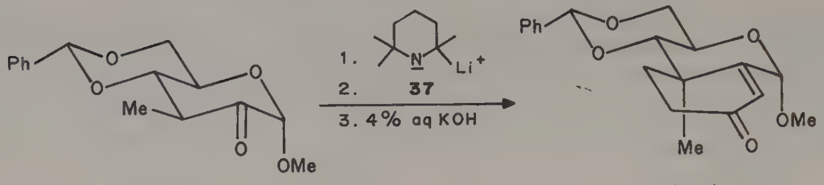




As earlier stated, the Robinson annelation has been continuously developed, the introduction of α-trialkylsilyl vinyl ketone **37** as a substitute for methyl vinyl ketone **2** being one important improvement[25]. For example, **37** adds the lithium enolate of cyclohexanone in THF in a Michael fashion to give **38** which, when heated in 5% sodium methoxide in methanol, undergoes condensation with elimination of the silyl group to yield $\Delta^{1,9}$-2-octalone **5** in 80% overall yield. The advantageous use of **37** will be better appreciated if this result is compared with the < 5% yield from methyl vinyl ketone **2**, reacting with cyclohexanone enolate under the same reaction conditions.

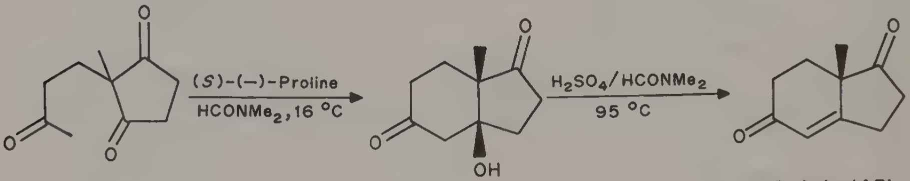


Since its introduction, the α-silyl vinyl ketone has been widely used in the synthesis of cyclic enones[26,27], including the stereospecific annelation[28] of carbohydrate derivative **39** to give **40** as the result of Michael addition at the less hindered β-face of the enolate.

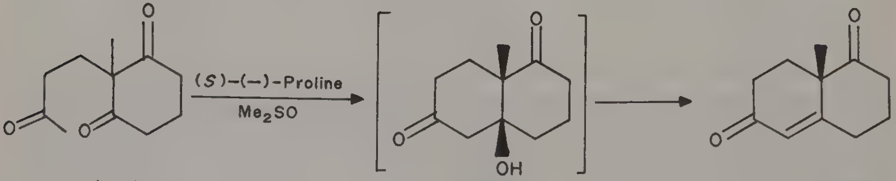


(39) (40)

Applications of the Robinson annelation have surged in recent years. The use of (*S*)-(−)-proline to catalyze the asymmetric aldol condensation of triketones **41** and **44**, the second step in the Robinson annelation, leads to (+)-tetrahydroindenedione **43** and (+)-tetrahydronaphthalenedione **46**, both in very high enantiomeric purities[29,30]. These optically active products **43** and **46** are versatile building blocks in the synthesis of terpenoids and steroids. The mechanism of the asymmetric induction, however, still needs to be clarified[31–33]. It might be of interest to note that optically active **43** and **46** were first obtained in 1958 and 1956 respectively by biological means[34,35] and then later via classical optical resolution[36,37].



(41) (42) *S*-(+)-(43)

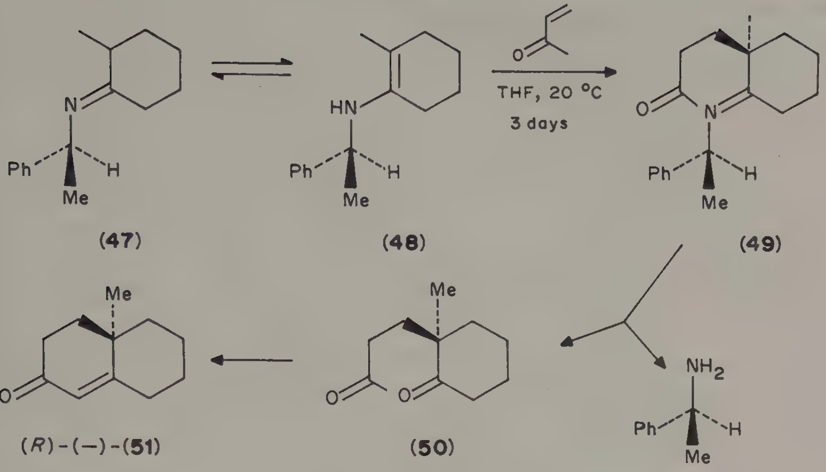


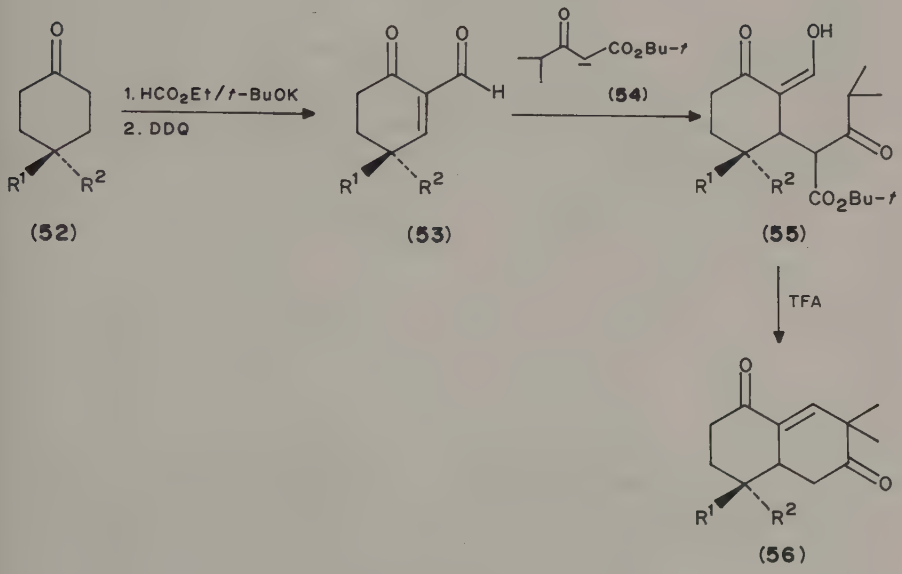
(44) (45) *S*-(+)-(46)

It is now also possible to achieve asymmetric Michael addition in the first step in the Robinson annelation. Optically active enamine **48**, prepared from the corresponding cyclohexanone and amine, undergoes asymmetric Michael addition to give **49** which, after acid hydrolysis, gives **50** in 88% yield with 91% enantiomeric excess. (*R*)-(−)-**51** can subsequently be obtained from **50** by base-catalyzed condensation.

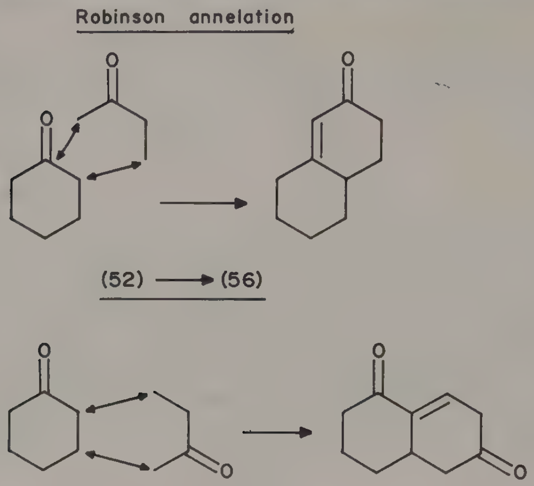
In all the Robinson annelations considered so far, the new ring is attached by a condensation that sacrifices the cyclic carbonyl group. Now, however, there is a new procedure in which the new ring is attached at the α- and β-positions and the carbonyl group survives[38,39]. Thus cyclohexanones such as **52** are first converted into their *Z*-formyl derivatives, e.g. **53** before reacting with the β-keto ester enolate **54**, followed by acid-catalyzed cyclodehydration to the final product **56**. The difference between the methods is shown in Scheme 3.

This mode of annelation is strategically applied in the total synthesis of several important natural products, for example, di-*O*-methyl carnosic acid **58**[38] and *O*-methyl pisiferic acid **59**[40], starting from precursor **57**.

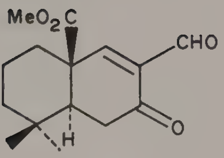




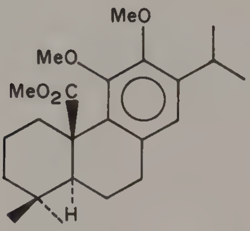
Nevertheless, the procedure is limited because, for it to operate well, the starting cyclohexenone must be fully substituted at its γ-position as shown in **53** (R^1, $R^2 \neq H$) and **57**. If not, abstraction of the proton by the keto-ester enolate (e.g. **54**) will occur to form dienolate **60**, and prevent the annelation reaction. This drawback can be overcome by using an enamine instead of an enolate. Reaction between **53** (R^1, R^2 = alkyl or H) and **61** in benzene to give **62** proceeds at room temperature, and subsequent acid hydrolysis gives a mixture of isomeric **64** which, when treated with trifluoroacetic acid, dehydrates to give **56** in exceptionally high overall yield[41]. However, to obtain the maximum yield, two equivalents of **61** must be used because it reacts with hydroxymethylene ketone **62** to form



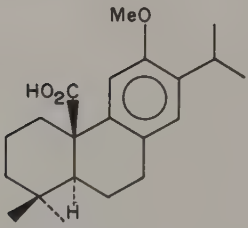
SCHEME 3



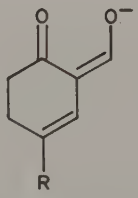
(57)



(58)



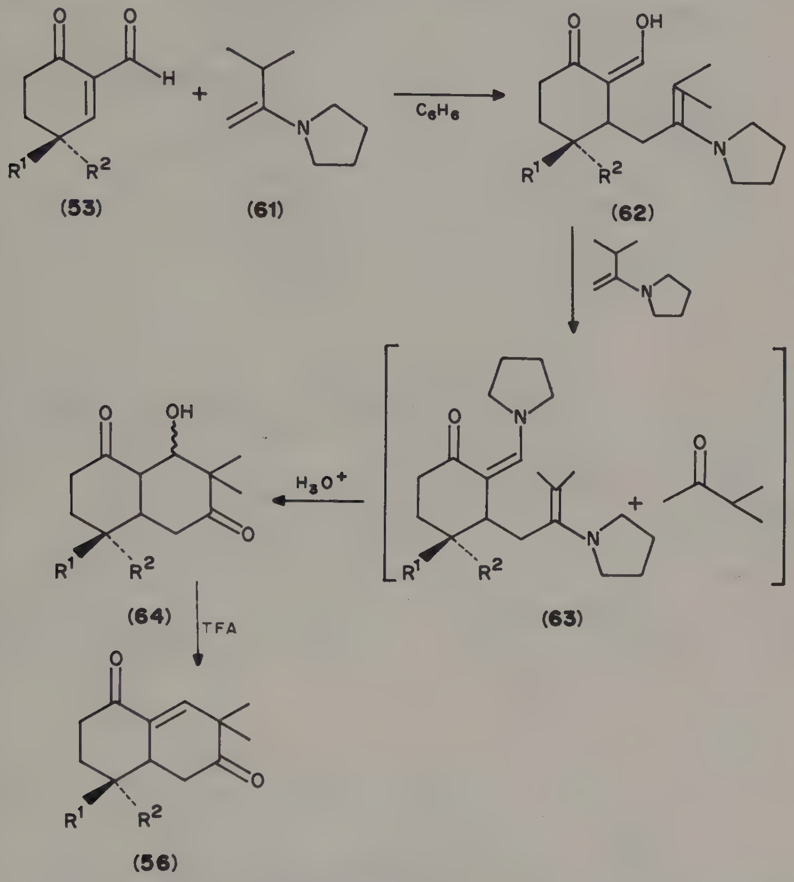
(59)



(60)

the corresponding pyrrolidinomethylene ketone **63**, which is the true intermediate that cyclizes to give, after hydrolysis, **64**, and thence **56**.

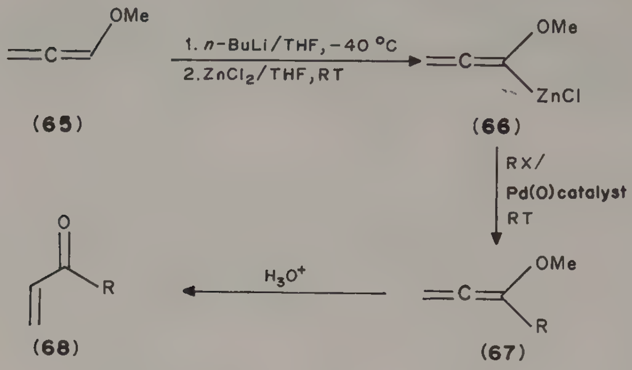
In the foregoing discussion of the Robinson annelation and its modifications, an alkyl vinyl ketone (or an equivalent) features prominently as the necessary reagent in the process. It is not surprising, therefore, that the last decade or so has been a flood of reports on the methods of synthesis of the vinyl ketone, which is, of course, itself an enone. The various approaches range from acylation of vinyl lithium with carboxylic acid[42] or reaction of vinyl magnesium bromide with aldehyde followed by manganese dioxide oxidation[43], to the use of vinyl acyl anion equivalents[44,45]. Notwithstanding all these methods, new syntheses of vinyl ketones continue to appear, and recent examples will be briefly treated here.

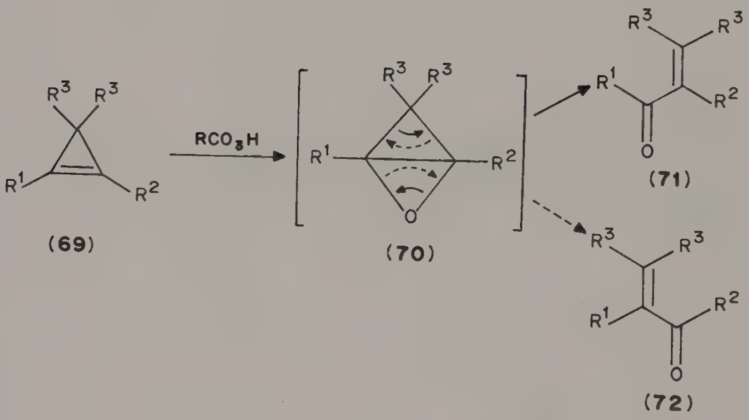


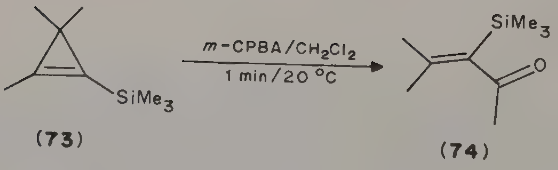
One technique[46] begins with lithiation of allenic ether **65** by *n*-butyllithium in THF at − 40 °C followed by transmetallation with zinc chloride to give the zinc salt **66**, which can react with a variety of alkyl and aryl halides in the presence of palladium(0) catalyst to yield the substituted allenic ether **67**, acid hydrolysis of which affords the vinyl ketone **68**.

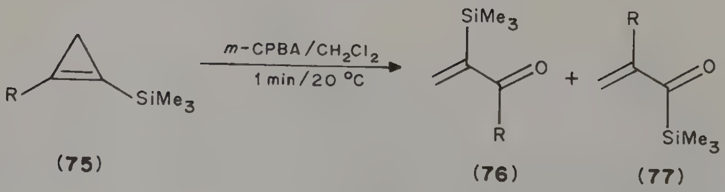
Since the report of Prinzbach and Fischer[47], twenty years ago, that peracid oxidation of the cyclopropene **69** gives **71** and/or **72**, the mechanism of this reaction has been extensively studied[48–50]. The process is now generally believed to involve the oxabicyclo[1.1.0]butane **70** as an intermediate, from which different modes of bond breaking would then lead to **71** and **72** with little regiospecificity.

It was not until very recently that a fresh observation by Baird and Hussain[51] showed that the reaction of 1-trimethylsilylcyclopropene **73** with one mole equivalent of 3-chloroperbenzoic acid (*m*-CPBA) in dichloromethane for 1 min at 20 °C gives, regiospecifically, the valuable α-silylenone **74** in high yield. However, the reaction is less stereoselective when applied to **75**.

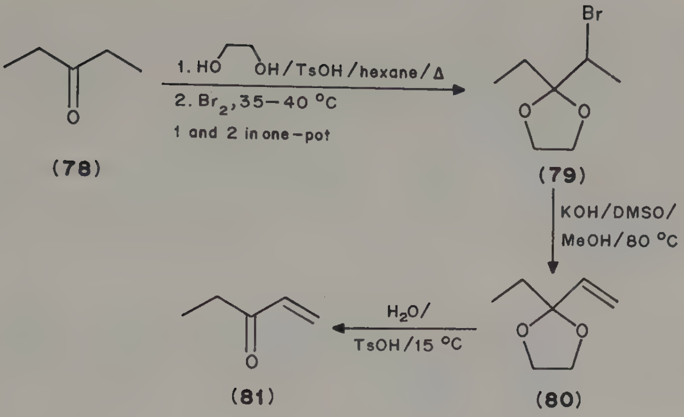


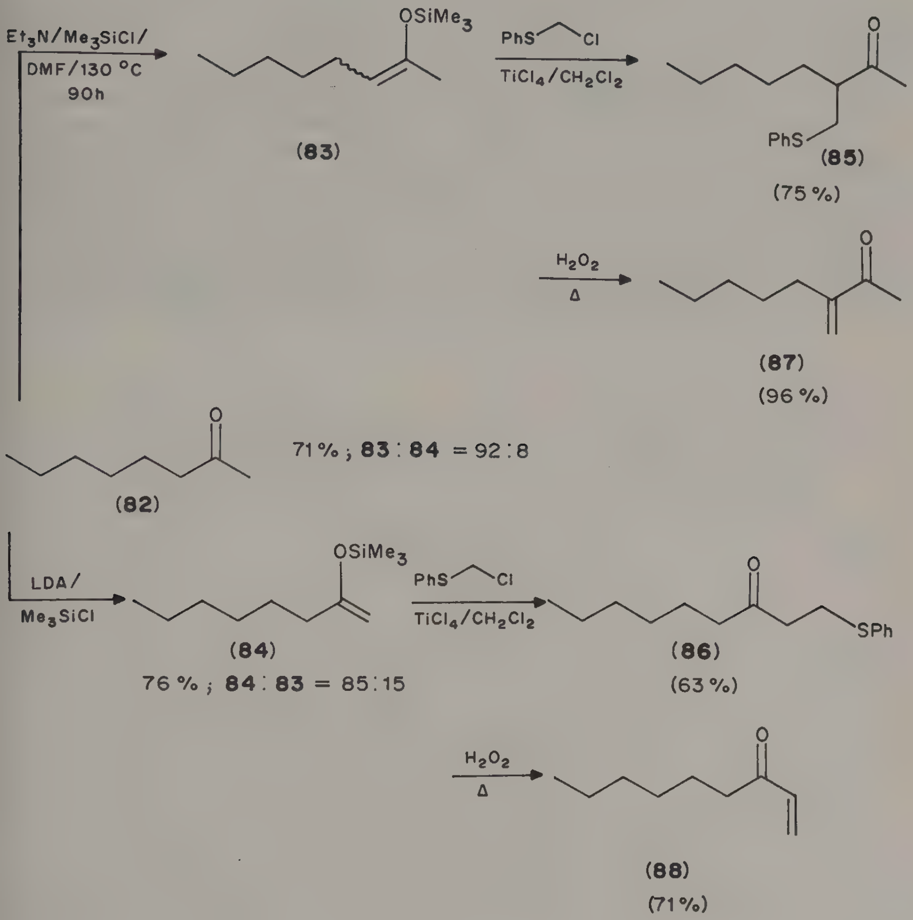






	(76)	(77)
R = *i*-Pr	66.5%	15%
R = *t*-Bu	66%	17%


(78)
1. HO OH/TsOH/hexane/Δ
2. Br2,35–40 °C
1 and 2 in one-pot
Br
O O
(79)
KOH/DMSO/
MeOH/80 °C
O O
(80)
H2O/
TsOH/15 °C
O
(81)


Et3N/Me3SiCl/
DMF/130 °C
90h
OSiMe3
(83)
PhS Cl
TiCl4/CH2Cl2
O
PhS
(85)
(75%)
H2O2
Δ
O
(87)
(96%)
O
(82)
71%; 83 : 84 = 92 : 8
LDA/
Me3SiCl
OSiMe3
(84)
76%; 84 : 83 = 85 : 15
PhS Cl
TiCl4/CH2Cl2
O
SPh
(86)
(63%)
H2O2
Δ
O
(88)
(71%)

Another useful enone intermediate, ethyl vinyl ketone, which has usually been prepared by a method[52] yielding 42% overall, is now available from a short and convenient synthesis[53] starting from diethyl ketone (**78**). The new sequence employs inexpensive and readily available materials in all the steps and results in a 67% overall yield of ethyl vinyl ketone (**81**) according to the scheme on the preceding page.

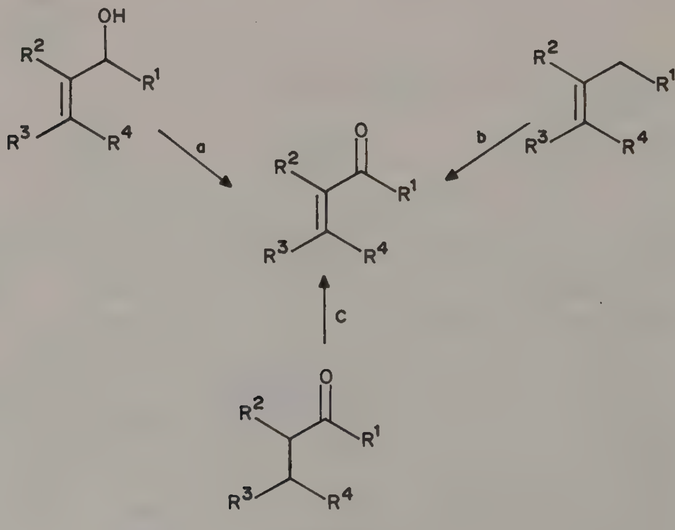
Yet another synthesis of vinyl ketones advantageously employs the 'thermodynamic' **83** and 'kinetic' **84** silyl enol ethers of 2-octanone. These are reacted with chloromethyl phenyl sulfide (titanium chloride as catalyst) to give **85** and **86** respectively. Conventional oxidative elimination of the sulfide group yields 3-methyleneoctan-2-one **87** and hexyl vinyl ketone **88**, respectively[54].

III. OXIDATION

The synthesis of enones via oxidation reactions can be divided into three general types: (a) oxidation of allylic alcohols, (b) oxidation of allylic methylenes, and (c) oxidation of saturated ketones, as outlined in Scheme 4.

The most frequently used oxidative route to enones is route a, adaptable to the use of many variations in oxidizing agents; for example manganese dioxide[55], pyridinium dichromate $[(C_5H_5NH^+)_2Cr_2O_7^=]$[56-59], pyridinium chlorochromate $(C_5H_5NH^+ClCrO_3^-)$[60,61], Jones' reagent $(CrO_3–H_2SO_4)$[62], Collins' reagent (CrO_3–pyridine complex)[63], nickel peroxide[64,65] and silver carbonate on celite[66].

Pyridinium dichromate (PDC) was introduced by Corey and Schmidt[56] as the result of a search for a reagent with suitable properties for the oxidation of alcohols to carbonyl compounds. In fact, Corey and coworkers introduced pyridinium chlorochromate (PCC)[60,61] before PDC, but PCC, with its acidic properties, could not be applied in the case of acid-sensitive substrates or products. Pyridinium dichromate, on the other hand, has quite a broad application: in dimethylformamide (at 0 °C) it rapidly oxidizes allylic alcohols to α, β-unsaturated carbonyl compounds and (at 25 °C) oxidizes non-conjugated aldehydes to the corresponding carboxylic acids; in dichloromethane at 25 °C it oxidizes both conjugated and non-conjugated primary and secondary alcohols to the correspond-

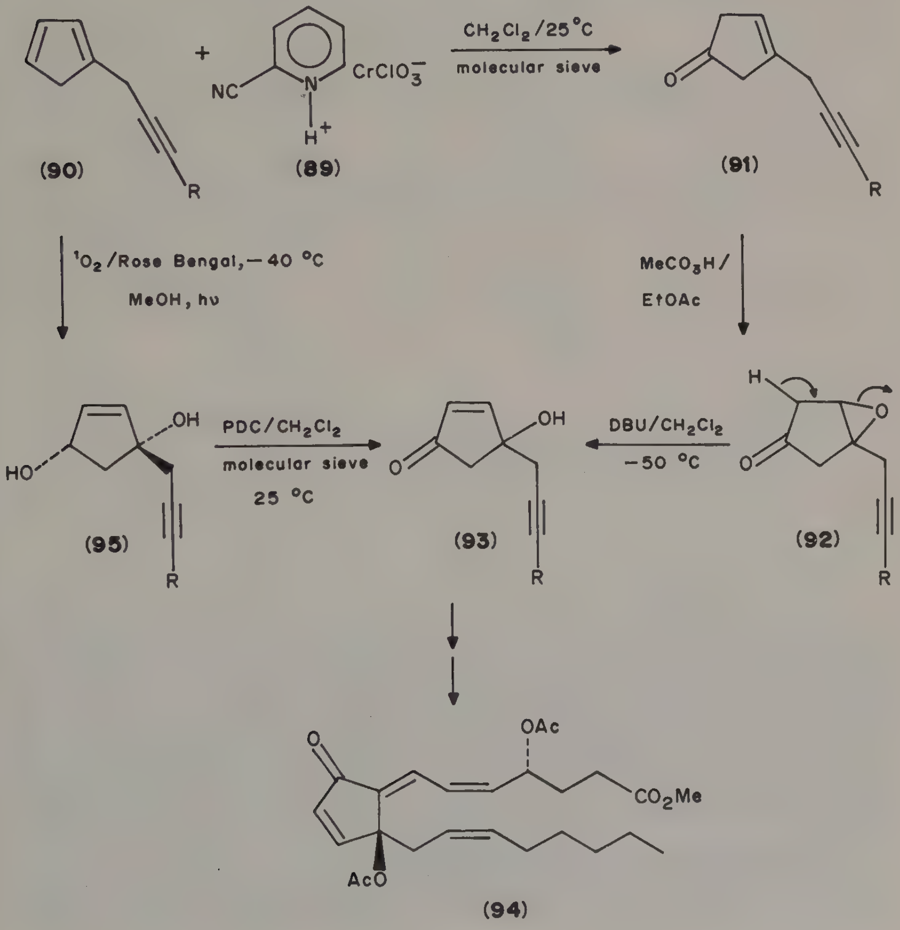


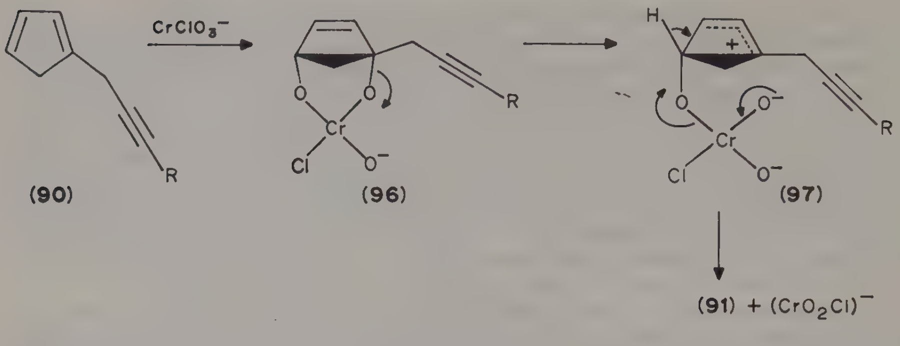
SCHEME 4

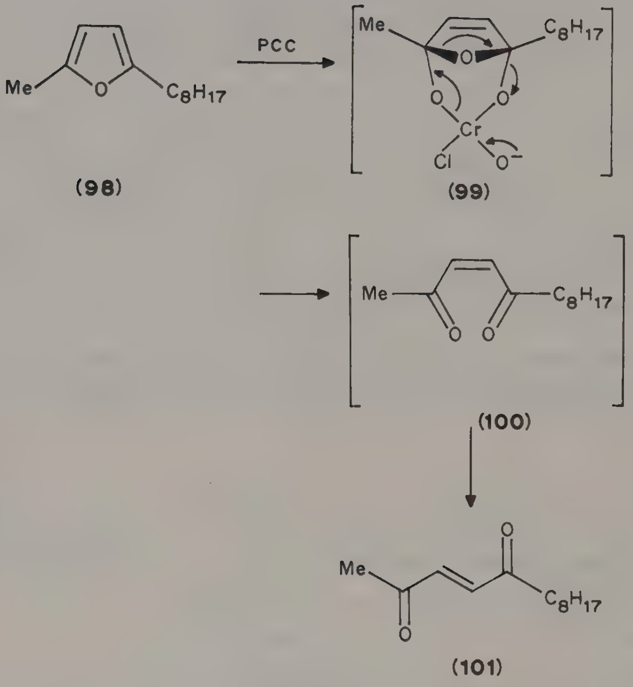
ing aldehydes and ketones, and no further. However, there are also reports of practical difficulties in the use of PDC[57,58], and a modified procedure of oxidation is now adopted which involves the addition of anhydrous acetic acid and freshly activated molecular sieve powder to the mixture of substrate and PDC in dichloromethane at room temperature[59].

Another interesting reagent, 2-cyanopyridinium chlorochromate **89**, an even more effective oxidant[67] than PCC, is used in a novel 1,4-oxygenation of the 1-alkylated cyclopentadiene **90** to yield **91**, which can be readily converted to the ketol **93**[68], an important precursor in the synthesis of the clavulone family of compounds (these are marine eicosanoids[69] isolated from *Clavularia viridis*, e.g. clavulone I, **94**). A prior synthesis of **93** had involved the photooxygenation reaction of **90** followed by oxidation with pyridinium dichromate[70], but is not suitable for large-scale synthesis.

A possible mechanism[68] for the new oxidation is 1,4-addition of chlorochromate ion to the diene **90** to form adduct **96**, which then undergoes decomposition to **91**. In fact this type of intermediate had been proposed earlier to account for the oxidation of substituted furan **98** by PCC which yields, initially, 1,4-enedione **100**. This compound apparently isomerizes and **101** is obtained as the final product in very high yield[71–73].



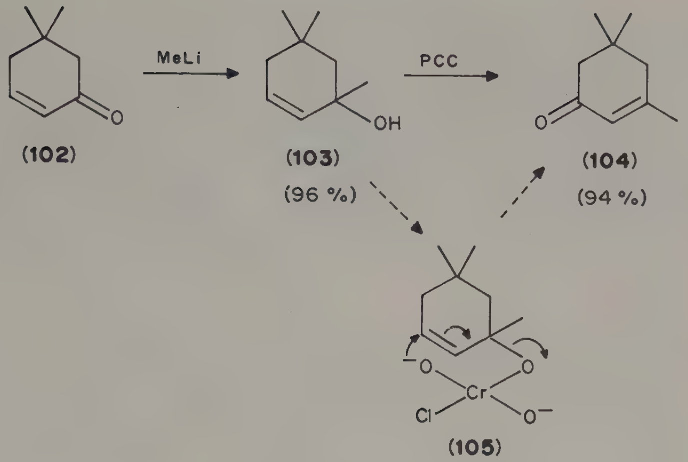


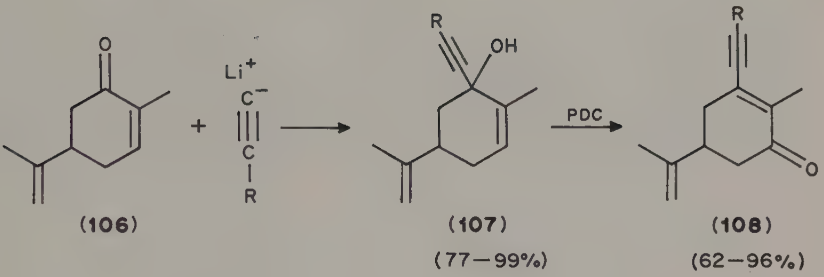


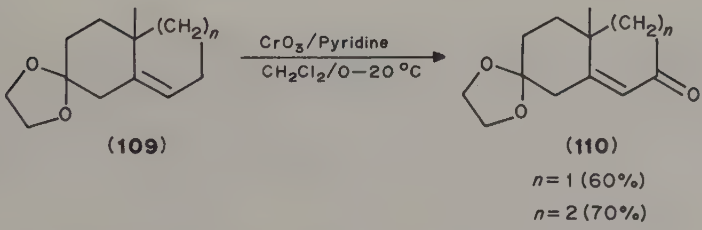
A related use of PCC effects the conversion of allylic alcohol **103** into enone **104**, the overall reaction **102** → **104** being an alkylative carbonyl transposition[74]. When modified by using PDC the reaction provides yne-enones **108**[75].

The synthesis of enones via the oxidation of allylic methylene compounds and alkyl ketones (routes b and c in Scheme 4) is not widely used. This is probably due to poor yields from drastic reaction conditions, and/or lack of regiospecificity. The few reports on these methods include the oxidation of cycloalkenes **109**, at the allylic methylene position, with Collins' reagent prepared *in situ*[76] in anhydrous dichloromethane to yield cycloalkenones **110**[77].

Another example is the use of *t*-butyl hydroperoxide in the presence of chromium tricarbonyl–acetonitrile complex [Cr(CO)$_3$(CH$_3$CN)$_3$] prepared *in situ* from chromium hexacarbonyl and acetonitrile[78]. This interesting system oxidizes cholestenyl acetate **111**

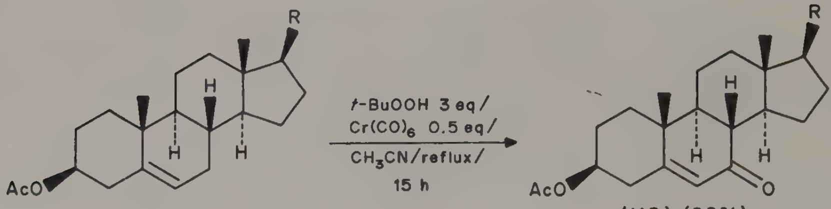




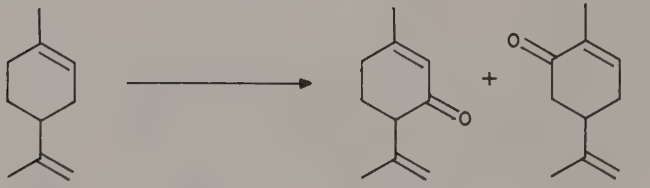


to the enone derivative **112** in 80% yield[79], but in other cases the reagent fails to afford regiospecificity; for example, the oxidation of limonene **113** under the same reaction conditions results in a mixture of **114** and **115**. The exceptional value of this oxidizing agent, however, is its ability to oxidize the allylic methylene group without affecting the alcohol function whatsoever, e.g. **116** → **117**, whereas the standard Collins' reagent would give ketone **118** with only a trace of **117**.

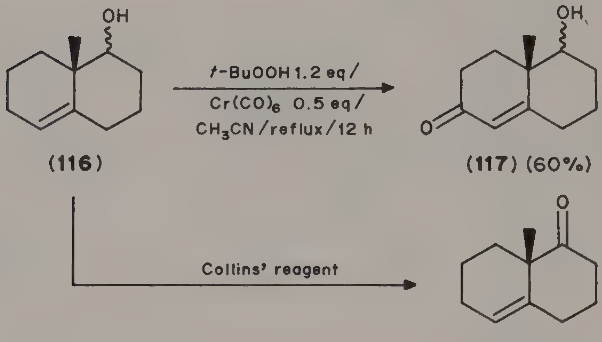
Direct dehydrogenation of saturated ketones to the corresponding enones as outlined in Scheme 4 (route c) cannot be regarded as a general synthetic method for the preparation of enones because yields are generally low, and, in the case of unsymmetrical ketones, products are complicated as a result of lack of regiospecificity. Nevertheless there are reports on dehydrogenation, using Pd(II)Cl_2 catalyst, leading to enones[80,81].



(111) (112) (80%)



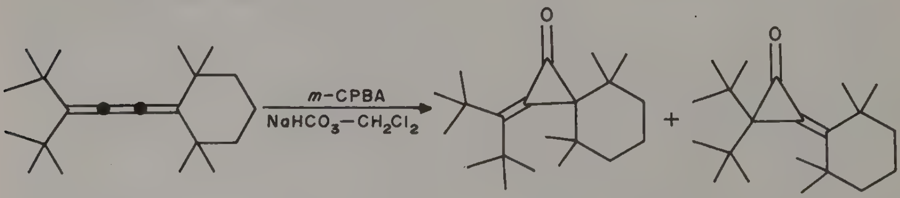
(113) (114) (26%) (115) (39%)



(116) (117) (60%)

(118)

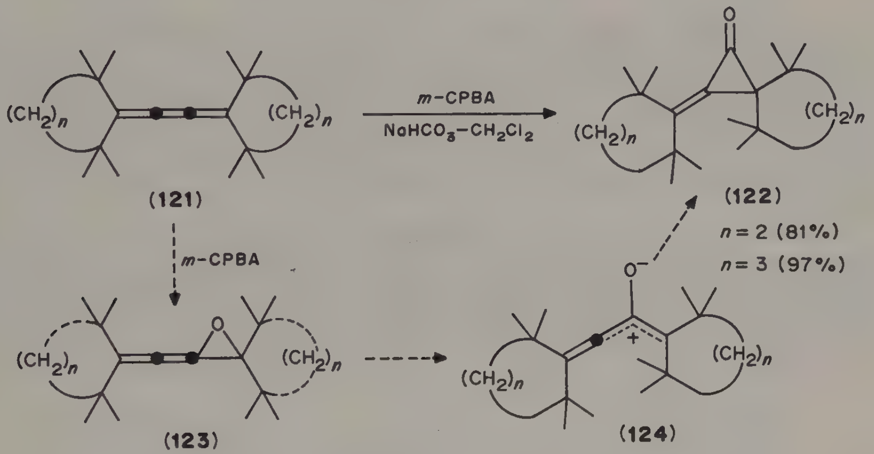
Quite a few oxidation methods, not included in Scheme 4, are also interesting. For example, the use of peracid to oxidize cyclopropene **69** with subsequent rearrangement to enones **71** and **72**, deserves mention. This type of oxidation–rearrangement reaction can be nicely applied to the synthesis of enones, viz: oxidation of 1,2,3-butatriene **119** with *m*-CPBA–NaHCO$_3$–CH$_2$Cl$_2$ in a biphasic system yields methylene cyclopropanones **120** (81–97% yield)[82]. The mechanism may be analogous to the allene oxide → cyclopropanone rearrangement[83], and involves epoxidation of the butatriene with *m*-CPBA to **123** which rearranges to the product.

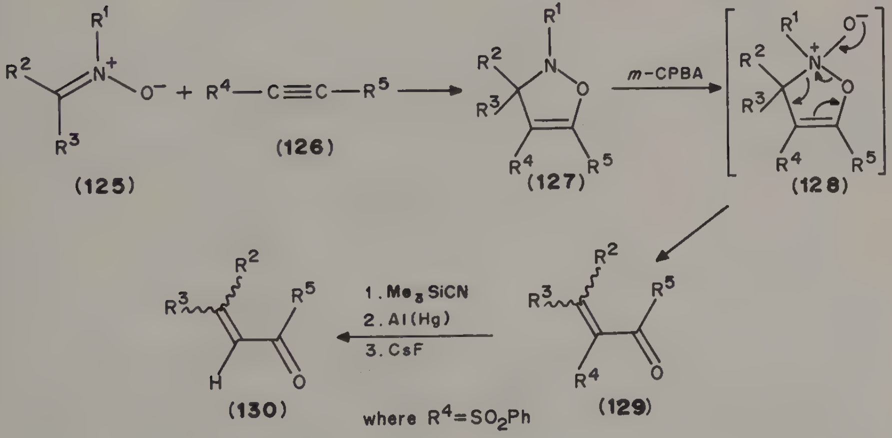


(119) (a) (120) (b)

(a : b = 3:1) (81%)

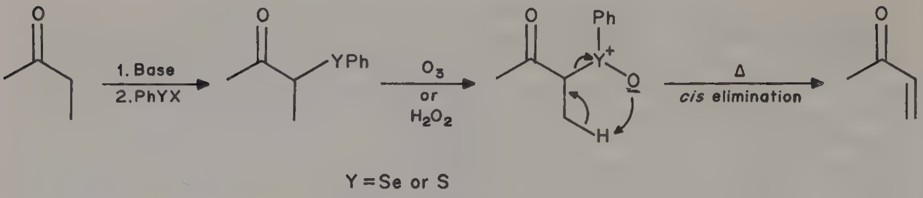
Recently, Δ^4-isoxaxoline **127**, derived from the dipolar cycloaddition reaction of nitrone **125** with acetylene **126**, is reported[84] to undergo oxidation with *m*-CPBA to give the enone **129** in excellent yield ($>90\%$). The oxidation is believed to proceed via the intermediate *N*-oxide **128**, from which nitrosoalkane is expelled in the ensuing cheletropic reaction. In order to facilitate cycloaddition in the initial construction of the isoxazoline **127**, R^4 must be a strongly electron-withdrawing group such as $—SO_2Ph$, consequently the final enone product **129** can be easily converted into **130** by reductive cleavage of the sulfonyl group. This is carried out in three simple steps: first, carbonyl protection with trimethylsilyl cyanide; second, reductive cleavage of SO_2Ph using aluminium amalgam[85]; and third, carbonyl deprotection with cesium fluoride.





IV. ELIMINATION

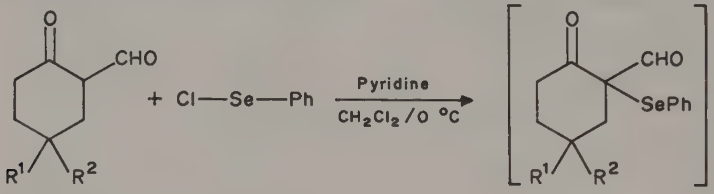
The use of elimination reactions in the synthesis of enones is very well established. The classical method involves consecutive α-bromination of the ketone and elimination of



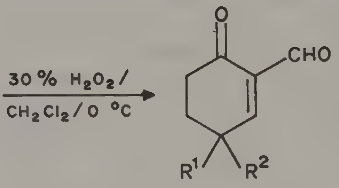
SCHEME 5

hydrobromic acid with base. Although this classical procedure is still useful[86,87], it has nevertheless been greatly developed and improved through the years. A discovery that might be considered a milestone in the process is the use of selenium and sulfur groups, by Sharpless and coworkers[88] and Trost and colleagues[89] respectively, in elimination reactions leading to the synthesis of α,β-unsaturated carbonyl compounds. These reactions are mild, easy to manipulate, give highly superior yields, and are presently probably the most widely-used elimination reactions in the synthesis of enones (Scheme 5).

A good example of the application of the reaction is the preparation of enone **53**, an important intermediate in the synthesis of complex natural product molecules. In the synthesis of **53** shown below, reaction conditions are compatible with a variety of functional groups and yields are nearly quantitative[90].



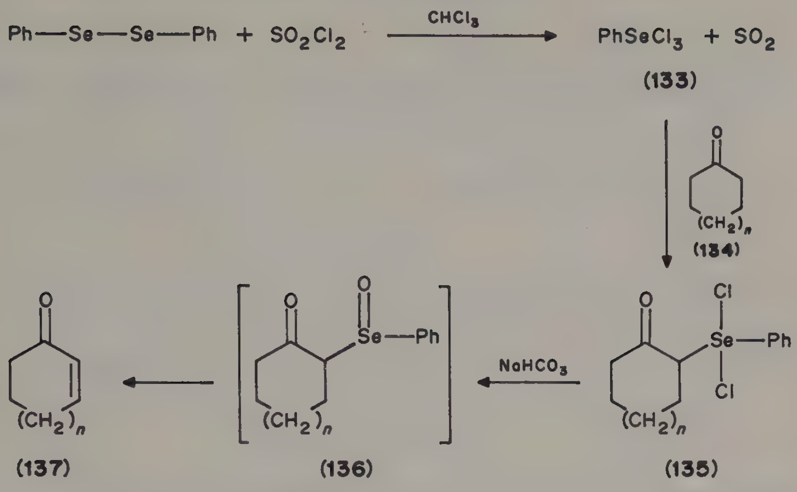
(131) **(132)**



(53)

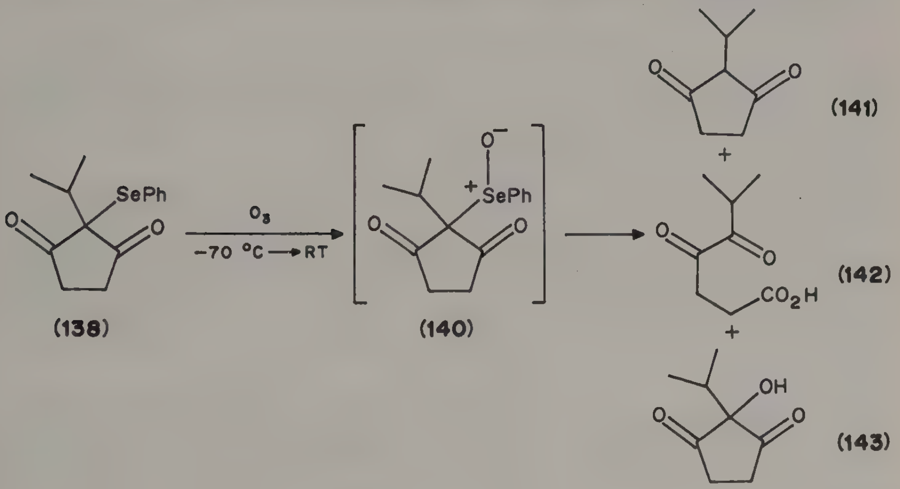
Phenyl selenium trichloride, recently made available by a convenient preparation from diphenyl diselenide and sulfuryl chloride, readily introduces the $PhCl_2Se$— group into ketones at the α-position. This is important because the functional group can be easily hydrolyzed by sodium bicarbonate to the selenoxide which readily eliminates to afford the enone[91] while avoiding an oxidation step. In fact the procedure is similar to the use of benzeneselenic anhydride (PhSeO—O—OSePh) by Barton and coworkers[92] and by Back[93] for introducing double bonds into steroidal ketones and azasteroidal lactams.

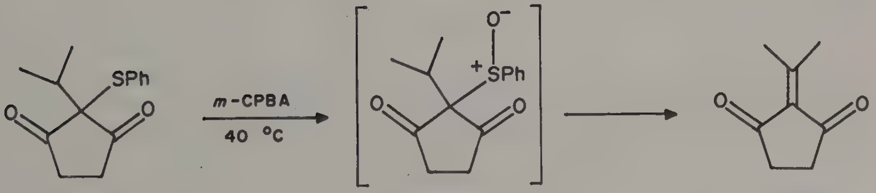
An idea of the difference between the elimination of selenoxide and of sulfoxide intermediates can be gained from a comparison of the oxidation of **138** and **139**. When



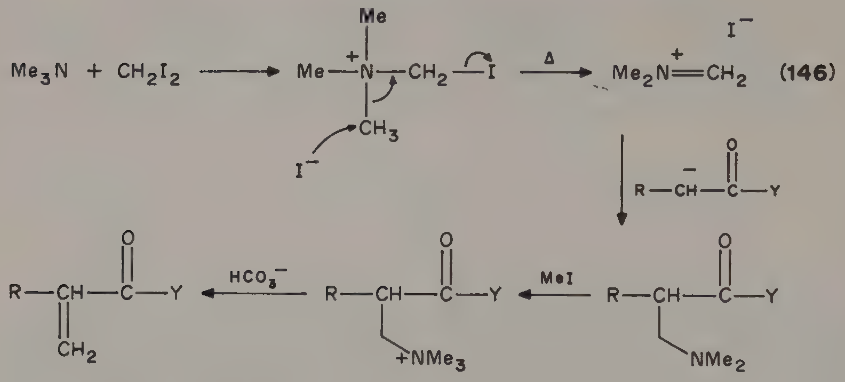
$n = 0, 1, 2, 3, 7$

treated with ozone at −70 °C, followed by warming to room temperature, **138** gives a mixture of deselenylated material **141**, ring-cleaved acid **142** and alcohol **143**, whereas **139**, upon oxidation with *m*-CPBA, undergoes elimination of the first-formed sulfoxide intermediate **144** to produce the interesting 2-alkylidene-1,3-cyclopentanedione **145**[94].





(139) (144) (145)



Y = alkyl, aryl, OR, etc.

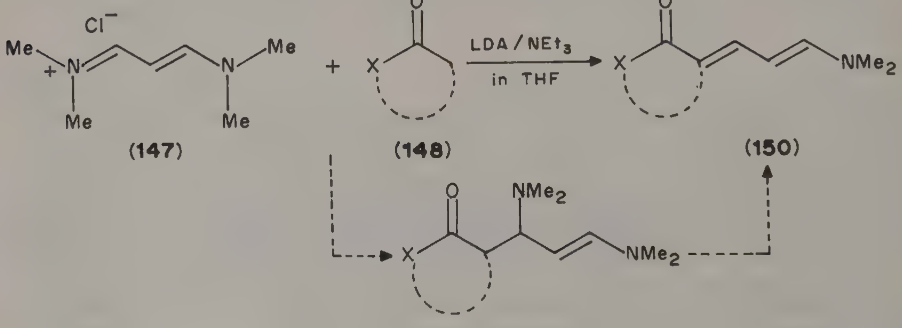
SCHEME 6

A good reagent for the synthesis of α-methylene carbonyl compounds[95-97] is *N*,*N*-dimethylmethyleneammonium iodide **146**, which operates via a different mode of elimination. The compound is an important Mannich intermediate which can easily be prepared by the method of Eschenmoser and coworkers[95] (Scheme 6) and is consequently called 'Eschenmoser's salt'.

Despite the fact that Eschenmoser's salt is now commercially available, new and more convenient methods of preparation are still being sought and reports quote yields ever nearer to quantitative[98,99].

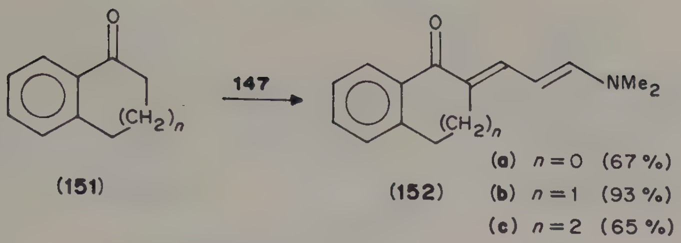
Derivatives of Eschenmoser's salt with extended conjugation, for example 1,5-diazapentadienium chloride **147**[100], also behave as alkenylating agents similar to **146** (as shown below). Thus they can be used to synthesize aroyl ketones containing 3-carbon substituents at the α-position[101] such as **152**, which can be regarded as potential synthetic intermediates for complex natural products.

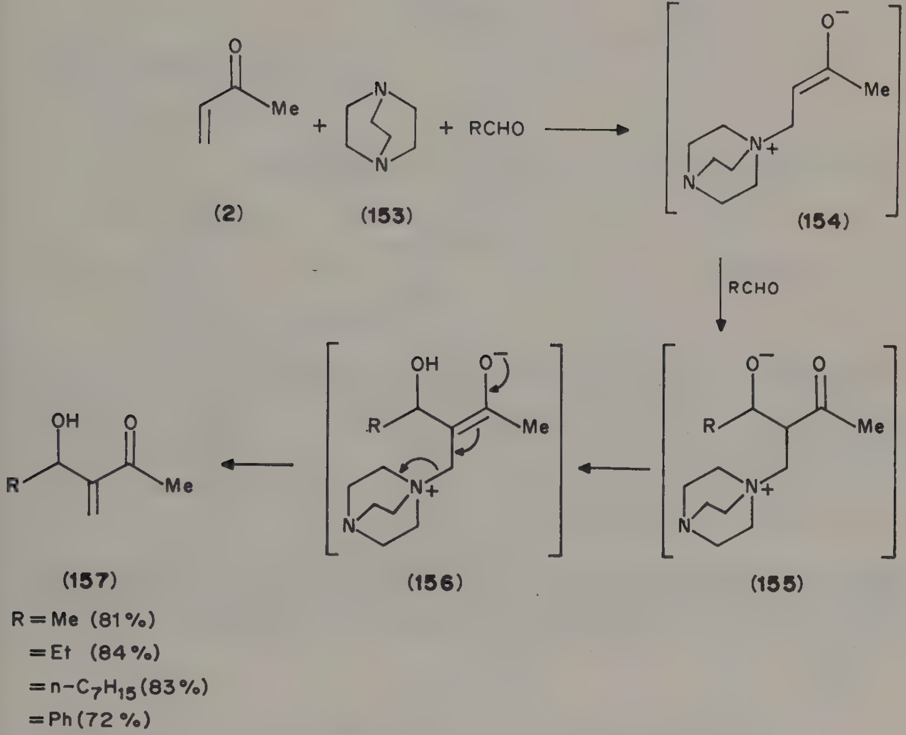
The elimination of ammonium salts is also cleverly applied in the functionalization of enones exemplified by the addition–elimination reaction of methyl vinyl ketone with the commercially available 1,4-diazabicyclo[2.2.2]octane (DABCO) **153**[102]. DABCO adds in a Michael addition fashion to methyl vinyl ketone to form the enolate **154** which readily undergoes reaction with an aliphatic or aromatic aldehyde to give intermediate **155**, and thence a new enolate **156** by a prototropic shift. A fast elimination of DABCO now takes place and α-methylene-β-hydroxyketone **157** is obtained as the product in high yield.



(147) (148) (150)

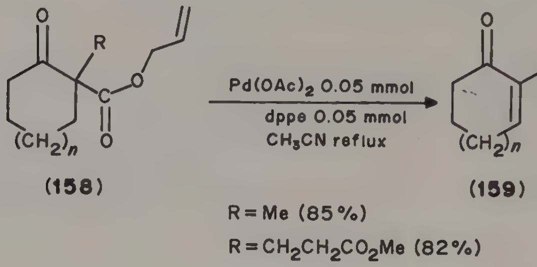
(149)



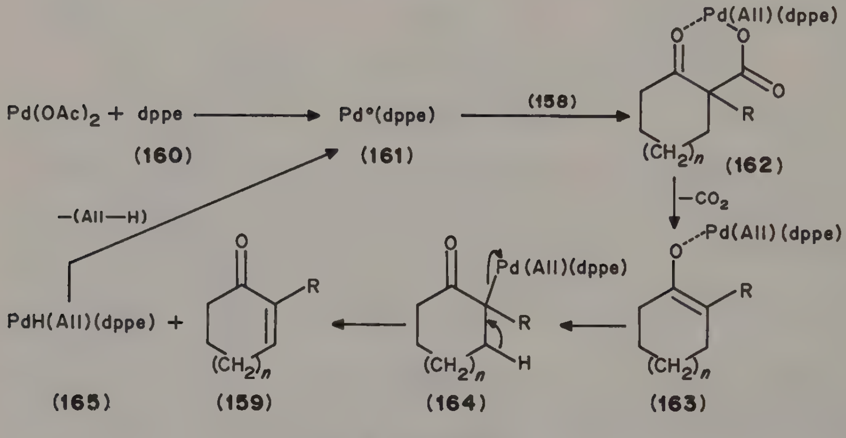


Palladium-catalyzed elimination is also a good route to enones[103,104]. The first example was the decarboxylation–dehydrogenation of allyl β-keto carboxylate **158** with palladium acetate and 1,2-bis(diphenylphosphino)ethane (dppe) **160** as catalysts, yielding enone **159**. A reasonable mechanism is presented in Scheme 7. The reaction is also applicable to the synthesis of open-chain enones[105]. One drawback, however, is the significant requirement that $R \neq H$, otherwise yields are low and accompanied by complicating side-products.

The favourable nature of the palladium-catalyzed decarboxylation–dehydrogenation reaction is reflected in its being the reaction of choice for the synthesis of 2-methyl-2-cyclopentenone **169**. Although a simple-looking molecule, **169** is a very important starting material for the construction of cyclopentenoid natural products, which accounts for the numerous reports in the literature on its synthesis[106,107]. However, the procedure given below also has the advantage of being suitable for adapting to large-scale synthesis[108],



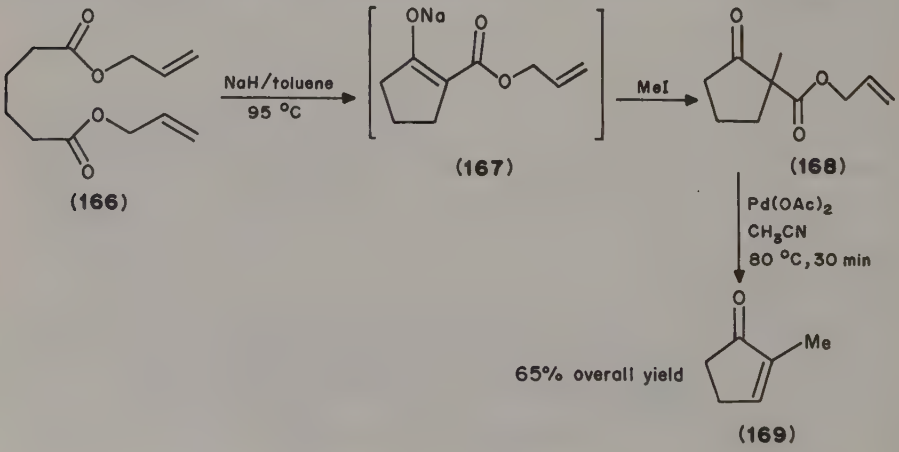
SCHEME 7

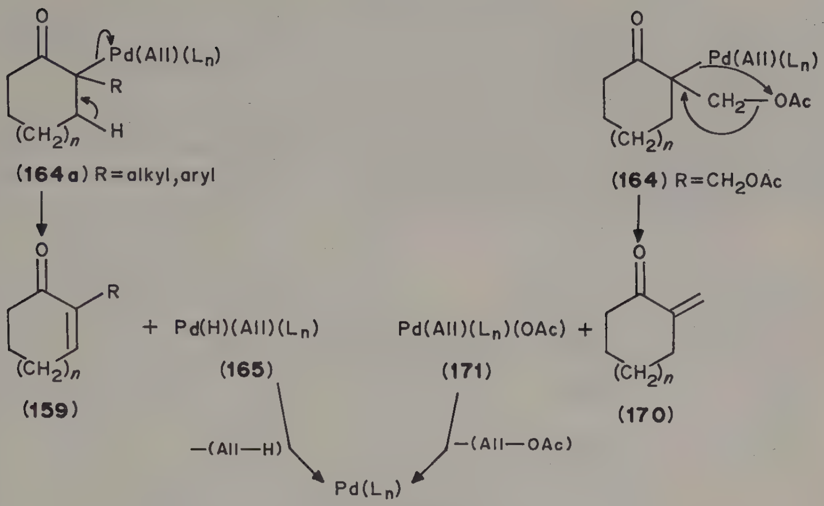


dppe = $Ph_2PCH_2CH_2PPh_2$

All = $CH_2{=}CHCH_2$—

starting from Dieckmann condensation of diallyl adipate **166**, followed by methylation and then subjecting the product **168** to palladium-catalyzed decarboxylation–dehydrogenation to yield the target molecule **169** in 65% overall yield from **166**.



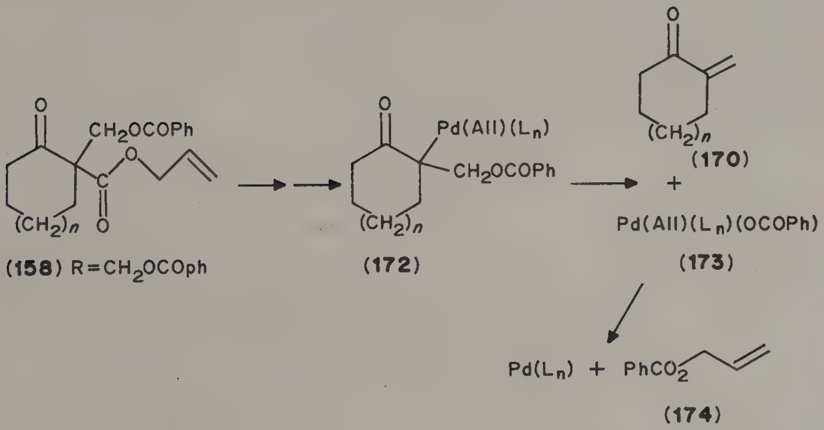


L_n = ligand; All = $CH_2{=}CHCH_2{-}$

SCHEME 8

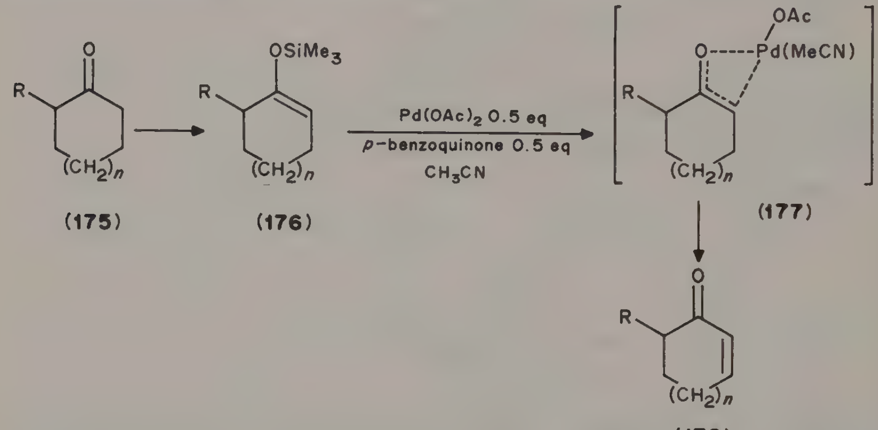
It should be noted that, in the sequence depicted in Scheme 7, when R is an acetoxymethyl group the mechanism of elimination deviates from that shown. That is, the dehydrogenation of **164a** to enone **159** does not occur; and instead, elimination of the acetoxy group takes place to yield α-methylene ketone **170** and (π-allyl)palladium acetate complex **171**. This now suffers the same fate as complex **165** in undergoing reductive elimination to expel the allyl component and regenerate Pd(0) catalyst as depicted in Scheme 8. This method affords a high yield of **170** and is generally applicable to various ring sizes ($n = 1, 2, 8$) as well as to acyclic systems[109].

The mechanism of the formation of α-methylene ketone **170** in Scheme 8 is confirmed by using α-benzoyloxymethyl-β-keto carboxylate **158** as starting material, when allyl benzoate **174** is isolated from the product mixture in 93% yield.



Besides the synthesis of enones by consecutive decarboxylation–dehydrogenation (or deacetoxylation) with palladium as catalyst as discussed above, there are several other methods which employ Pd(0) or Pd(II) to catalyze the synthesis of enones, some of which will be briefly mentioned here.

Silyl enol ether **176** undergoes a palladium(II) catalyzed dehydrosilylation[110], probably via an oxo-π-allylpalladium(II) complex **177**, to give a very high yield (> 90%) of enone **178**. The reaction allows the introduction of a double bond into an unsymmetrical ketone via the corresponding enol ether as shown below.

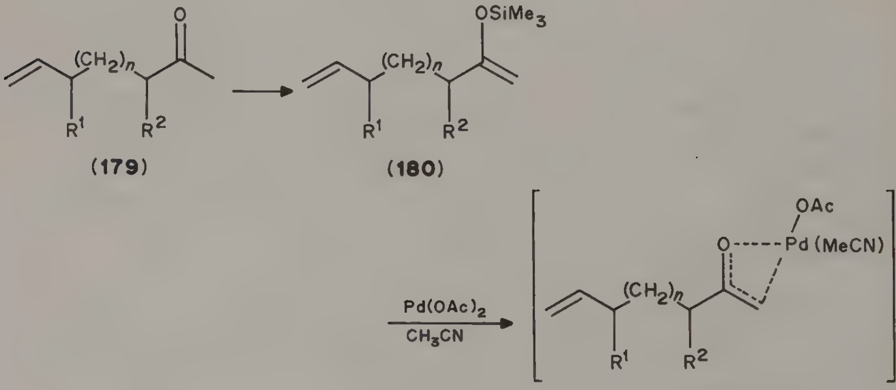


(175) (176) (177)

(178)

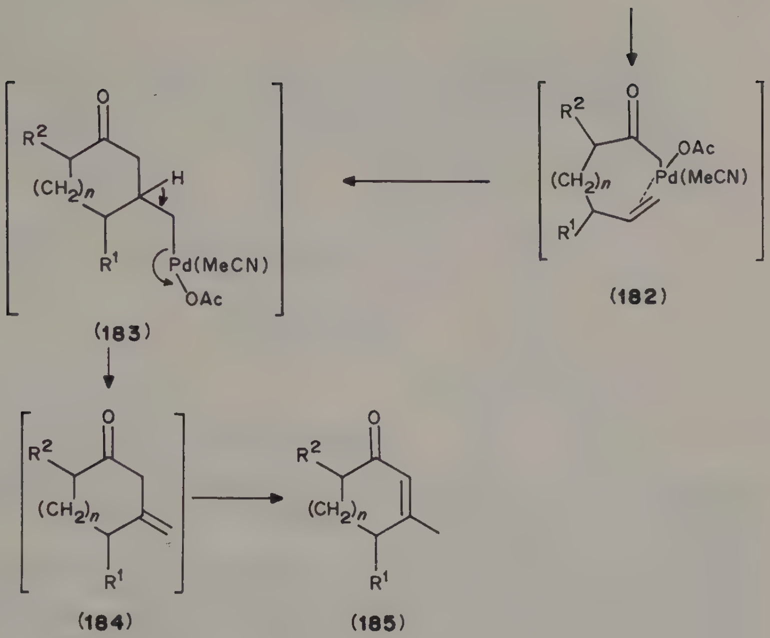
Even initially acyclic starting materials may be used in syntheses of this kind. Starting from aliphatic keto-olefins **179** with a suitable value of n[111], for example, cyclopentenones of type **185** ($n = 0$)[112] are readily obtainable. The proposed mechanism for the reaction is shown in Scheme 9, although later study does suggest that it might be more complex[113].

The reaction between aroyl chloride **186** and alkyl phenyl ketene **187** in the presence of catalytic amounts of tetrakis(triphenylphosphine)palladium, [$Pd(PPh_3)_4$], results in decarbonylation and dehydrogenation to give a mixture of *E*- and *Z*-enones **188**[114]. Detailed mechanistic study reveals that the key steps involve decarbonylation of the palladium aroyl chloride complex **189** to **191**, which, after adding the ketene **187** to form **192**, undergoes triethylamine induced dehydropalladation to enone **188**[115,116].

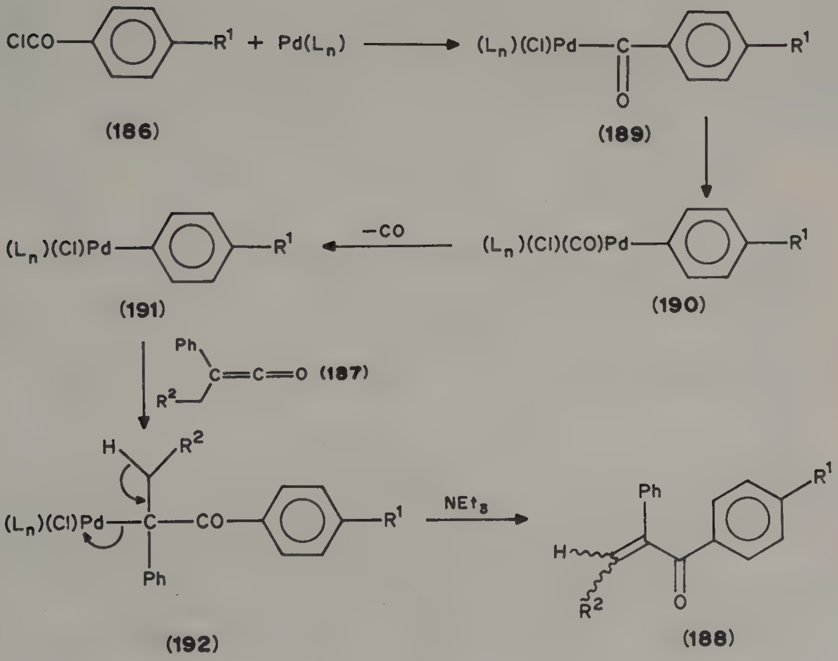


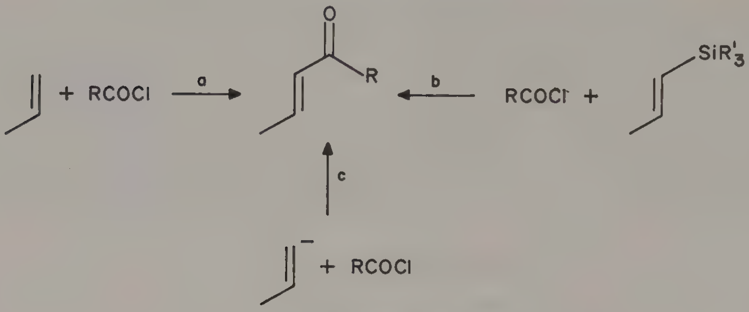
(179) (180)

(181)


(182)
(183)
(184)
(185)
R2
R1
(CH2)n
OAc
Pd(MeCN)
H
O

SCHEME 9


ClCO
R1
+ Pd(Ln)
(Ln)(Cl)Pd—C
(186)
(189)
(Ln)(Cl)(CO)Pd
(190)
−CO
(Ln)(Cl)Pd
(191)
Ph
R2
C═C═O (187)
H
(Ln)(Cl)Pd—C—CO
Ph
(192)
NEt3
(188)



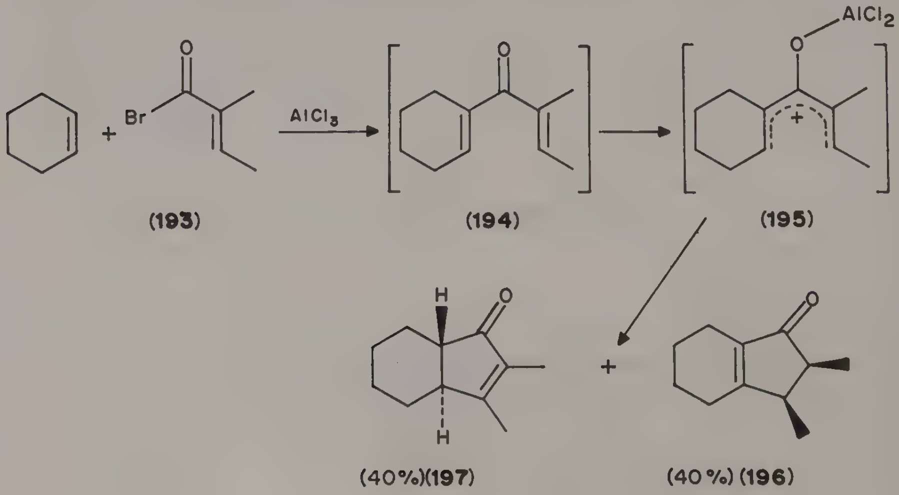
SCHEME 10

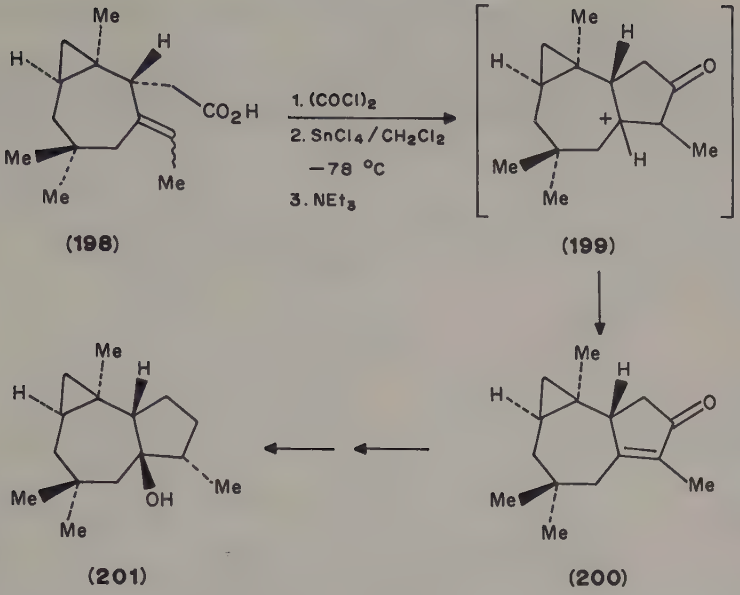
V. ACYLATION

Acylation routes to enones can be summarized as falling into three main categories: (a) Friedel–Crafts acylations, (b) Acylations of vinylsilanes and (c) Acylations of vinyl anions (or equivalents) as shown in Scheme 10.

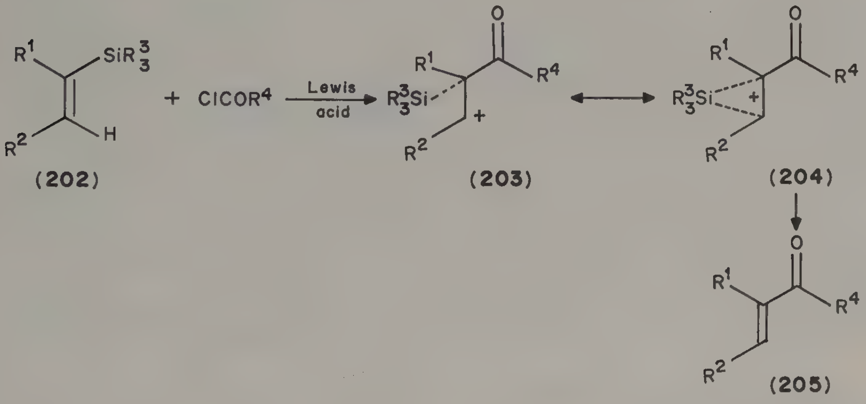
(a) The Friedel–Crafts acylation is a long-established classical method which can still be employed effectively in certain cases, especially in the preparation of cyclopentenone derivatives. A simple example is found in the Friedel–Crafts acylation of cyclohexenone with acid bromide **193**, which gives **196** and **197**[117] via Nazarov cyclization[118] of the acylation product **194**.

In the total synthesis of marine sesquiterpene, africanol **201**[119], Paquette and Ham employed cyclopentenone **200** as the precursor of **201**[120]. The key step in the preparation of **200** is the $SnCl_4$-catalyzed intramolecular Friedel–Crafts acylation reaction between the acid chloride and olefin segments of the intermediate derived from the olefinic acid **198**. The success of the reaction is ascribed to the crucial fast deprotonation of the intermediate carbocation **199** to enone **200** before other reactions, such as rearrangements, could occur.





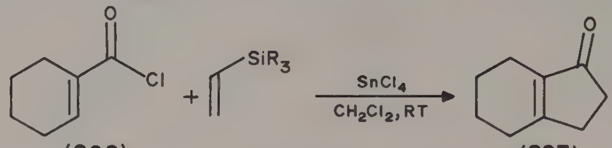
(b) It has been found that aliphatic Friedel–Crafts acylations can be successfully carried out by employing vinylsilanes (e.g. **202**) and acid chlorides[121,122]. The reaction is regiospecific, that is, it takes place at the carbon atom carrying the trialkylsilyl group to give enone **205**. The regiospecificity is attributed to the preferred formation of the intermediate carbocation at the position β to the silyl group for maximum stabilization by silicon, for which the term 'β effect' has been coined[123,124].



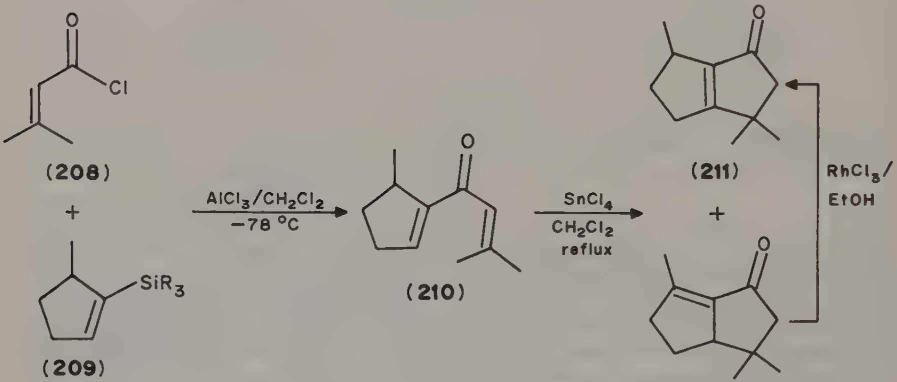
Lewis acids which can be used in vinylsilane acylations include aluminium chloride ($AlCl_3$), stannic chloride ($SnCl_4$), titanium chloride ($TiCl_4$), zinc chloride ($ZnCl_2$), ferric chloride ($FeCl_3$) and boron trifluoride etherate ($BF_3 \cdot Et_2O$)[65].

Taking advantage of this type of acylation, one can prepare fused cyclopentenones either by a one-pot tandem acylation-Nazarov cyclization of acid chloride **206** and vinylsilane to give **207**[125], or by a two-step procedure in which the aluminium-chloride-catalyzed acylation of **209** with **208** gives a divinyl ketone **210** that yields **211** and **212** when treated with stannic chloride[126].

The use of vinylsilanes to promote acylation and/or cyclization reactions has since been widely investigated[127–129] and applied in organic synthesis, for example in the synthesis of spiro-compound **214**[130] and the C,D ring portion (**218**)[131–133] of the corticosteroids **219**.



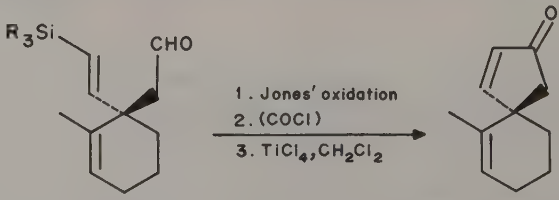
(206) (207)



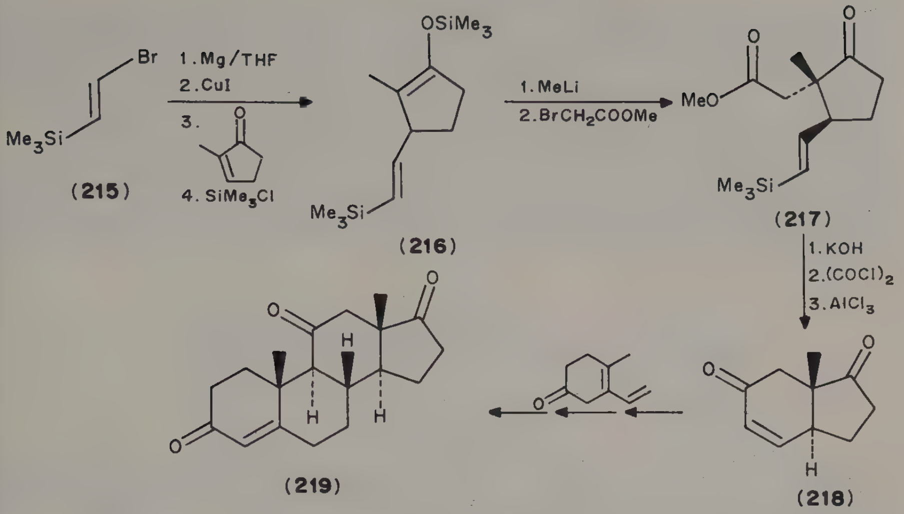
(208) (209) (210) (211) (212)

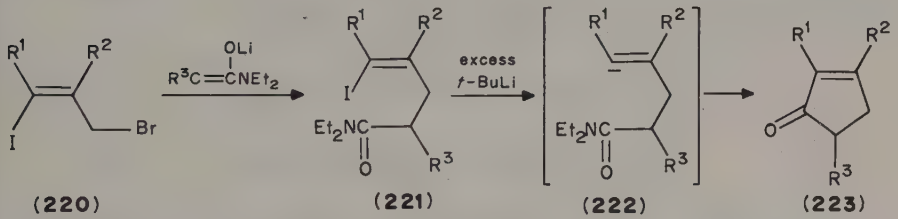
A stereoselective synthesis of **218** can be achieved by the sequence shown below. 2-Methyl-2-cyclopentenone is reacted with the cuprate derived from the Grignard reagent obtained from **215**, and the resulting enolate is quenched with trimethylsilyl chloride to give **216** (78%). Subsequent alkylation with methyl bromoacetate yields **217** (87%) with > 95% *trans* relationship as shown. Conventional conversion of the ester functionality to acid chloride, followed by $AlCl_3$ promoted cyclization, leads to **218** (54%)[131], the key intermediate in the synthesis of **219** via cycloaddition of a dienone[134] as shown below.

(c) The third main acylation route to enones, route c in Scheme 10, involves the use of the vinyl anion or its equivalent. For example, trisubstituted cyclopentenones such as **223** can be synthesized by direct intramolecular acylation of vinyl anion **222**, prepared from iodoolefin **221** by treatment with *t*-butyllithium[135], while the olefin **221** itself, in turn, is obtained from the reaction of the readily available **220**[136] with *N*,*N*-diethylalkylacetamide anion. The groups R^1, R^2, R^3 in **223** may be hydrogen, alkyl or aryl. The role of *t*-butyllithium is essential since the use of other bases results in poor yields.

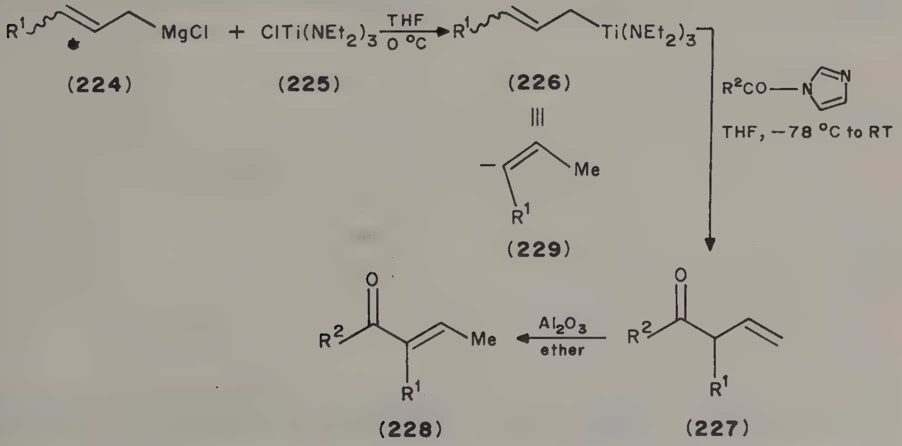


(213) (214)

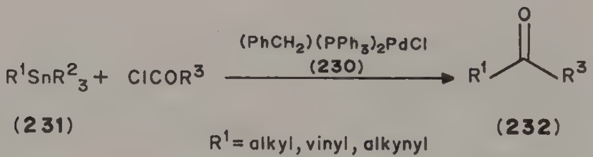

(215) (216) (217) (218) (219)


(220) (221) (222) (223)

Allyltitaniumtris(diethylamide) **226**, which can be prepared by a *trans*-metallation reaction between allylic Grignard reagent **224** and **225**, is a good synthon of vinyl anion **229**. When **226** is reacted with an acylimidazole, regiospecific acylation ensues to yield β,γ-enone **227** with *complete inversion of the allylic system*. Stereoselective isomerization of **227** to enone **228** can be accomplished with aluminium oxide in ether at room temperature to give the E-α,β-unsaturated ketone **228**[137].


(224) (225) (226) (229) (227) (228)

The discovery that benzyl(chloro)bis(triphenylphosphine)palladium **230** can catalyze the coupling reaction of alkyl-, vinyl- and alkynyl-tins **231** with acyl chlorides to produce the corresponding ketones[138–140] led to a detailed study of the nature of the coupling reaction[141–143], especially of derivatives of vinyltin to produce enones. The reaction can be performed in chloroform under mild conditions and affords good yields of products. In the case of unsymmetrical organotin substrates (e.g. **231**, R^1 = vinyl, alkynyl; R^2 = alkyl) it is found that the reaction never involves the transfer of the alkyl, but only of the vinyl or alkynyl groups, to yield enones or ynones (e.g. **232**, R^1 = vinyl or alkynyl) respectively). Hence it provides a good method, known as the 'Stille reaction', for a high-yield synthesis of enones[144].



(231) (232)

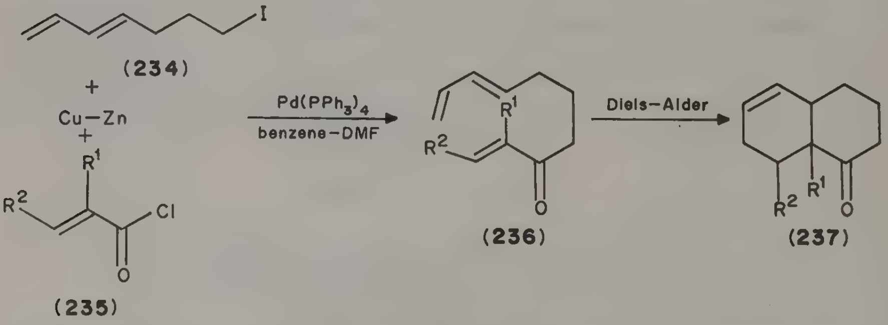
Apart from the Stille reaction which employs organotin, variations on organometallic compounds in acylation include the use of organozinc which can undergo coupling reactions very efficiently, for example the reaction between organozinc halide **233** and acid chloride with tetrakis(triphenylphosphine)palladium as catalyst[145].

$$R^1ZnX + R^2COCl \xrightarrow{Pd(PPh_3)_4/THF} R^1COR^2$$

(233)

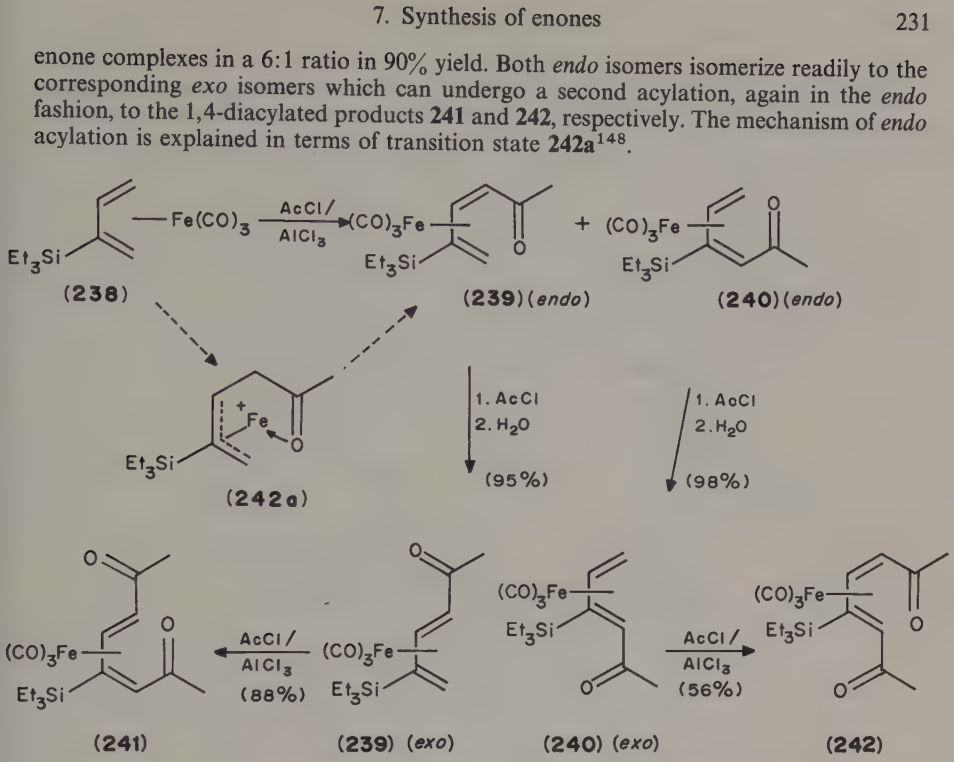
R^1 = alkyl, aryl; R^2 = alkyl, aryl, vinyl, OMe
X = Cl, I

Alkylzinc iodide can be prepared *in situ* by the reaction of alkyl iodide with Zn–Cu couple in benzene in the presence of dimethylformamide. The reagent reacts with a wide variety of acid chlorides in the presence of Pd(0) catalyst at room temperature to produce excellent yields of ketones, including enones. An example is the reaction between heptadienezinc iodide (prepared *in situ* from the reaction of the corresponding iodide **234** with Zn–Cu couple) and acid chloride **235**, which gives keto-triene **236** in an almost quantitative yield. Compound **236** simultaneously undergoes intramolecular Diels–Alder reaction to the bicyclic ketone **237**[146].



(234) (235) (236) (237)

Another interesting reagent, butadieneiron tricarbonyl complex **238**, prepared from the requisite butadiene[147], undergoes Friedel–Crafts acylation to **239** (*endo*) and **240** (*endo*) enone complexes in a 6:1 ratio in 90% yield. Both *endo* isomers isomerize readily to the corresponding *exo* isomers which can undergo a second acylation, again in the *endo* fashion, to the 1,4-diacylated products **241** and **242**, respectively. The mechanism of *endo* acylation is explained in terms of transition state **242a**[148].

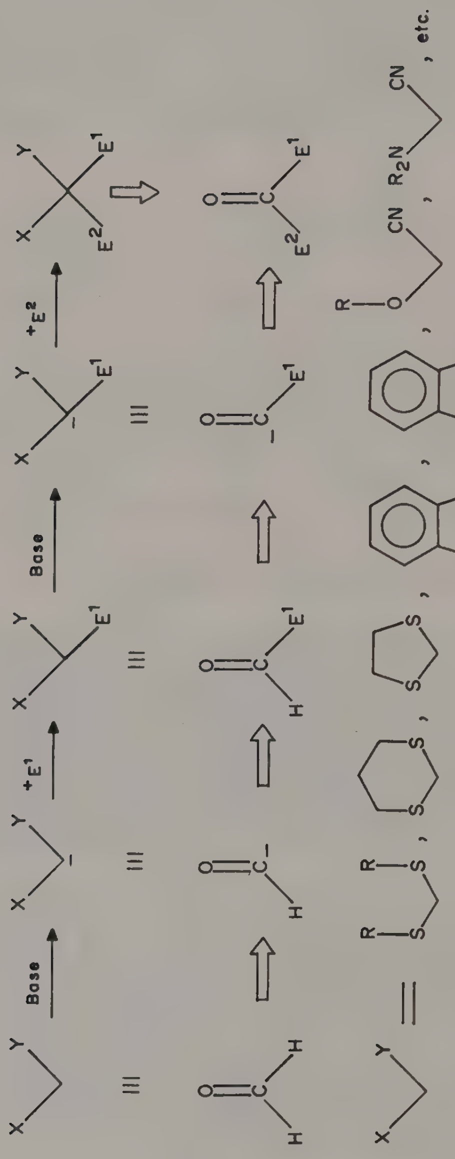


In addition to direct acylation, the last twenty years or so have witnessed the growth of an exciting complementary approach to acylation syntheses of carbonyl compounds. 'Reverse activity' or 'Umpolung', a new idea in organic synthesis, is applied to carbonyl compound synthesis through the use of a 'masked-acyl anion', as illustrated in Scheme 11. In this scheme, X and Y are atoms or groups which can stabilize the negative charge and can be easily hydrolyzed to the carbonyl group when required[149]. They may both be the same, e.g. both sulfur[150–152], or different, e.g. sulfur and oxygen[153], oxygen and cyano[44], dialkylamino and cyano[45], etc. Application of the masked-acyl anion has led to the synthesis of a variety of enones[149,154–156] but only a few recent applications will be considered here.

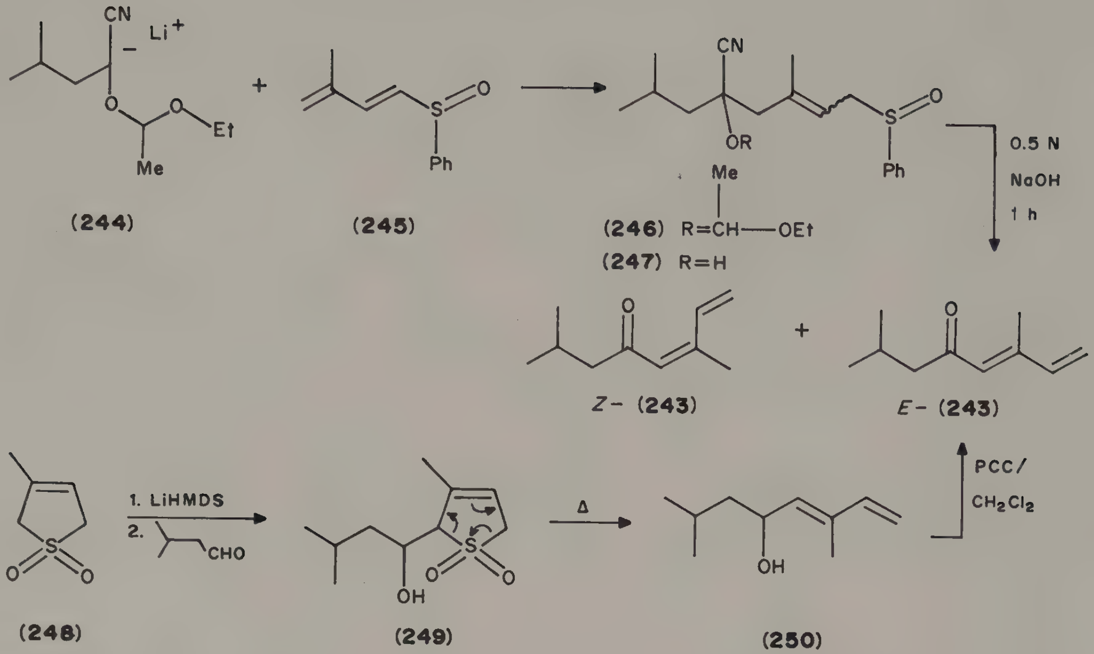
The synthesis of the monoterpenoid dienone, tagetone **243**, can be accomplished by two different methods. The first utilizes **244** as the masked-acyl anion[44] in a conjugate addition reaction with sulfoxide **245** to yield adduct **246**. Acid hydrolysis followed by treatment of the resulting cyanohydrin **247** with 0.5 N sodium hydroxide for 1 h gives a 1:1 mixture of *E*- and *Z*-tagetone **243** (50% overall yield from **245**)[157].

The second method, on the other hand, is a stereoselective synthesis starting with 3-methyl-2,5-dihydrothiophene *S,S*-dioxide **248** as the masked isoprene unit. The anion obtained from **248** using lithium hexamethyldisilazide (LiHMDS) reacts with isovaleraldehyde to give **249** which, upon desulfonylation via a cheletropic reaction, yields exclusively *E*-dienol **250**. PCC oxidation of **250** to *E*-tagetone **243** completes the synthesis in a 35% overall yield[158,159].

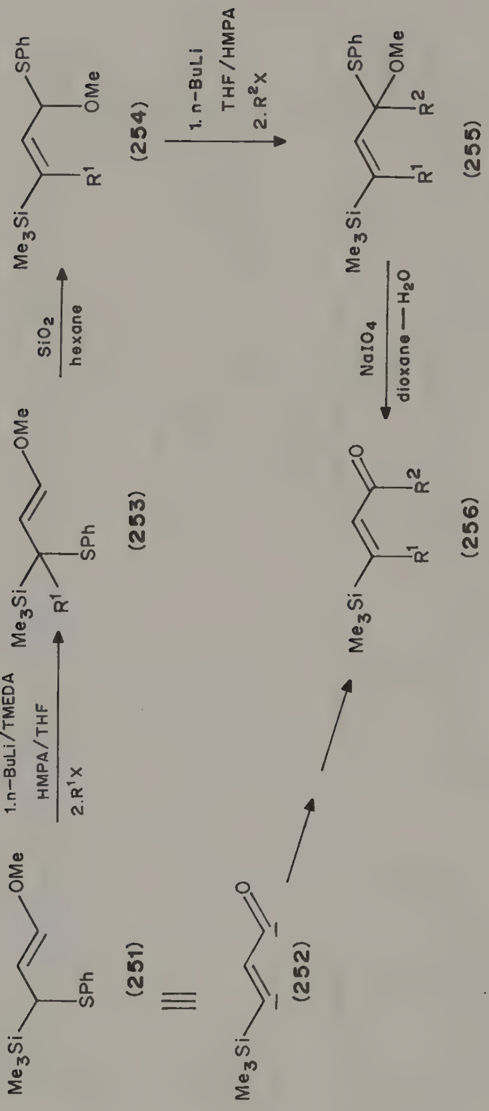
β-Silylenones such as **256** are important intermediates in synthetic work and can be obtained from dianion **252**. An interesting equivalent of dianion **252** is 1-methoxy-3-phenylthio-3-trimethylsilyl-1-propene **251**[160,161], which allows easy preparations of



SCHEME 11



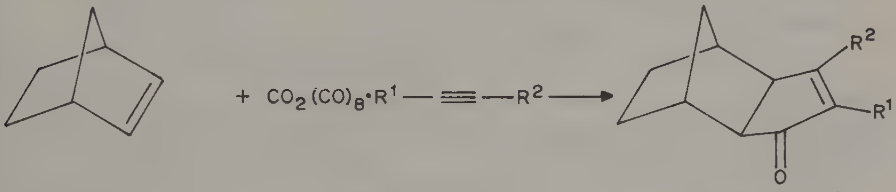
CN
Li$^+$
Et
Me
(244)
+
Ph
(245)
CN
OR
Ph
0.5 N
NaOH
1 h
(246) R=CH(Me)—OEt
(247) R=H
Z- (243)
+
E- (243)
PCC/
CH$_2$Cl$_2$
(248)
1. LiHMDS
2.
CHO
OH
(249)
Δ
OH
(250)


Me3Si
SPh
OMe
(251)
(252)
Me3Si
O
1.n-BuLi/TMEDA
HMPA/THF
2.R1X
Me3Si
R1
SPh
OMe
(253)
SiO2
hexane
Me3Si
R1
OMe
SPh
(254)
1. n-BuLi
THF/HMPA
2. R2X
Me3Si
R1
R2
SPh
OMe
(255)
NaIO4
dioxane—H2O
Me3Si
R1
R2
O
(256)

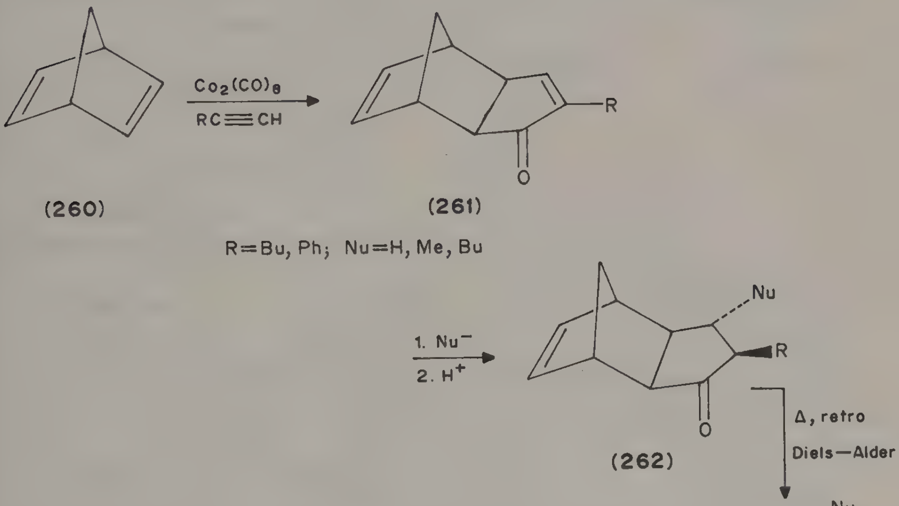
various β-trimethylsilylenones **256**[162] by the simple manipulations shown here. The key steps involve silica gel-promoted allylic rearrangement of the phenylsulfide group (from **253** to **254**) and the oxidation of **255** with sodium periodate to silylenone **256**[163].

VI. INSERTION OF CARBON MONOXIDE

Metal-promoted carbonylation reactions to give enone products have been known for some time. The first was discovered[164] as a low-yield reaction between strained alkenes, e.g. **257**, and an alkyne–dicobalt octacarbonyl complex **258**, producing cyclopentenone **259**. The reaction was later applied[165] to the synthesis of 4,5-disubstituted cyclopentenones **263** and the same group of workers also demonstrated an intramolecular version of the reaction[166] which yielded the bicyclic enones **266** and **267**.



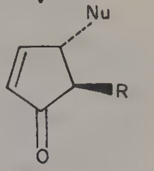
(257) (258) (259) $R^1 > R^2$



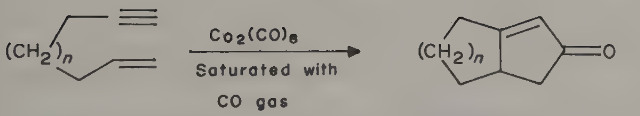
(260) (261)

R=Bu, Ph; Nu=H, Me, Bu

(262)



(263)

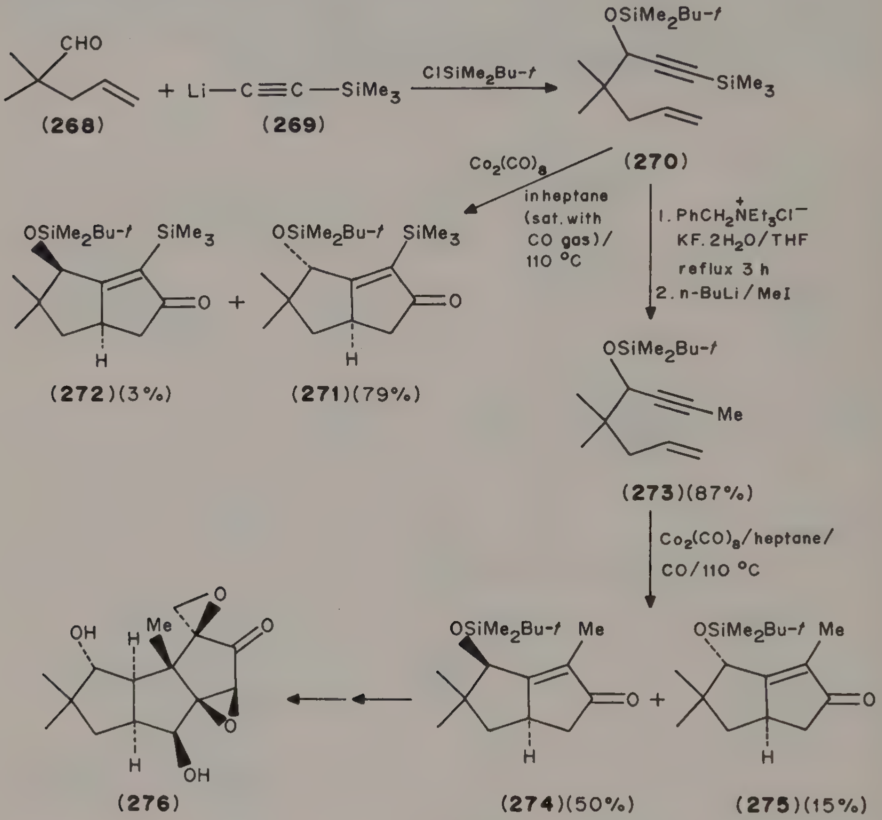


(264) $n=1$
(265) $n=2$

(266) $n=1$
(267) $n=2$

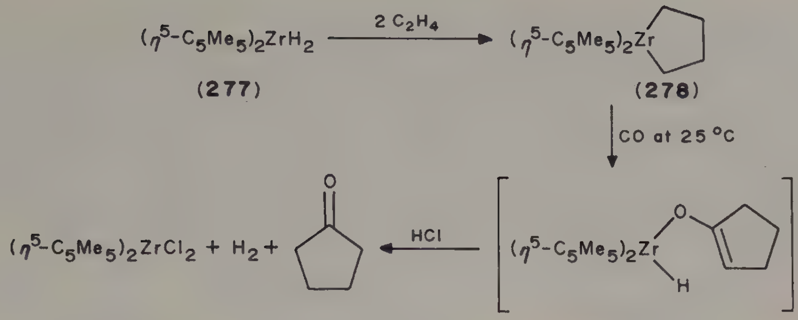
More recently Exon and Magnus[167] emphasized the usefulness of this reaction by the synthesis of (dl)-coriolin **276**, a hirsutane antitumor sesquiterpene isolated from the culture broth of Basidiomycete *Coriolus consors*[168], via the key intermediate **274**.

Interestingly, the cobalt carbonyl-promoted intramolecular cyclization–carbonylation reaction of the terminal trimethylsilyl acetylene **270** yields **271** and **272** in a ratio of 26:1, while the same reaction with the terminal methyl acetylene **273** results in a 3.3:1 mixture of **274** and **275**. Evidently the terminal group on the acetylene exerts a major influence on the stereochemical course of the reaction[169].



It was earlier mentioned that zirconium complexes, such as dicyclopentadienylzirconium dihydride $[(C_5H_5)_2ZrH_2]$[14], catalyze cross aldol condensations and are employed[16] in the synthesis of α-methylene cycloalkanones (e.g. **18**) and cycloalkenones (e.g. **19**). In addition, similar reagents also promote carbonylation reactions. For example, di(pentamethylcyclopentadienyl)zirconium dihydride **277** reacts with ethylene to form complex **278** which, when treated with carbon monoxide, undergoes carbonylation to give the enol ether complex **279** which can be hydrolyzed with acid to yield cyclopentanone and the zirconium salt **280**[170].

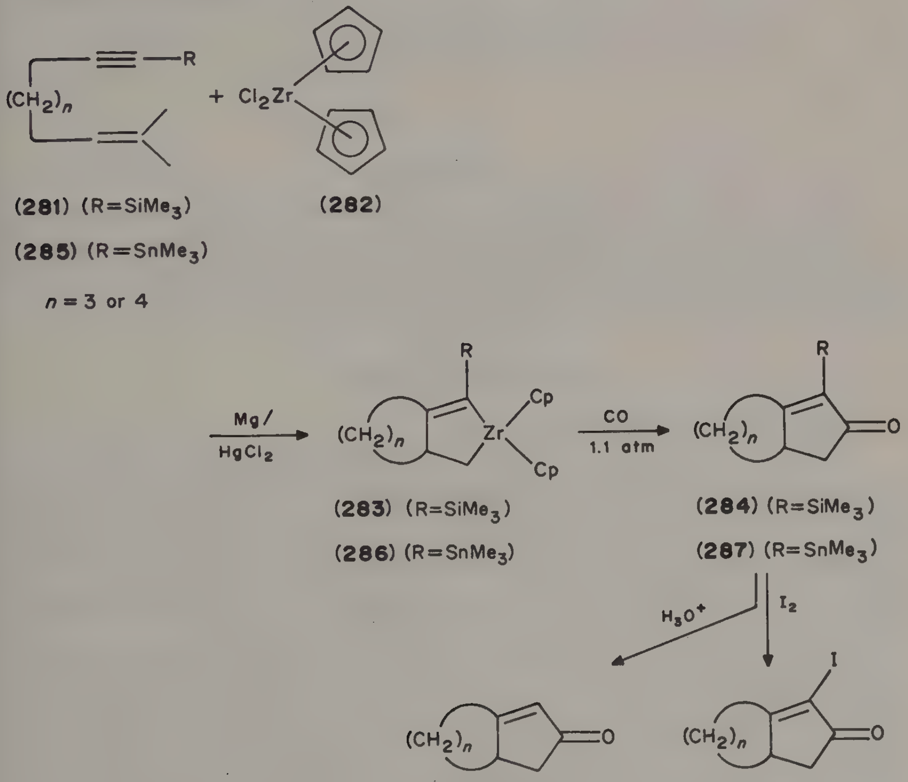
Another example is the double cyclization of trimethylsilylenyne **281** with dicyclopentadienylzirconium dichloride **282**, in the presence of magnesium and mercuric chloride, to form complex **283**, which can be isolated and characterized, and which undergoes



(277) **(278)** **(279)** **(280)**

carbonylation upon treatment with carbon monoxide (1.1 atmosphere) to give α-silylcyclopentenone **284** in reasonable yields[171].

However, problems encountered in the subsequent removal of the trimethylsilyl group in **284** have led to its replacement by the trimethylstannyl group[172]. Thus, starting with **285**, the zirconium complex obtained is **287** which, when treated with aqueous acid, gives **288** or, with iodine, gives **289**. The detailed mechanism of this reaction has also been studied and clarified[173].



(281) (R=SiMe$_3$)

(285) (R=SnMe$_3$)

n = 3 or 4

(282)

(283) (R=SiMe$_3$)

(286) (R=SnMe$_3$)

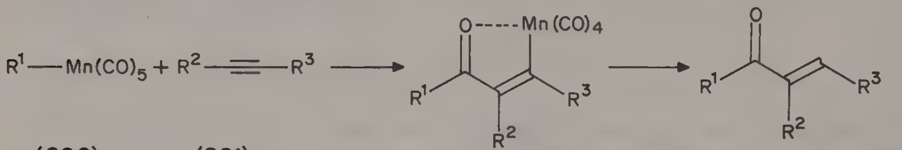
(284) (R=SiMe$_3$)

(287) (R=SnMe$_3$)

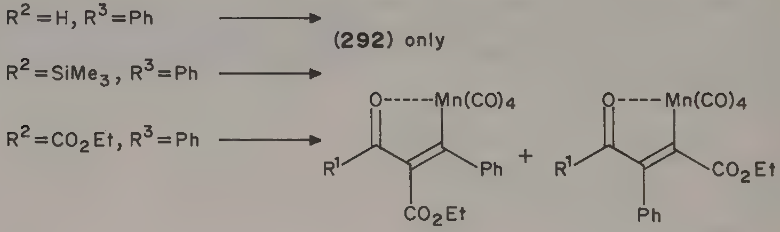
(288)

(289)

Apart from the use of complexes of cobalt and zirconium in carbonylation reactions in the synthesis of enones, carbonyl complexes of rhodium[174] and manganese[175] have also been employed, although the reactions are not yet developed to the state where they can be considered as general. Nearly two decades ago it was reported that methyl and phenylmanganese pentacarbonyls undergo sequential insertions of carbon monoxide and terminal alkyne to produce manganacycles, e.g. **292**, in low yields at atmospheric pressure[176]. Very recently there was a report that the reaction proceeds with **290** and **291** under high pressure, in a regiospecific manner, and in high yield[175]. The resulting manganacycle can be treated with acid to give enone **293** in reasonable yield.



(290) (291) (292) (293)



(292a) (51%) (294) (34%)

It should be noted, however, that the regio-control is observed only in alkynes which carry substituents (R^2 and R^3 in **291**) that differ in electronic properties. Thus, the reaction between manganese carbonyl complex **290** and alkyne **291** gives only **292** when R^2 is hydrogen or trimethylsilyl (67% and 55% respectively), but yields a mixture of **292a** and **294** (51% and 34%) when R^2 is carboethoxy and R^3 is phenyl.

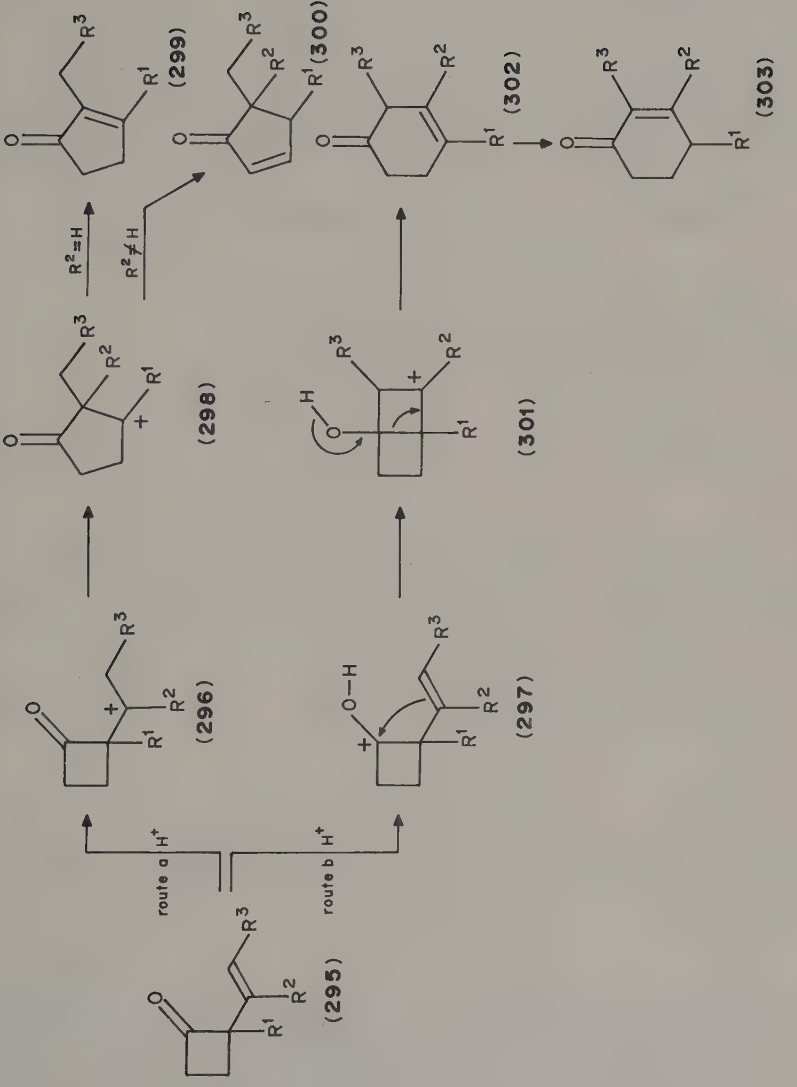
VII. OTHER METHODS

A. Ring Expansion and Ring Contraction

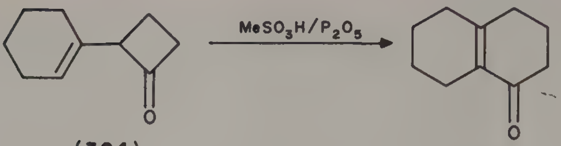
2-Vinylcyclobutanones such as **295** undergo acid-catalyzed rearrangements via cationic intermediates **296** (route a) to the corresponding cyclopentenones **299** or **300** and via **297** (route b) to cyclohexenones **303**, depending on the substituents, as depicted in Scheme 12. The overall reaction is, in fact, a 1,2- (route a) or 1,3- (route b) migration of the acyl group.

Accordingly, treatment of the easily obtainable vinylcyclobutanones **304–307**[177–179] with methanesulfonic acid results in the corresponding cyclic enones **308–312** in moderate yields via 1,2- or 1,3-acyl migration[179,180].

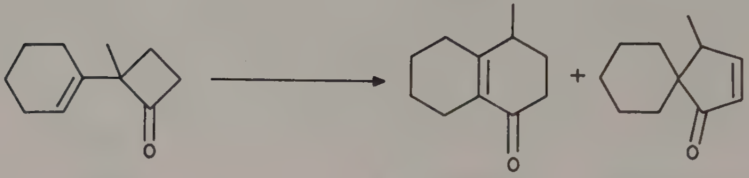
Substituted keteniminium salts **314** have been shown to add alkyl and arylacetylenes **315** in a cycloaddition fashion to give, after basic hydrolysis, a good yield of cyclobutenones **316**[181]. Addition of anion **317** to the cyclobutenone results in enol **318**, which can be made to undergo ring expansion by treatment with thallous ethoxide in chloroform, to yield cyclopentenone **320**[182]. The proposed mechanism for this reaction involves the generation of dichlorocarbene from chloroform and subsequent attack of the carbene on selenium to form ylide **319** which readily undergoes ring expansion to **320**[183].



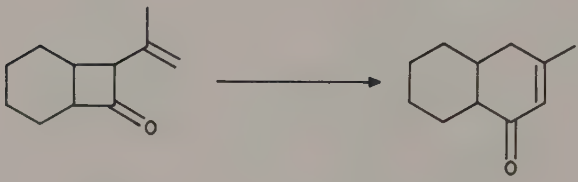
SCHEME 12



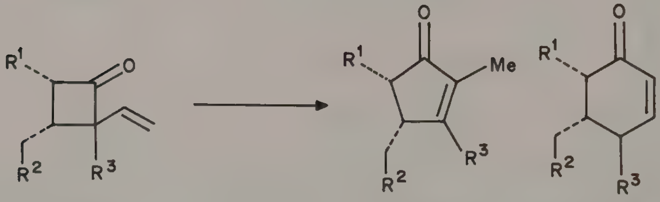
(304) (308)



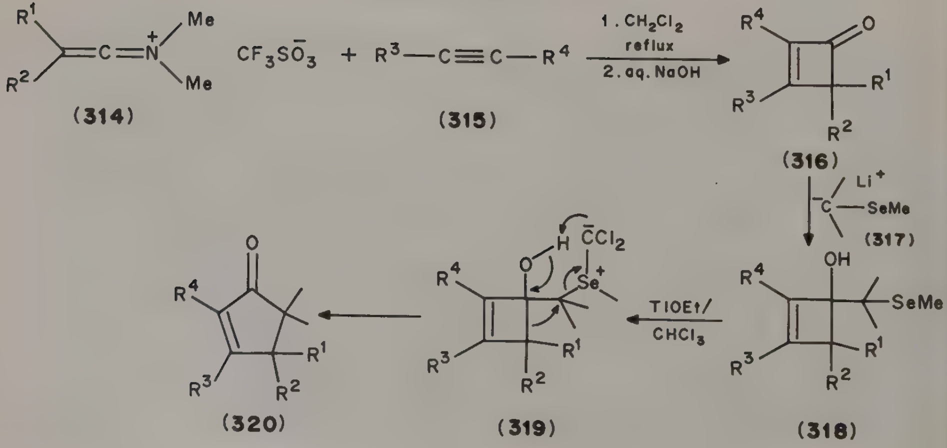
(305) (309) (13%) (310) (51%)



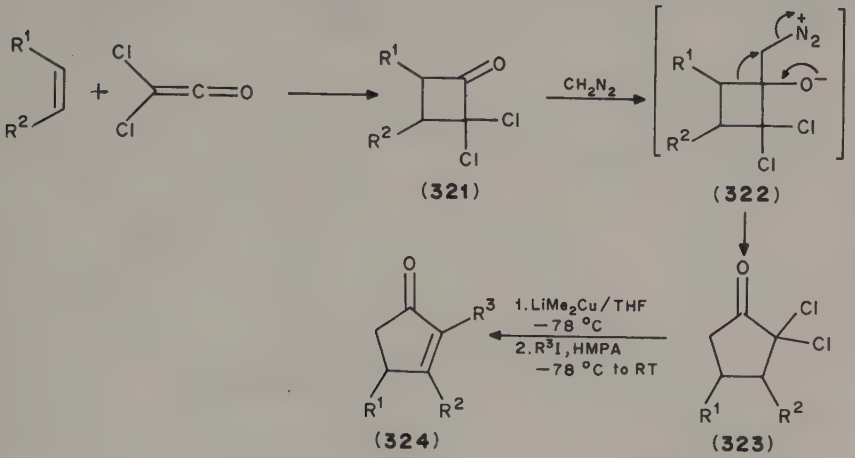
(306) (311)

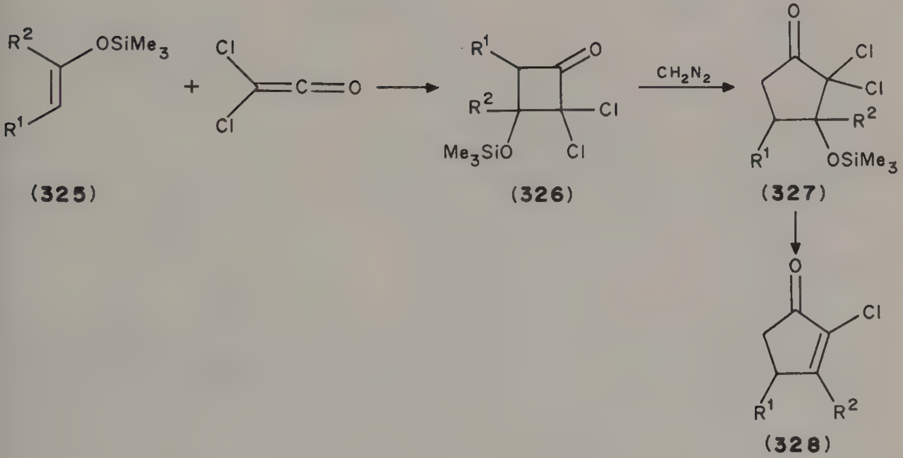


(307) (312) only (313) none



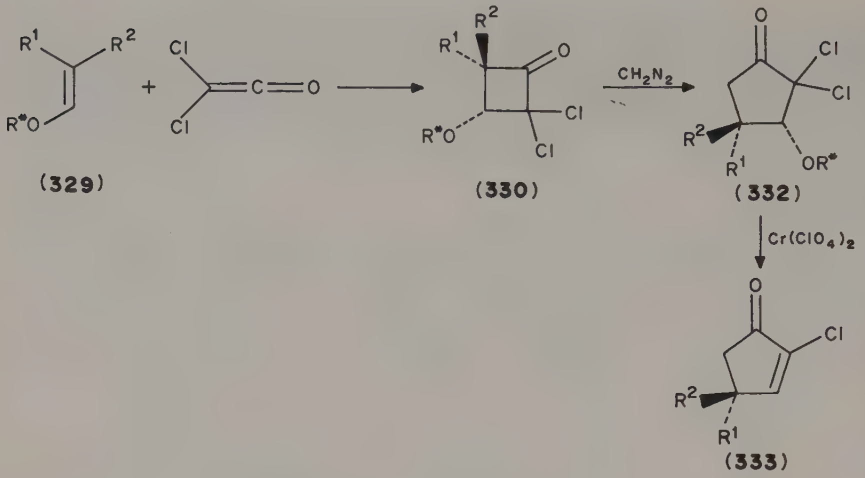
A similar ring expansion occurs in the reaction between 2,2-dichlorocyclobutanone **321** (obtained from cycloaddition of dichloroketene to the corresponding olefin[184]) and diazomethane, to give, regiospecifically, dichlorocyclopentanone **323**[185], which can be easily converted into enone **324**[186]. By using silyl enol ether **325** in the preparation of the starting cyclobutanone one can also achieve the synthesis of 1-chlorocyclopentenones **328**.



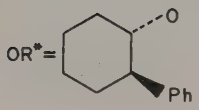


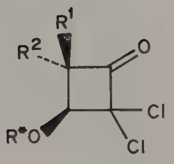
Further elaboration using a chiral enol ether such as **329** in the cycloaddition provides a 9:1 mixture of cyclobutanones **330** and **331** and leads to the preparation of optically active cyclopentenone **333**[187]. This is an important intermediate (where $R^1 = p\text{-MeC}_6H_4$, $R^2 = Me$) in the synthesis of (−)-α-cuparenone **334** and (+)-β-cuparenone **335**[188], sesquiterpenes from the essential oil of *Mayur pankhi* and liverwort *Mannia fragrans*[189].

The reaction between allenylsilanes, e.g. **336**, and α,β-unsaturated acylsilanes, e.g. **337**, in the presence of titanium tetrachloride at −78 °C for a short period affords acylcyclopentenes **341** in good yields. On exposure to $TiCl_4$ at higher temperatures **341** undergoes ring enlargement to produce β-silylcyclohexenone **344**[190]. It is therefore

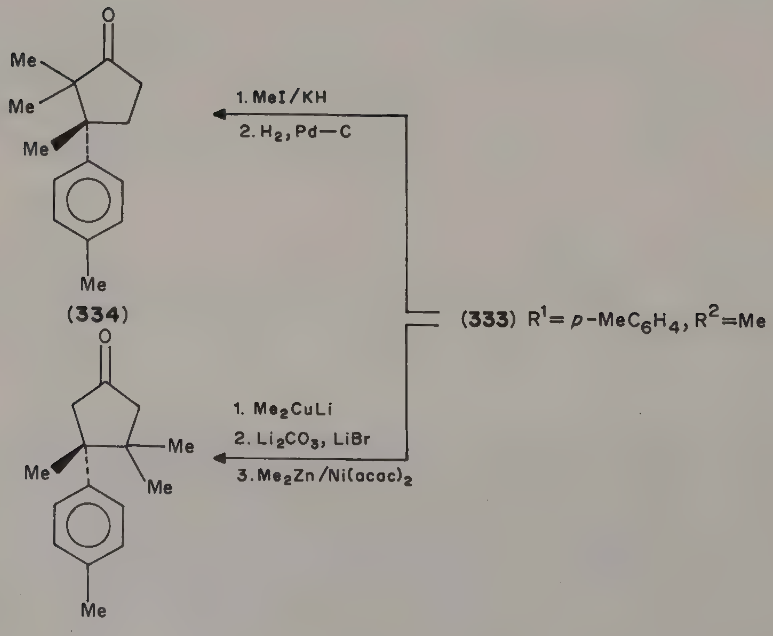


(329) (330) (332) (333)





(331)

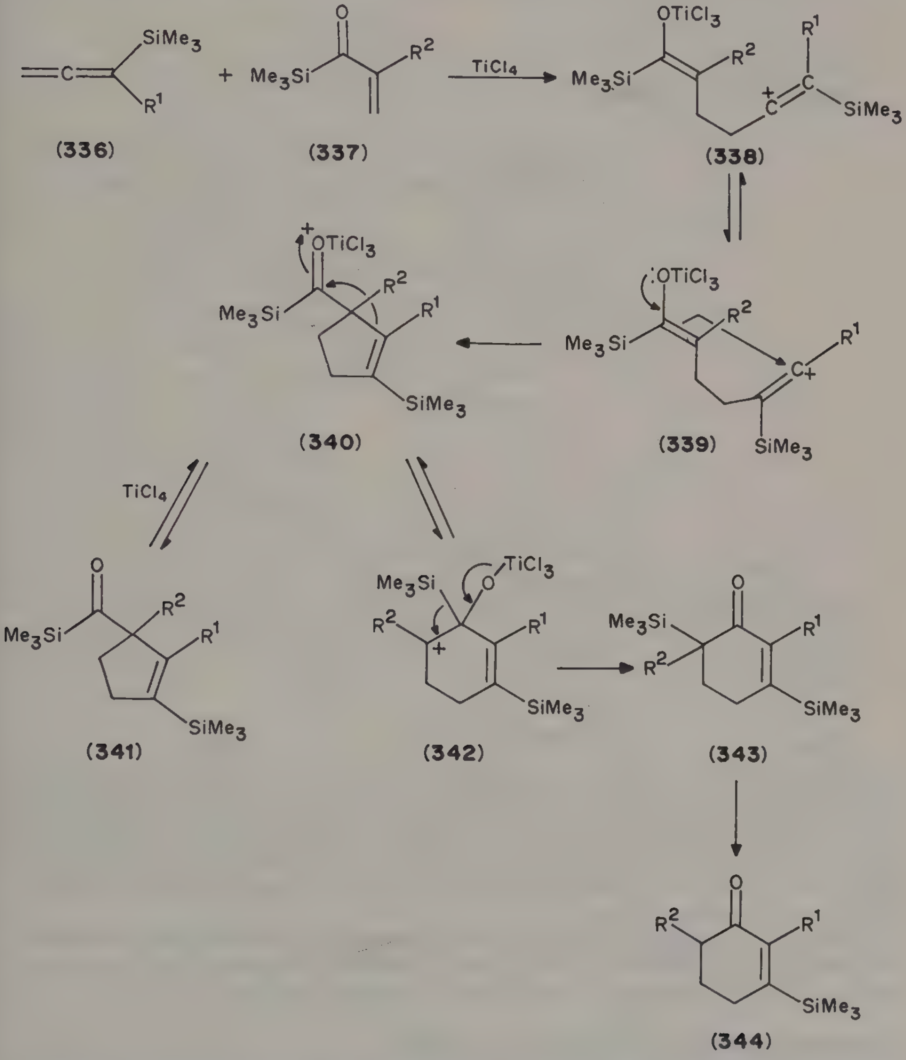


(334)

(333) R^1 = p-MeC$_6$H$_4$, R^2 = Me

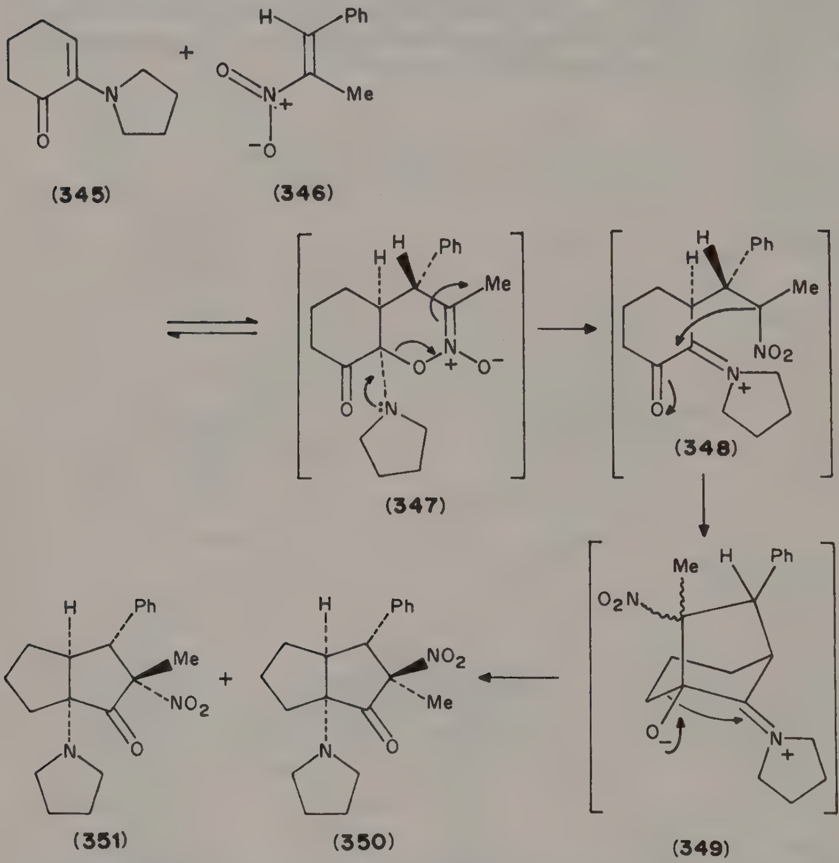
(335)

practicable to leave the reaction between **336** and **337** longer at a temperature higher than − 78 °C to yield directly enone **344**. A feasible mechanism is regiospecific addition at C-3 of the allenylsilane to the unsaturated acylsilane, producing carbocation **338**. The regiospecificity can be explained by the '*β* effect' of the silyl group as discussed earlier. Subsequent migration of the silyl group followed by ring closure results in cyclopentene **340** which, after work up, is isolated as acylcyclopentene **341**. At higher temperatures with longer reaction times, however, **340** undergoes ring enlargement to **342** which then proceeds via a series of steps to the final six-membered ring enone **344**.



Besides ring enlargement, ring contraction is used for constructing the enone functionality. The following examples illustrate the advantageous use of this method to synthesize enones that are otherwise difficult to construct.

The reaction between ketoenamine **345** and nitroalkene **346** takes place rapidly, in the absence of solvent, to form, initially, 1,2-oxazine *N*-oxide **347**. This then reacts via a series of steps which terminate in ring contraction according to the arrows in **349** to yield fused cyclopentenones **350** and **351** as products[191,192].



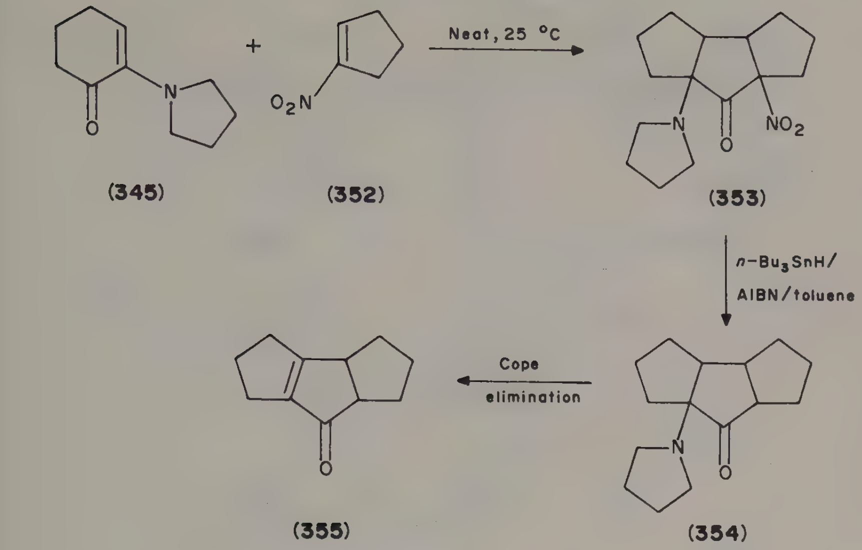
(345) (346) (347) (348) (349) (350) (351)

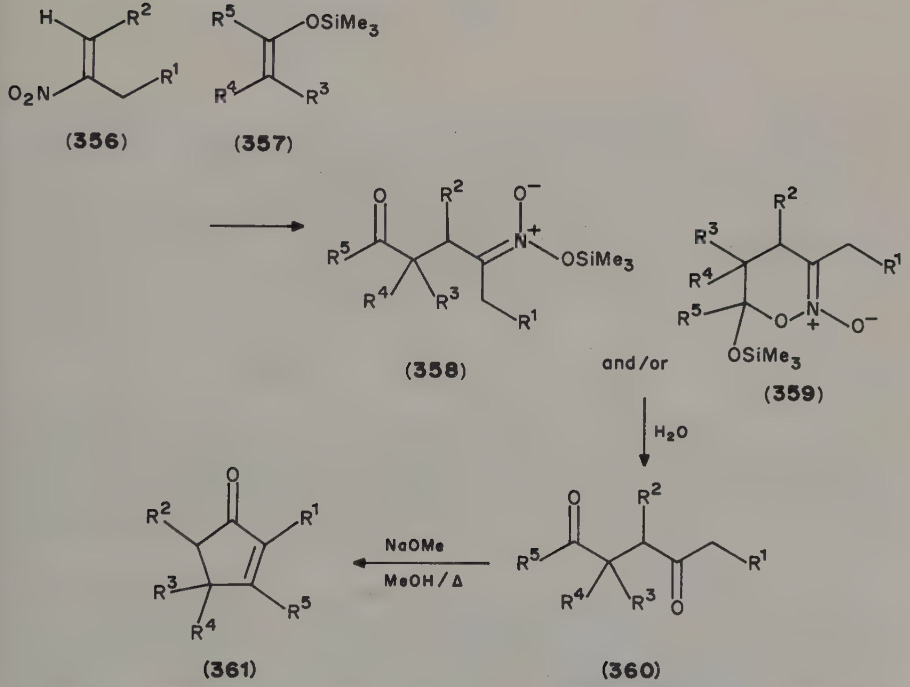
An application of this reaction is exemplified in the synthesis of the triquinane system **355**[193] from ketoenamine **345** and nitrocyclopentene **352**. A neat mixture of **345** and **352** at 25 °C furnishes a quantitative yield of **353**. Reductive removal of the nitro group with tributyltin hydride and azoisobutyronitrile (AIBN) in refluxing toluene[194] produces **354**. Finally, Cope elimination of the pyrrolidine group delivers the target triquinane derivative **355** in a very high overall yield.

It is worth noting that the use of nitroalkene in cycloaddition reactions can be applied to the synthesis of 1,4-diketone derivatives **360**[195], themselves important precursors in the synthesis of cyclopentenones by the classical condensation method[196].

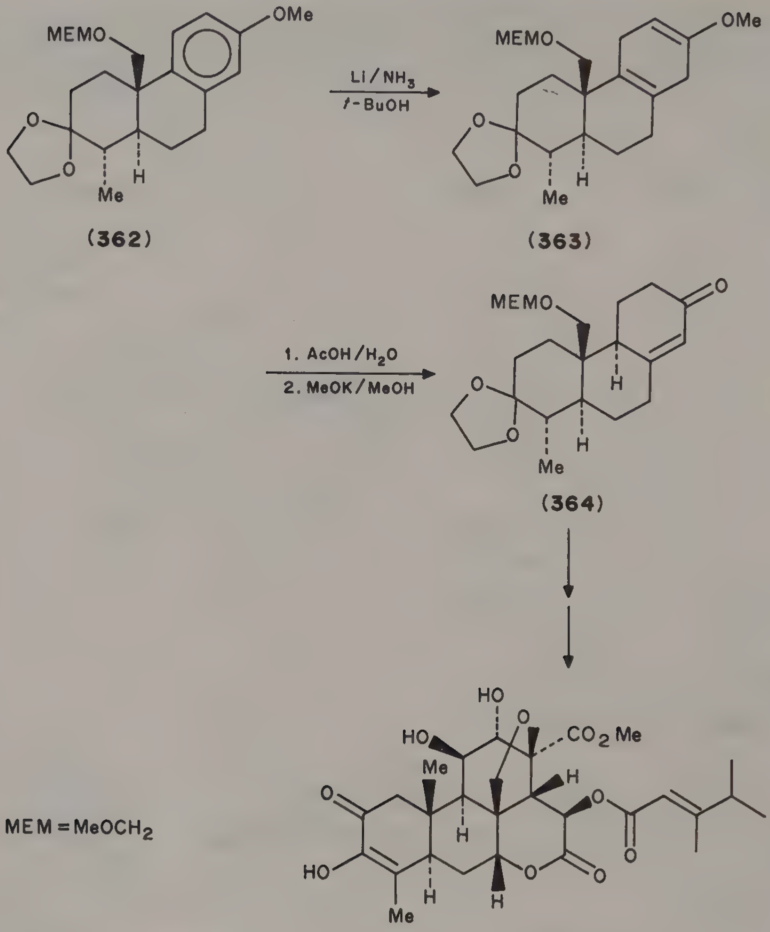
B. Oxidation/Reduction of Aromatic Compounds

Aromatic compounds provide a good source for enones and dienones. The Birch reduction of aromatic ethers, for example, is still currently important, particularly in the preparation of cyclohexenone derivatives.





The total synthesis of bruceantin **365**, the antileukemic quassinoid from *Brucea antidysenterica*[197], employs enone **364** as the key intermediate. This is synthesized[198] from **362** by Birch reduction, followed by acid hydrolysis and double-bond isomerization as shown below.

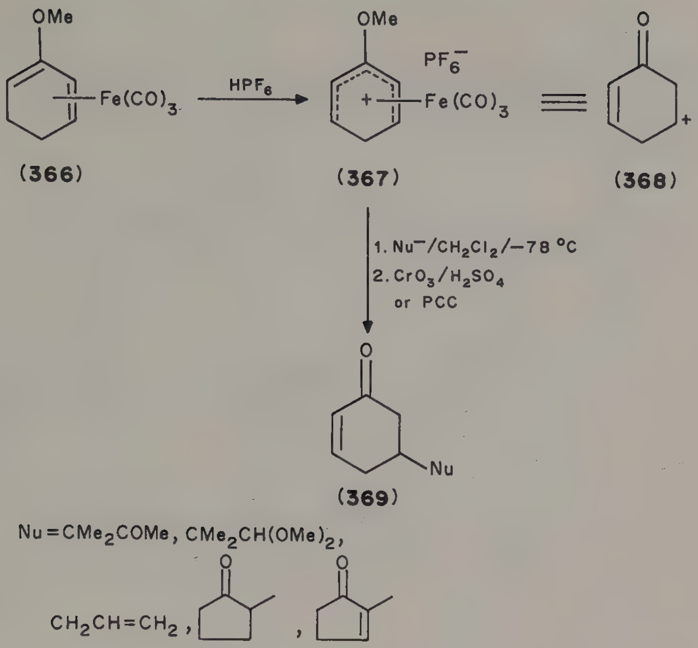


(362) (363) (364) (365)

MEM = $MeOCH_2$

The hexafluorophosphate salt of tricarbonyl(3-methoxycyclohexa-2,4-dien-1-yl)iron **367** can be prepared[199] by hydride abstraction from the iron complex **366** which, in turn, is obtainable by Birch reduction of the corresponding aromatic compound. This salt is synthetically equivalent to the 5-cyclohex-2-enone cation **368**[200] and is a useful precursor to 5-substituted cyclohex-2-enones **369** through its reaction with a nucleophile, followed by oxidation and hydrolysis.

Another example is the synthesis of 2,3-disubstituted cyclopentenones **375**. Birch reduction of **370** and subsequent quenching of the enolate **371** with an alkyl halide yields **372**. Ozonolysis of the electron-rich double bond provides the intermediate aldehyde **373** which can be oxidized with Jones' reagent to the acid and decarboxylated to the required cyclopentenone **375**. Various substituents may be employed, although a higher overall yield is observed when R is a good electrophile[201]. The process was used to synthesize[202] tetrahydrodicranenone B **376**, a member of the fatty acid group of antimicrobial natural products isolated from Japanese mosses[203].

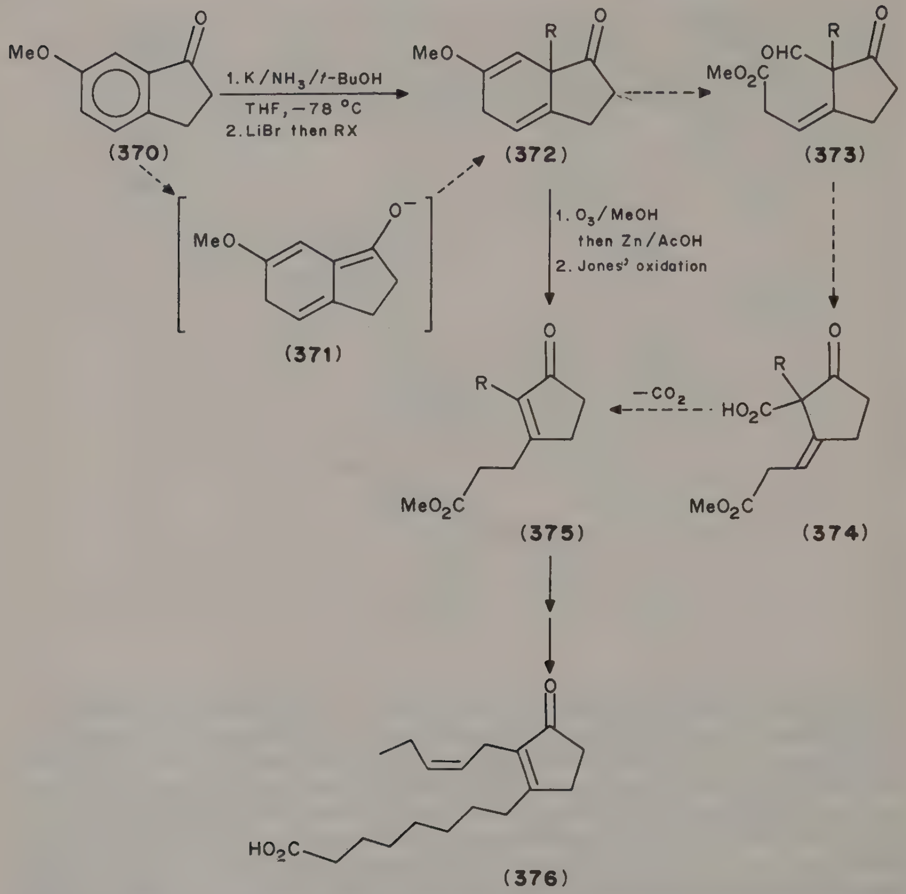


Complementary to the reduction of aromatic ethers is the oxidation of phenols which constitutes a straightforward route to six-membered ring dienones. For example, direct oxygenation[204] of **377** with a cobalt catalyst leads immediately to **378**. Alternatively, bubbling oxygen through a solution of **377** in diethylamine containing an excess of sodium amide at 20 °C gives **378** in excellent yield[205]. Moreover, the oxidation can be accomplished with the use of thallium nitrate; several 4-methoxy- **379** and 4-alkyl-phenols **380** have been oxidized with thallium nitrate (in methanol with or without trimethyl orthoformate) to yield 4,4-dimethoxy- and 4-alkyl-4-methoxy-cyclohexa-2,5-dienones **381** and **382**, respectively[206].

In the synthesis of (±)-solavetivone **387**, isolated from the fungus *Phytophoria infestans* that infects potato tubers[207] and air-cured Burley tobacco[208], a Japanese group[209] employed spiro-annulation[210] by intramolecular cyclization of the phenolic α-diazoketone **383** to construct the spiro[4.5]decane framework **384**. They then made use of the effect of the neighbouring hydroxy group in metal-ammonia reduction, which is both regio- and stereoselective[211], to control the reduction of dienone **385** to enone **386**, an important precursor to (±)-solavetivone **387**.

C. Pericyclic Reactions

Many syntheses of enones, particularly of cyclopentenone derivatives, have involved pericyclic reactions. A well-known and widely used such reaction is the Nazarov cyclization[118] mentioned earlier in the discussion of acylation reactions. In fact it is an electrocyclic ring closure of the oxidopentadienyl cation (e.g. **195**) which, although long-known, has been developed and improved over the years. An example is the use of tributylstannylenone **389**, prepared[212] by Lewis acid catalyzed acylation of *trans*-1,2-(tri-*n*-butylstannyl)ethylene **388**, in a stepwise aldol condensation to give **391**, which

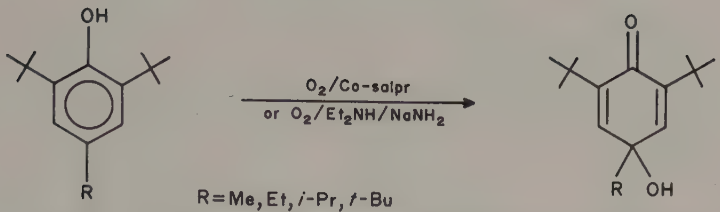


undergoes Nazarov cyclization with an excess of boron trifluoride etherate to yield 4,5-disubstituted cyclopentenone **392** as a mixture of *cis* and *trans* isomers in very good overall yields[213].

Hexahydroindene **397** is similarly synthesized via a Nazarov cyclization following the cycloaddition reaction between **395** and methyl maleate. It is interesting to note that, in this case, gallium(III) chloride is far more effective than other Lewis acids[214].

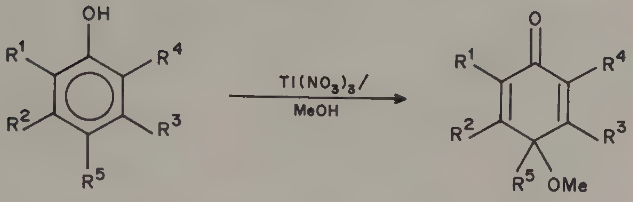
It is quite possible that nature itself also exploits the pericyclic reaction, for instance in the biosynthesis of clavulone **94** by the Pacific coral, *Clavularia viridis*[69]. It is believed[215–217] that preclavulone **402** is first formed via the allene oxide **400**, which undergoes allene oxide rearrangement to the pentadienyl cation **401** and then cyclizes by conrotatory mode to the *cis*-disubstituted cyclopentenone **402** as shown in Scheme 13. Interestingly, because of the similarity in structure, it has been proposed that *cis*-jasmonic acid **403** is also biosynthesized via this type of cationic intermediate[215].

The chemical feasibility of the above idea was recently tested in the laboratory[218]. Trimethylsilyl trifluoroacetate **404** was treated with anhydrous cesium fluoride in acetonitrile to accomplish desilylation to the intermediate allene oxide **405** which underwent the reactions shown in Scheme 13 to yield *cis*-disubstituted cyclopentenone **407** (20–35%) as one of the products.



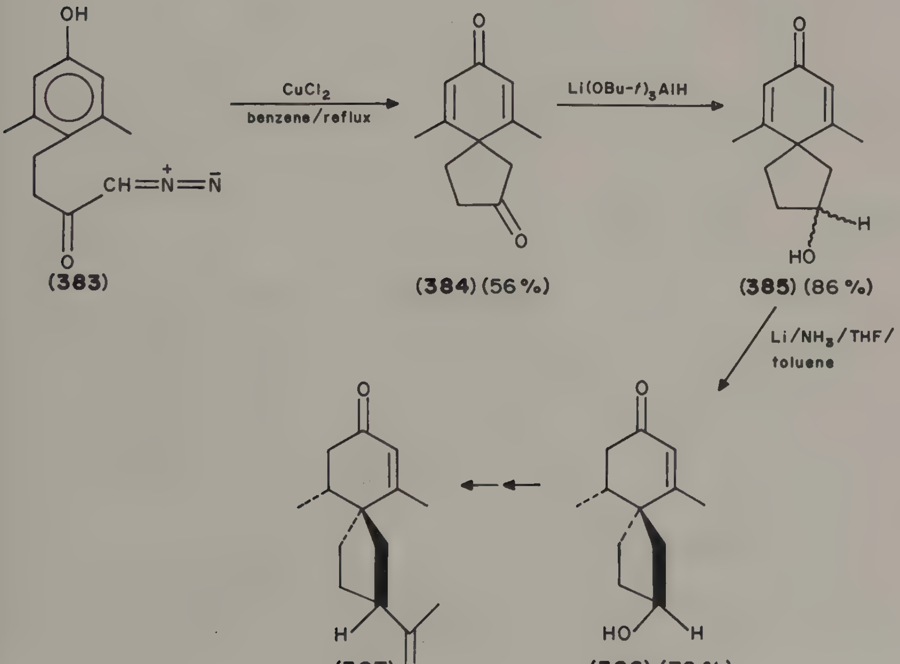
R=Me, Et, *i*-Pr, *t*-Bu

(377) salpr = bis(3—salicylidieneaminopropyl)amine **(378)**



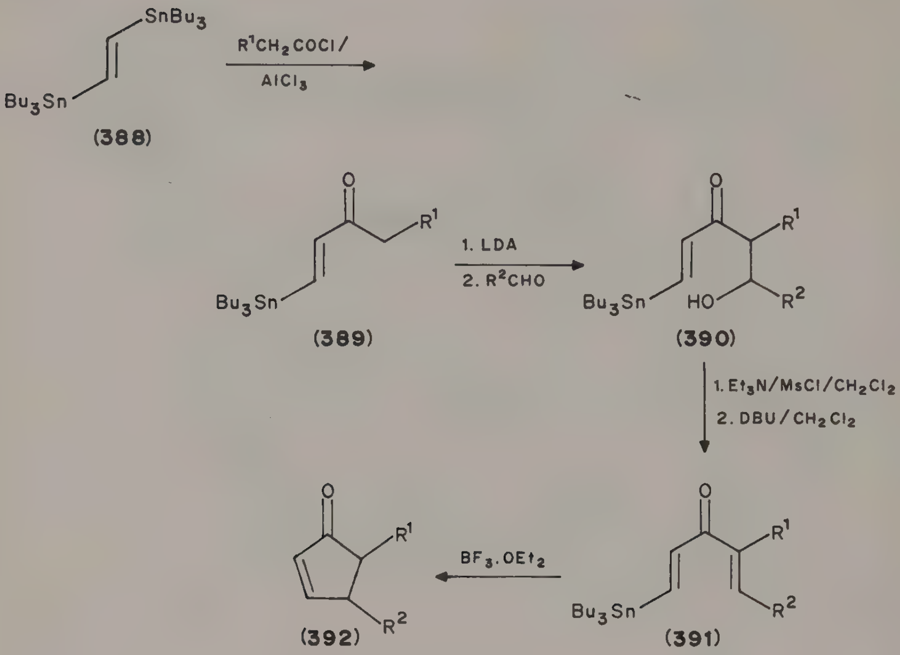
(379) R^1—R^4= H or alkyl, R^5=OMe **(381)**

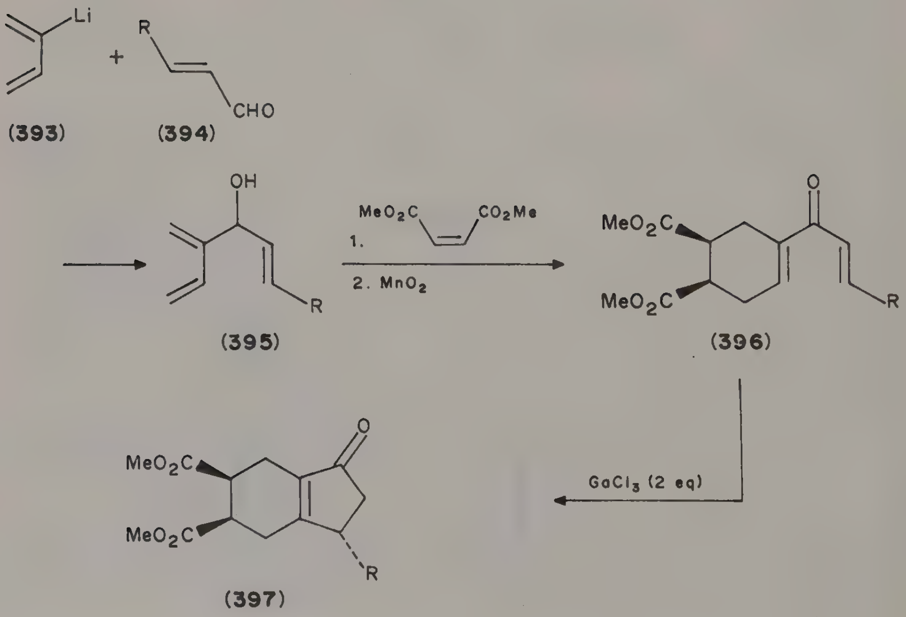
(380) R^1—R^4= H or alkyl, R^5=alkyl **(382)**

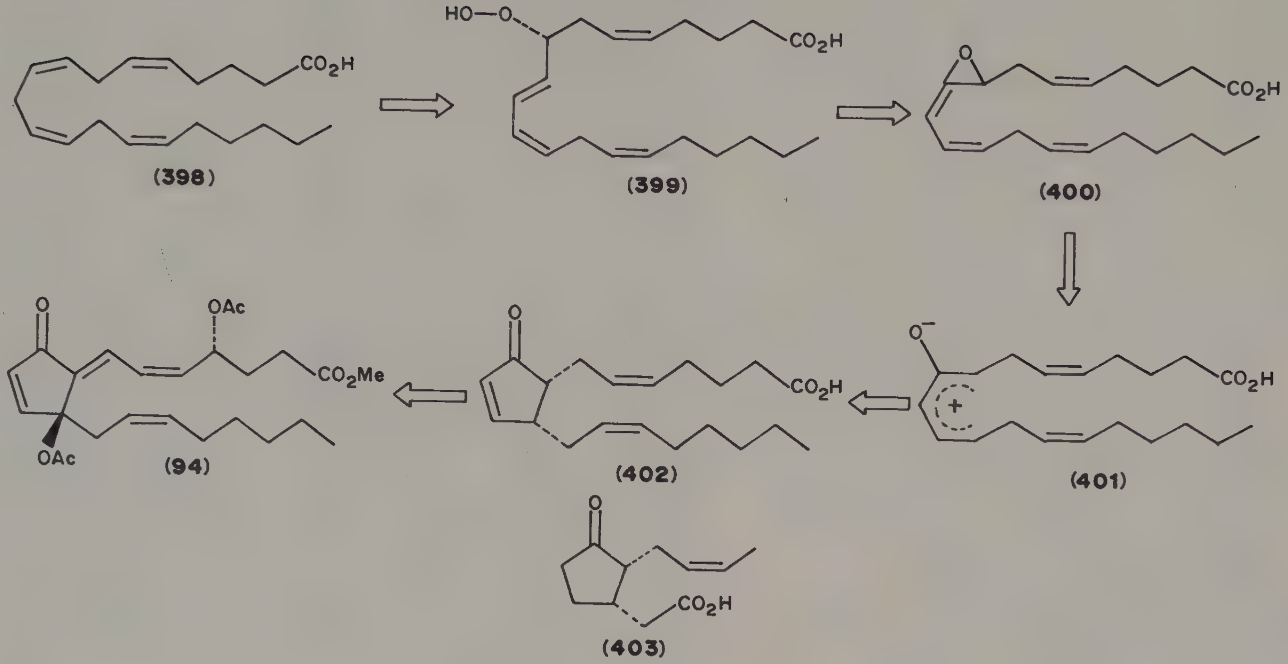


(383) **(384)** (56 %) **(385)** (86 %)

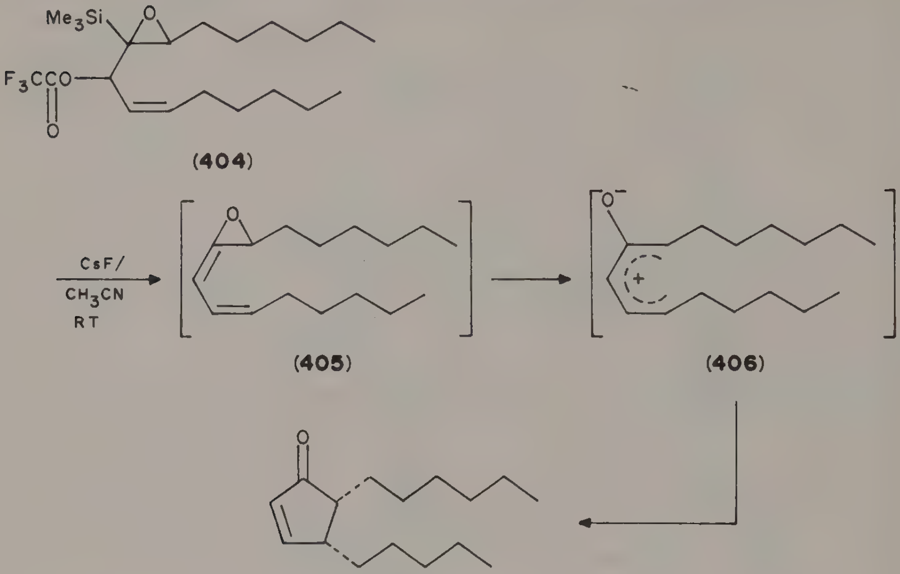
(387) **(386)** (78 %)


SnBu3
Bu3Sn
R1CH2COCl/
AlCl3
(388)
O
R1
Bu3Sn
(389)
1. LDA
2. R2CHO
O
R1
Bu3Sn
HO
R2
(390)
1. Et3N/MsCl/CH2Cl2
2. DBU/CH2Cl2
O
R1
Bu3Sn
R2
(391)
BF3.OEt2
O
R1
R2
(392)


Li
+
R
CHO
(393)
(394)
OH
R
(395)
MeO2C
CO2Me
1.
2. MnO2
MeO2C
MeO2C
O
R
(396)
GaCl3 (2 eq)
MeO2C
MeO2C
O
R
(397)


CO2H
(398)
HO—O
CO2H
(399)
O
CO2H
(400)
O−
+
CO2H
(401)
O
CO2H
(402)
O
OAc
CO2Me
OAc
(94)
O
CO2H
(403)

SCHEME 13



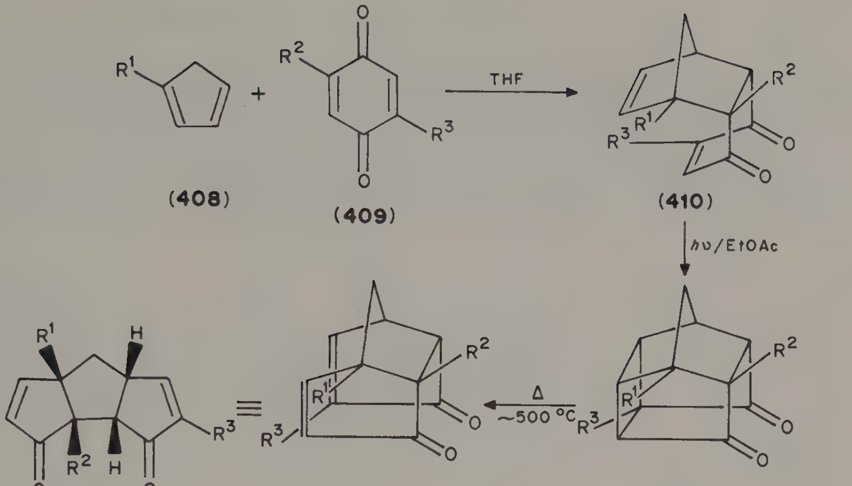
(407)

One of the most beautiful syntheses of fused enones to employ the pericyclic reaction is the construction of the *cis–syn–cis* triquinane carbon skeleton **412** by consecutive Diels–Alder reaction, photochemical [2 + 2]cycloaddition and ground-state cyclobutane ring-opening reaction. The cycloaddition reaction between cyclopentadiene **408** and *p*-benzoquinone **409** takes place readily at room temperature, giving the *endo* adduct **410**. When photolyzed in ethyl acetate, **410** undergoes intramolecular [2 + 2]cycloaddition to give the cage compound **411**, which can be transformed by heating at about 500 °C to the triquinane **412**. The obtained *cis–syn–cis* stereochemical relationship in **412** is also easily convertible into the *cis–anti–cis* stereochemistry. By this approach, therefore, the syntheses of various tricyclopentenoid natural products such as (±)-capnellene **413**[219] from the soft coral *Capnella imbricata*[220] and (±)-hirsutene **414**[221] from the fermentation broth of *Coriolus consors*[222] can be conveniently achieved.

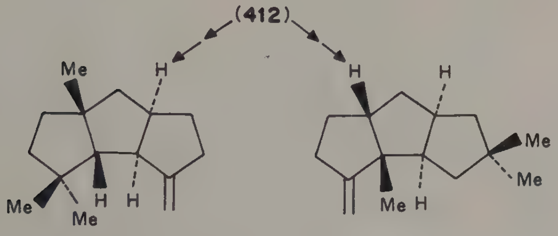
In tracing the carbon framework of product **412** back to the starting compounds **408** and **409**, the clever use of cyclopentadiene **408** as the synthon for pentane unit **415** and of *p*-benzoquinone **409** for hexanedione **416** can be better appreciated when emphasized by the construction lines in **417**.

A short route based on pericyclic reactions is reported for the synthesis of cyclooctenone **420**. Vinyl ketene **418**, generated by heating cyclobutenone or by the reaction of crotonyl chloride with base, undergoes [2 + 2]cycloaddition reaction with butadiene to give 2,3-divinylcyclobutanone **419** which further rearranges by a [3,3]sigmatropic rearrangement to octenone **420** in reasonable yields[223]. This sequence of pericyclic reactions can also be extended to the preparation of bicyclo[4.2.n]alkenones such as **422**.

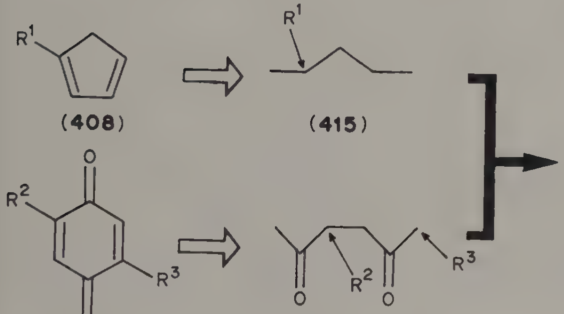
The use of the ene reaction in enone synthesis has also been investigated. One such application, reported a few years ago[224], involves titanium-catalyzed Michael addition between methallyltrimethylsilane **423** and α,β-unsaturated acyl cyanide **424** in a regiospecific manner (the β effect) to cleanly yield **426** via the cationic intermediate **425**. Vapour-phase pyrolysis of **426** effects an intramolecular ene cyclization (**427**) to give exclusively 3-methyl-2-cyclohexenone **429** and hydrogen cyanide[225].



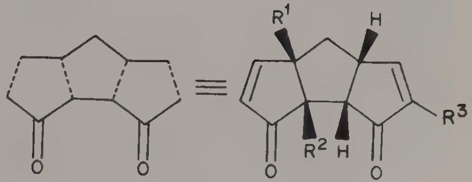
(408) (409) (410) (411)



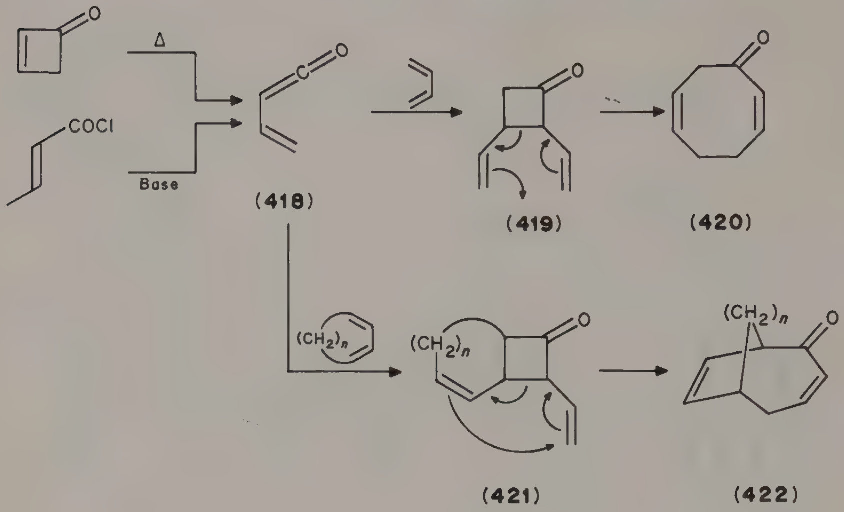
(413) (414)

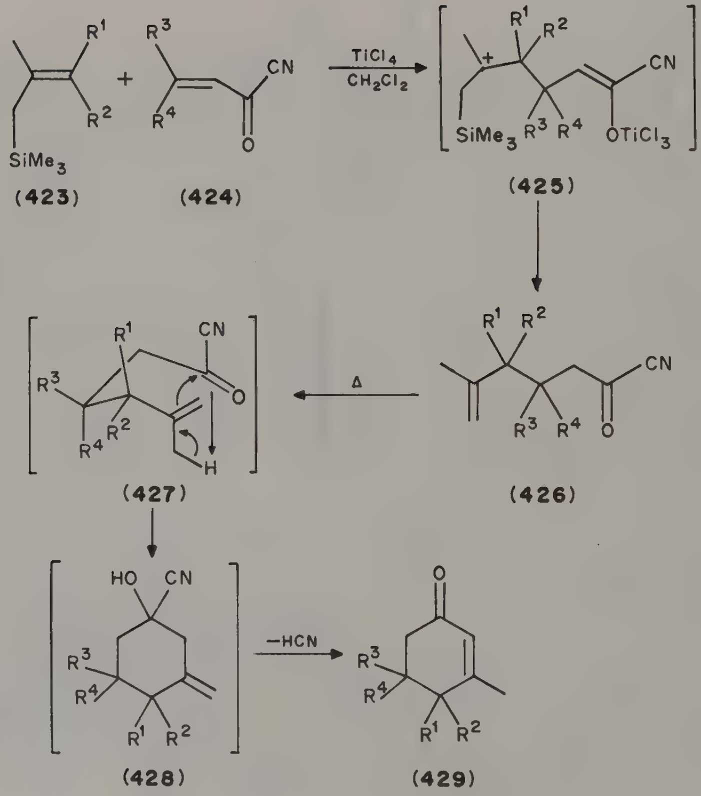


(408) (415) (409) (416)



(417) (412)

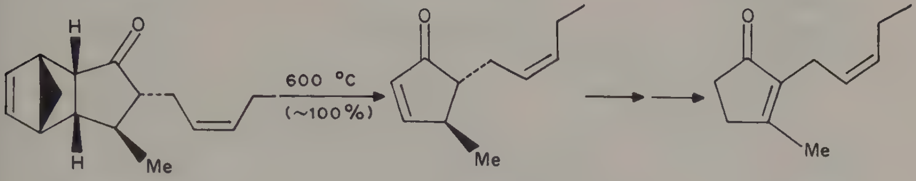

Δ
COCl
Base
(418)
(419)
(420)
(CH2)n
(CH2)n
(CH2)n
(421)
(422)


SiMe3
R1
R2
R3
R4
CN
+
TiCl4
CH2Cl2
OTiCl3
(423)
(424)
(425)
(426)
(427)
(428)
(429)
Δ
H
HO
−HCN

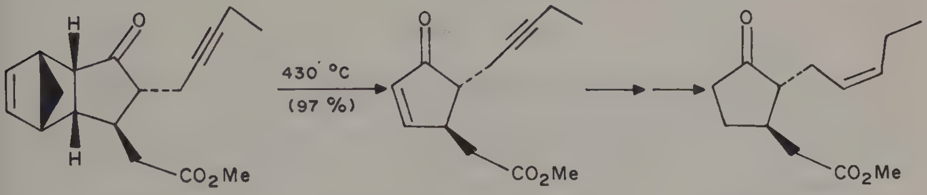
D. Retro Diels–Alder Reaction

Although the retro Diels–Alder reaction is technically only a class of pericyclic reactions, its extremely popular and widespread use in the synthesis of naturally occurring enones[226,227], especially exocyclic enones, warrants a section to itself.

It may probably be said that the retro Diels–Alder reaction owes its popularity in this area to the work of the group of Stork[228] and Ducos[229] who, in their respective syntheses of jasmone **432** and methyl jasmonate **435**, both employed the retro Diels–Alder reaction in the key step.



(430) **(431)** **(432)**

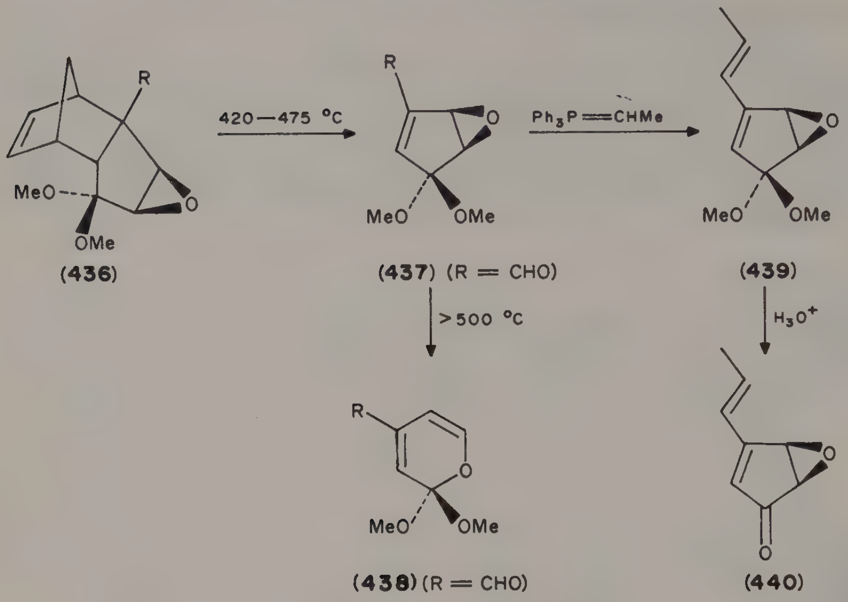


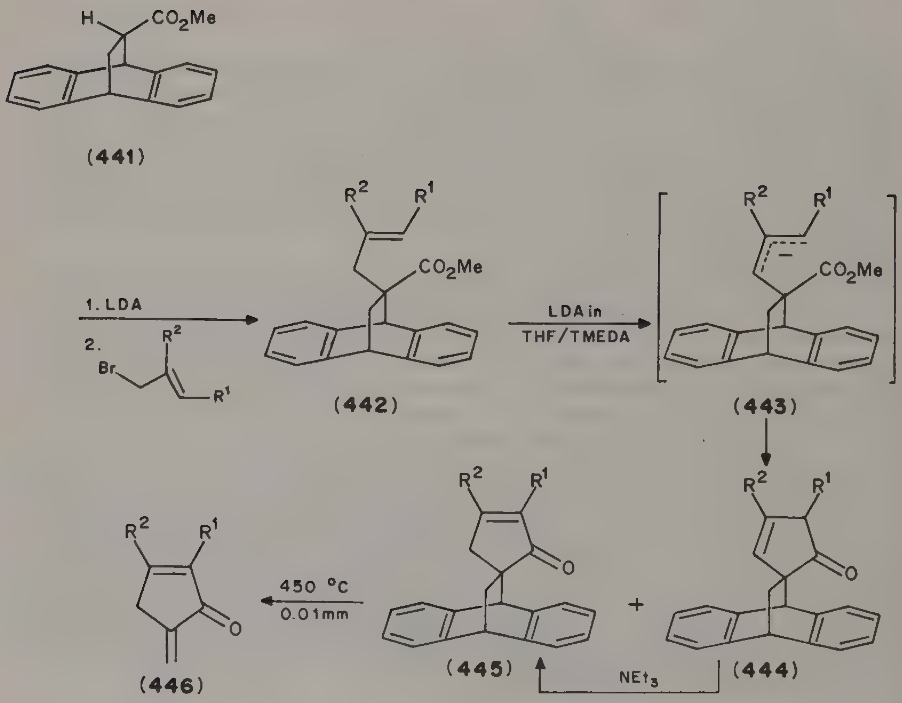
(433) **(434)** **(435)**

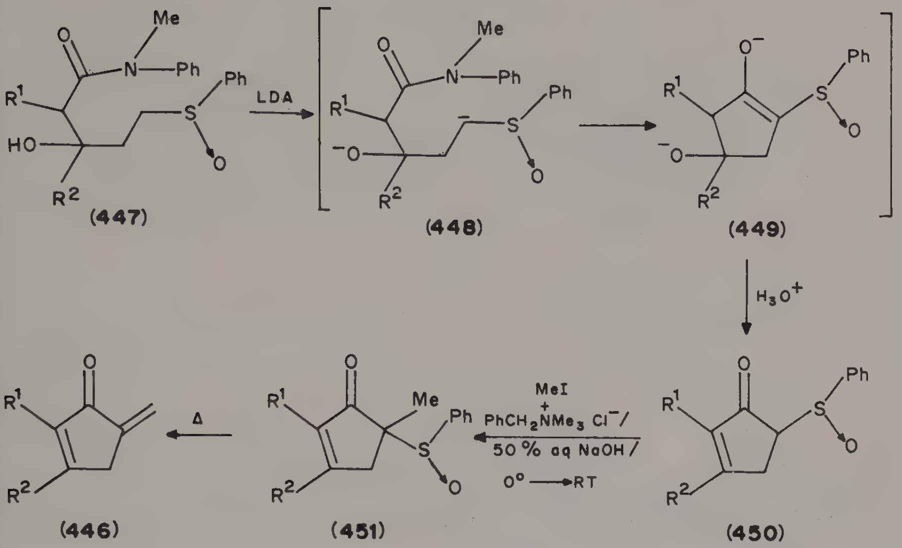
The synthesis of terrein **440**, a mold metabolite from *Aspergillus terreus*[230], via the retro Diels–Alder reaction is much better than other multi-step syntheses[231,232]. It was observed that flash vacuum pyrolysis of **436** gave a mixture of **437** and **438**, the ratio of which depended on the nature of R and the temperature of pyrolysis. When R was an electron-withdrawing group such as CHO, compound **436** gave exclusively **437** in nearly quantitative yield upon flash vacuum pyrolysis at 420–475 °C. Above 550 °C, however, **437** rearranged to **438**[233]. Application of these observations enabled terrein **440** to be efficiently synthesized as shown below[234].

The use of anthracene-methyl acrylate adduct **441** as a masked acrylate anion[235] allows easy construction of cyclopentenones via 3-carbon annelation reactions[236]. This technique, coupled with retro Diels–Alder flash-vacuum pyrolysis of the resulting spirocyclopentenones **445**, provides the most simple and efficient route to α-methylene cyclopentenones[237]. In this manner methylenomycin B (**446**, $R^1 = R^2 = Me$), a member of the class of 'cyclopentenoid antibiotics'[238] isolated from the culture broth of Streptomyces species[239], was synthesized as shown below.

As a matter of fact the first synthesis[240] of methylenomycin B, which led to a revision and hence the first true understanding of its structure (in 1979), had employed the classical condensation of 1,4-diketones[196] in constructing the cyclopentenone nucleus, followed by an elimination reaction to form the *exo*-methylene group. Since then several more syntheses have been reported[241–243]. One interesting example is that employing intramolecular acylation of an α-sulfinyl carbanion[244]. The sulfoxide group serves the dual function of stabilizing the α-anion needed for the internal acylation (**448** → **449**) and providing for the subsequent construction of the exocyclic double bond via elimination as shown in the sequence outlined below.


(436)
420—475 °C
(437) (R = CHO)
Ph$_3$P=CHMe
(439)
>500 °C
(438) (R = CHO)
H$_3$O$^+$
(440)


(441)
1. LDA
2. Br, R^2, R^1
(442)
LDA in THF/TMEDA
(443)
(444)
(445)
NEt$_3$
450 °C 0.01mm
(446)

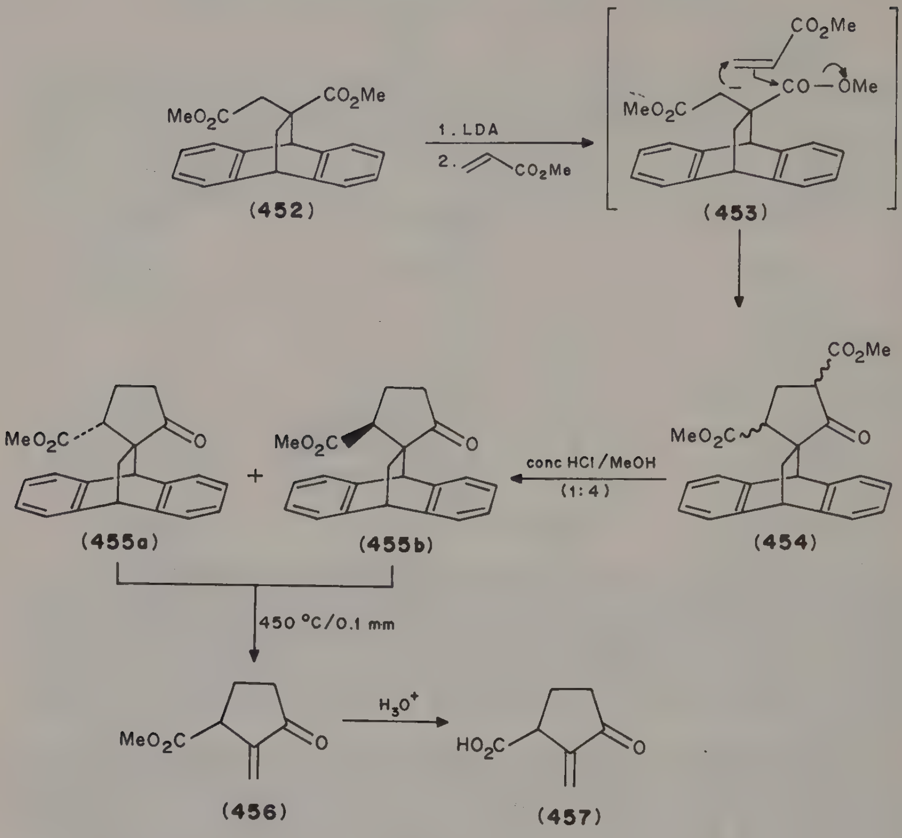


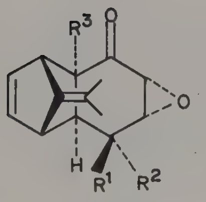
The high versatility of the anthracene adduct coupled with the synthetic utility of the retro Diels–Alder reaction is again demonstrated in the synthesis of sarkomycin **457**, a deceptively simple-looking molecule isolated from the culture broth of Streptomyces[245]. Because of its very interesting biological activities **457** has enjoyed repeated syntheses[246–256] in the last decade or so, but, again, the route employing the retro Diels–Alder reaction as the key step[257] appears to be the most convenient for large-scale preparation.

The anion **453** derived from anthracene-dimethyl itaconate adduct **452** readily reacts with methyl acrylate in a tandem Michael addition–Dieckmann condensation to give the diester **454** which can be selectively hydrolyzed and decarboxylated to yield a mixture of two isomers **455**. Flash-vacuum pyrolysis of **455a** and/or **455b** (single or mixed isomers) quantitatively yields sarkomycin methyl ester **456**. Upon acid hydrolysis **456** affords (±)-sarkomycin **457**.

The habitual excuse that many chemists make for avoiding the retro Diels–Alder reaction in synthesis is that it requires too high a temperature which might harm the product. However, this excuse is no longer necessarily valid since effective vacuum pyrolysis apparatus is now available. Also, with the proper choice of host molecule and reaction conditions, the temperature required to effect the retro Diels–Alder reaction can be lowered dramatically. For example, dimethylfulvene adducts such as **458** undergo the retro Diels–Alder reaction at relatively low temperatures and the reactions can be effected by simply boiling in xylene, diglyme, diphenyl ether, or by heating in a sealed tube[258]. Consequently, several bioactive natural products such as phyllostine **459**, epoxydon **460**, epiepoxydon **461**, epoformin **462** and epiepoformin **463** can be obtained by simply heating the corresponding **458** at 110–170 °C in a sealed tube.

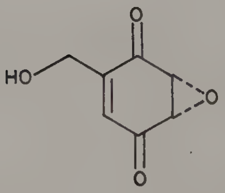
The rate of the retro Diels–Alder reaction, in contrast to the forward reaction, has not been widely studied[259,260]. However, recent results show that the spiropentanedione **464** undergoes the acid-catalyzed retro Diels–Alder reaction extremely readily, even at room temperature, giving 2-methylene-1,3-cyclopentanedione **465** which can be trapped with isoprene to give adduct **466**[261]. It is interesting to recall that methylene cyclopentanediones such as **465** have been employed in the synthesis via sulfoxide elimination starting from **467**[94].



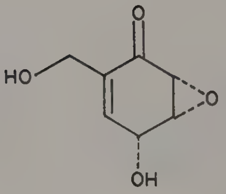


(458)

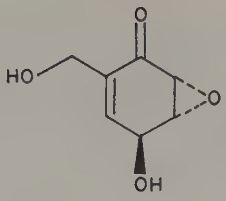
(a) $R^1, R^2 = {=}O, R^3 = CH_2OH$
(b) $R^1 = H, R^2 = OH, R^3 = CH_2OH$
(c) $R^1 = OH, R^2 = H, R^3 = CH_2OH$
(d) $R^1 = H, R^2 = OH, R^3 = Me$
(e) $R^1 = OH, R^2 = H, R^3 = Me$



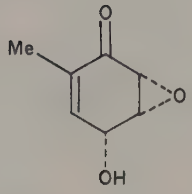
(459)



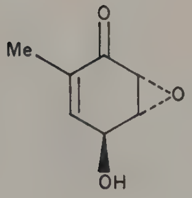
(460)



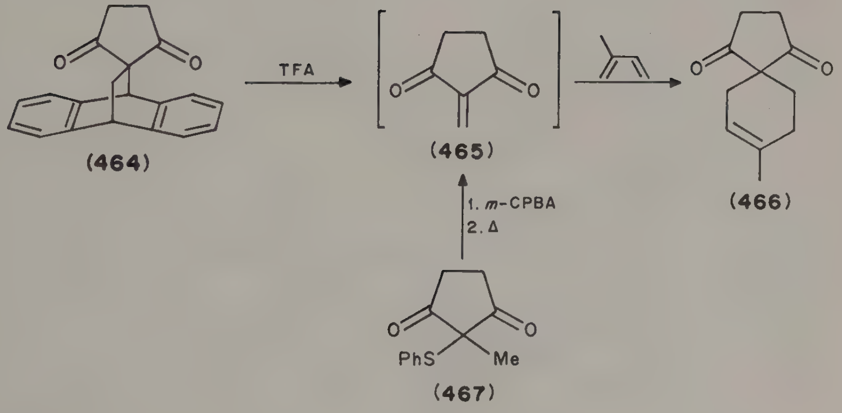
(461)



(462)



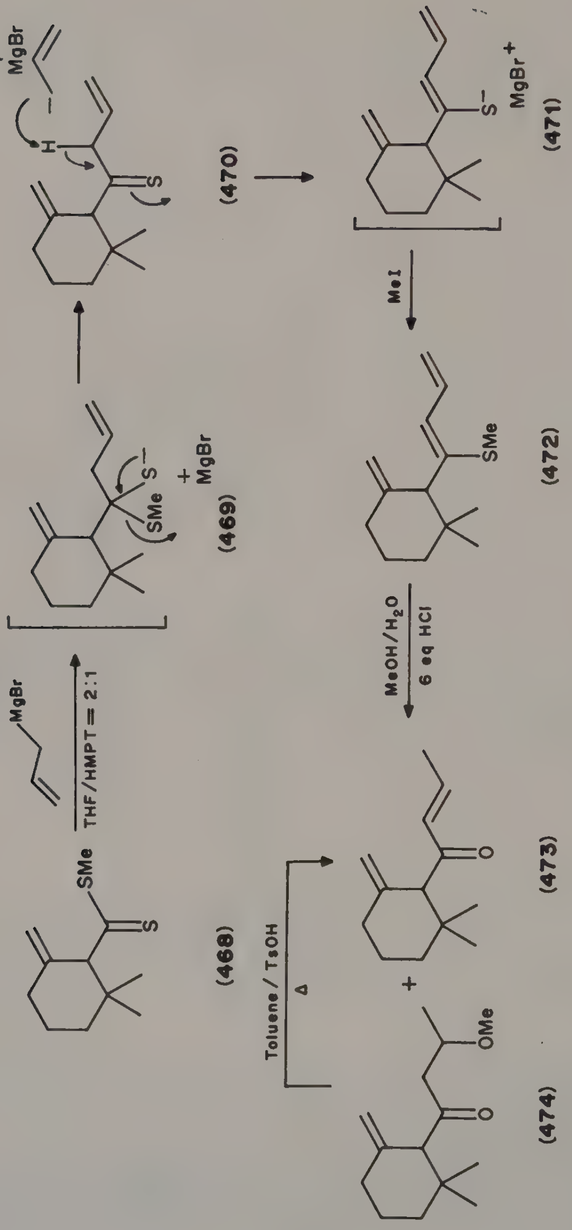
(463)



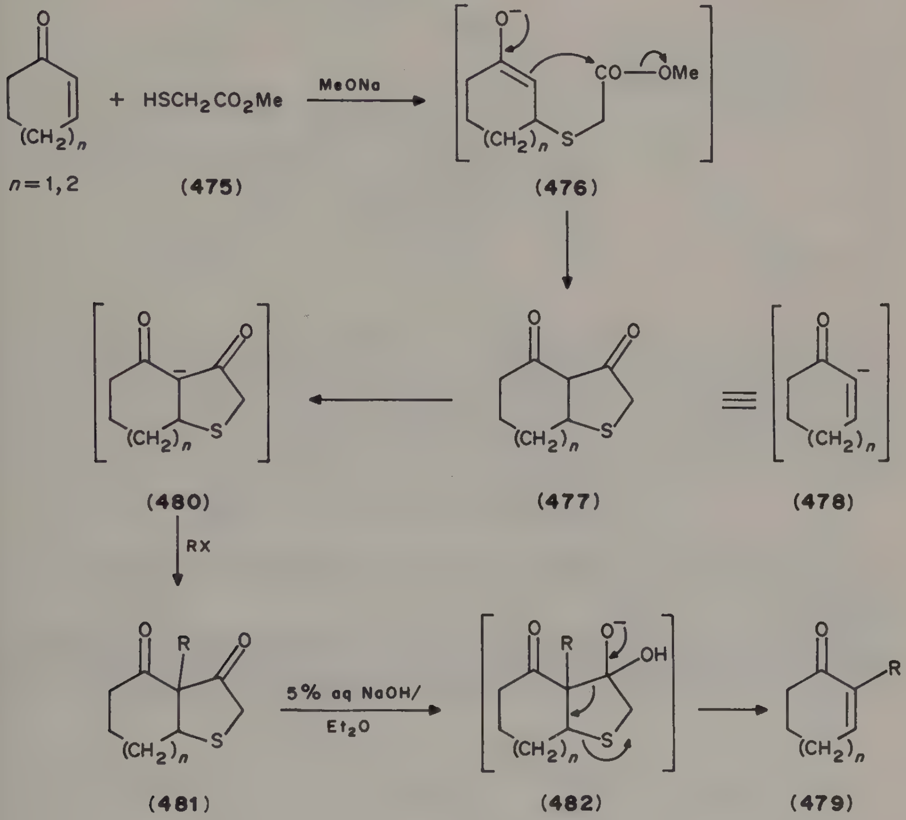
E. Miscellaneous

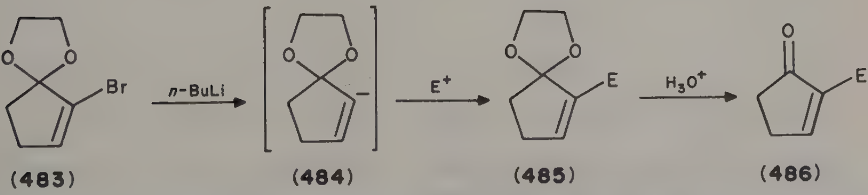
Many interesting syntheses of enones do not fall into any of the foregoing classes and are presented in this section.

A new high-yield route[262] to γ-damascone **473** starting from methyl γ-dithiocyclogeranate **468** employs the reaction of allyl magnesium bromide with **468**, in THF in the presence of hexamethylphosphorous triamide, to yield **471** which is methylated to give **472**. Acid hydrolysis of **472** yields γ-damascone **473** together with the methanolysis product **474** which can be converted into **473** by refluxing in toluene with *p*-toluenesulfonic acid.

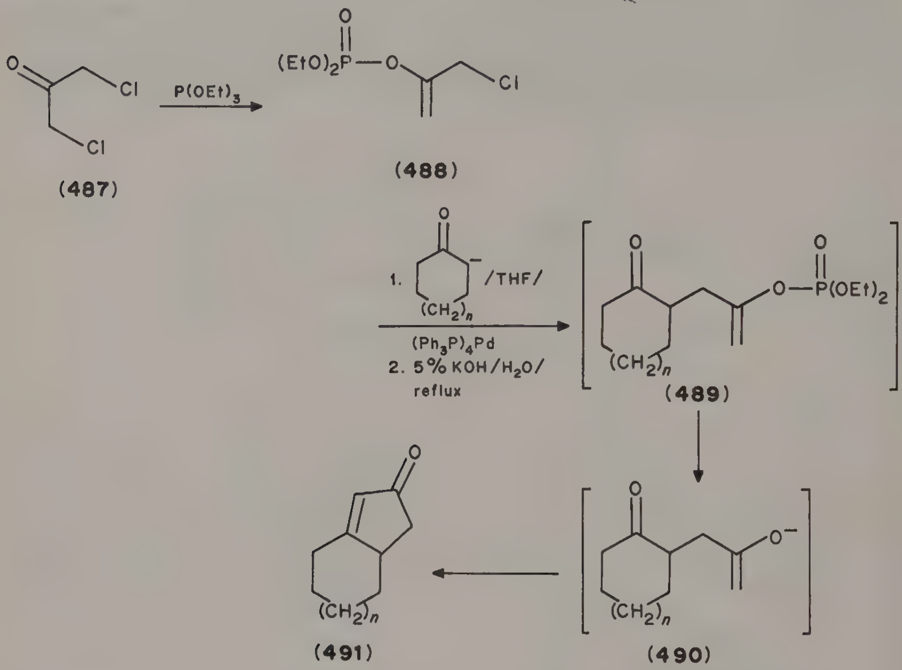

SMe
S
(468)
MgBr
THF/HMPT = 2:1
SMe
S⁻
+ MgBr
(469)
H
+ MgBr
S
(470)
S⁻
MgBr⁺
(471)
MeI
SMe
(472)
MeOH/H₂O
6 eq HCl
O
(473)
+
O
OMe
(474)
Toluene / TsOH
Δ

The use of fused-ring diketone **477**[263] as a synthon for the α-cycloalkenone anion **478** is very useful as shown below in the reaction sequence leading to **479** in good overall yield[264]. Diketone **477** is prepared by tandem Michael addition–Dieckmann condensation between cycloalkenones and methyl mercaptoacetate. It should be noted that α-cycloalkenone anion equivalents such as **478** have been extensively investigated as a result of their ready preparation from consecutive treatment of α-bromoketals with *n*-butyllithium and electrophile, followed by hydrolysis with oxalic acid. The method has led to various cyclopentenoid antibiotics[265].



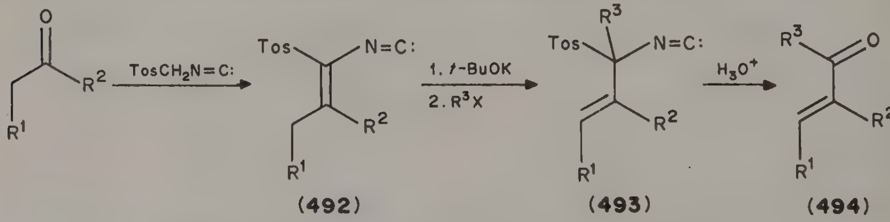


A new reagent, 3-chloro-2-diethylphosphoryloxypropene **488**, prepared from **487** by Perkow reaction[266], is employed as a three-carbon source in a 'one-pot' synthesis of cyclopentenones. The significant advantage here is that intermediate **489** can be hydrolyzed with dilute potassium hydroxide to furnish, via fission of the P—O bond, enolate anion **490** which readily undergoes intramolecular condensation to afford **491** in good yield[267,268].



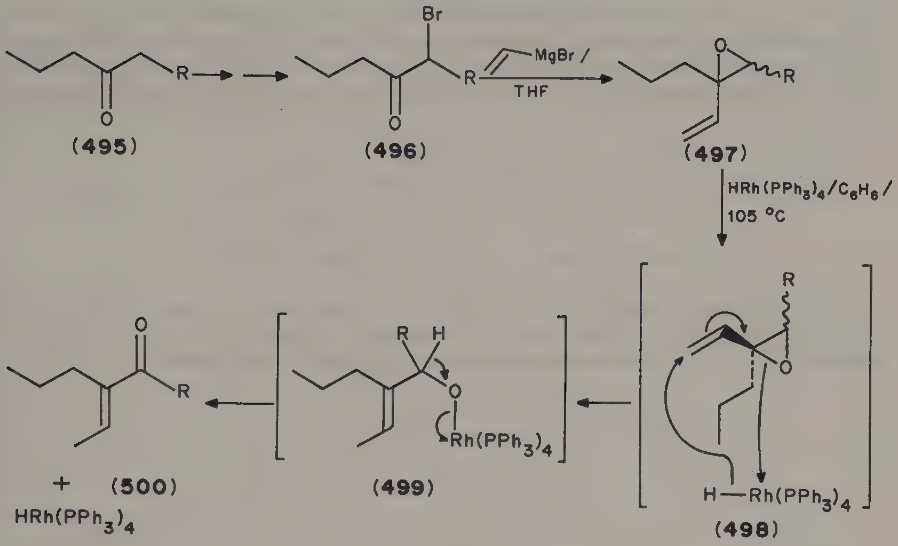
Homologation and 1,2-carbonyl transposition reactions also provide access to the enone system. Two examples which are simple, short and give good to excellent yields, are cited here.

Condensation product **492**, from the reaction of the requisite ketone with tosylmethyl isocyanide (TosMIC), suffers deprotonation with *t*-BuOK followed by alkylation with an alkyl halide to give **493** which can be easily hydrolyzed with acid to yield **494**[269].

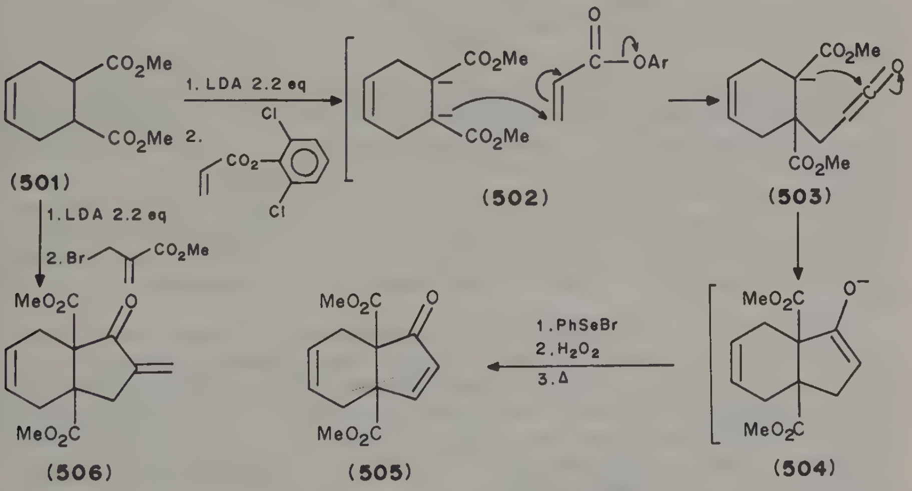


R^1, R^2 = H, alkyl, or —(CH$_2$)$_n$— (n = 2—4), R^3 = alkyl

The conversion of ketone **495** to enone **500** is an example of a 1,2-carbonyl transposition with concomitant introduction of an ethylidene group[270]. The key step in the synthetic sequence is the rhodium(I) hydride-catalyzed isomerization of vinyl epoxide derivative **497** to enone **500**, the mechanism of which is believed to be as shown. The reaction gives, stereospecifically, the *E*-enone in excellent yield with no trace of the *Z*-isomer.



Cyclopentenone **505** can be prepared[271] from the reaction of the dianion of diester **501** with 2,6-dichlorophenyl acrylate. This is believed to proceed via the intermediate ketene **503** which spontaneously cyclizes to enolate **504**, which can be converted by conventional methods to enone **505**. Support for the Michael addition-substituted phenoxide elimination as opposed to the Michael addition–Dieckmann condensation comes from the observation that substitution of phenyl acrylate for the 2,6-dichloro derivative retards the reaction and results in a poor yield of product. When methyl 2-bromomethylacrylate[272] is used, α-methylene cyclopentenone **506** is obtained in 83% yield.



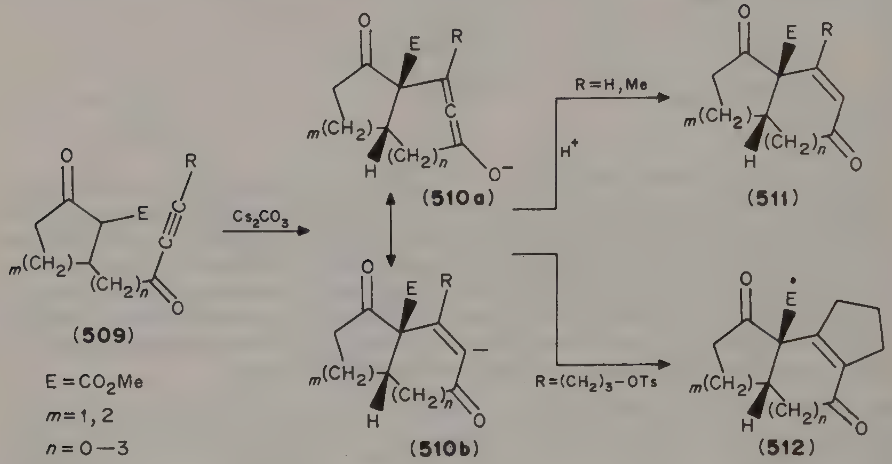
Although not widely exploited, inter- and intra-molecular addition to the electrophilic acetylenic bond, particularly in conjugated acetylenic ketone, provides another mode of access to enones[273]. An example is the addition of HF to the activated triple bond.

Formerly not very successful, the reaction is now much improved with the recent introduction of tetrabutylammonium dihydrogen trifluoride, a readily available reagent which delivers HF to conjugated ynones to give functionalized fluoroenones in reasonable yields. Thus enones **508** (R = Ph, A = COPh) can be prepared in 53% yield with exclusive *Z*-geometry[274].

$$\underset{\textbf{(507)}}{\mathrm{R{-}C{\equiv}C{-}A}} \xrightarrow{n\text{-}\mathrm{Bu_4N^+H_2F_3^-}} \underset{\textbf{(508)}}{\mathrm{R{-}CF{=}CH{-}A}}$$

R = alkyl, phenyl : A = CN, CO_2Me, COPh, CHO

The intramolecular addition of nucleophiles to ynones was investigated very recently with the result that a variety of enones with the general skeletons **511** and **512** can now be prepared[275–277] from cesium carbonate-induced intramolecular cyclization of **509**.

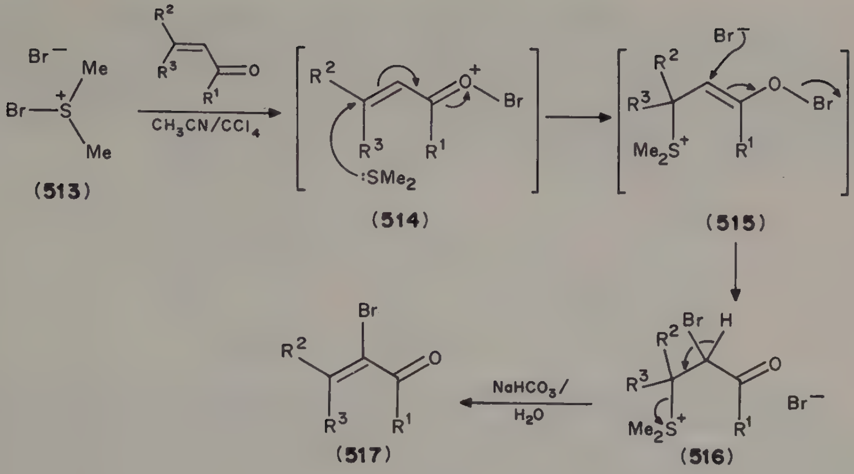


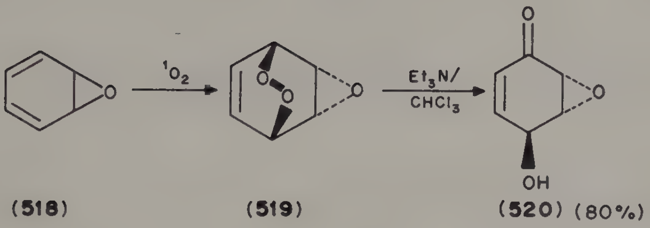
E = CO_2Me
m = 1, 2
n = 0–3

Apart from *β*-fluoroenones (e.g. **508**), *α*-bromoenones (e.g. **517**) are also readily available through the use of dimethylbromosulfonium bromide **513**. This versatile reagent, easily prepared from the reaction of dimethyl sulfide with bromine[278], has several uses; for example as a dethioacetalization agent[279] and as an oxidizing agent for the oxidation of thiols to disulfides[280]. The reagent adds to enones (after reaction with the oxygen to form **514**) in a nucleophilic fashion to give the stable salt **516** which readily liberates *α*-bromoenone **517** upon treatment with aqueous sodium bicarbonate[281]. The mechanism of the reaction, deduced from numerous experimental results, is thought to be as shown below.

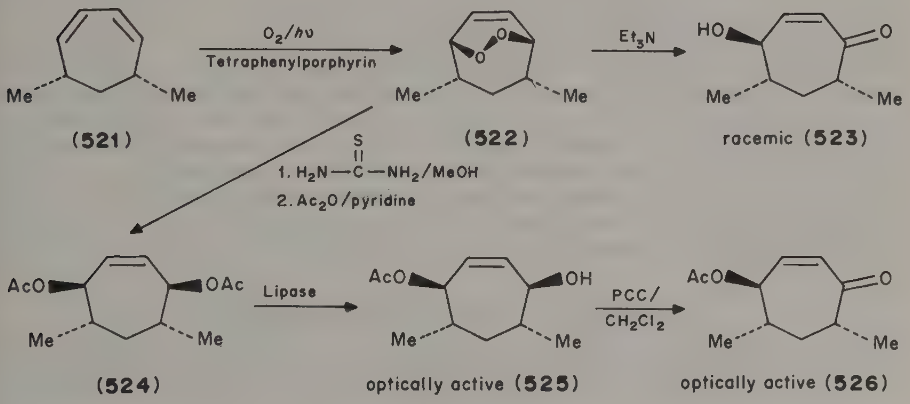
The last route to be discussed here is the synthesis of oxygenated enones from 1,3-dienes using singlet oxygen. The conversion is, in fact, a normal oxidation process, but has recently been developed for the preparation of optically active compounds that are important intermediates in the synthesis of natural products. The following reaction was reported[282] in 1975 and involves the addition of singlet oxygen to benzene oxide **518** to give **519** in a rather low yield. Subsequent triethylamine-promoted rearrangement of **519** yields oxygenated cyclohexenone **520**.

Recently this reaction was applied[283,284] to *cis*-5,7-dimethylcyclohepta-1,3-diene **521** to yield racemic **523**. Because of the importance of **523** as a synthetic intermediate, efforts were made to develop the synthesis further and the preparation of optically active **523** (in

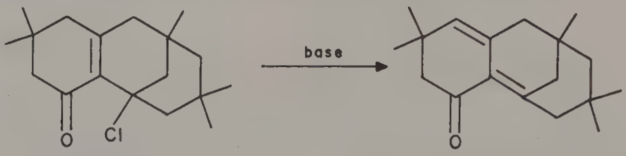




the form of its acetate derivative) was achieved[285]. Thus treatment of endoperoxide **522** with thiourea in methanol, followed by acetylation of the resulting diol, furnishes racemic diacetate **524**. Stereospecific enzyme (lipase) hydrolysis of **524** yields optically active alcohol **525** (61%) which can be oxidized with pyridinium chlorochromate (PCC) in dichloromethane at room temperature to supply the optically active seven-membered ring enone **526**.

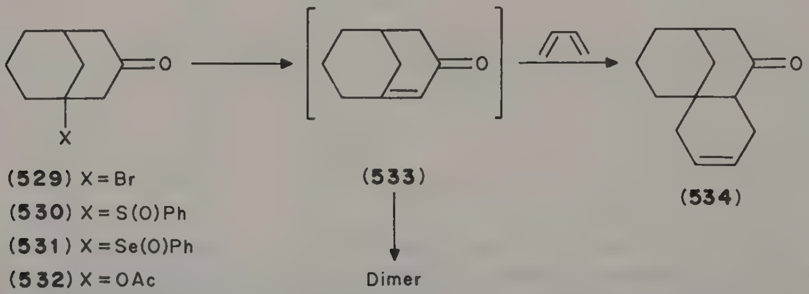


A mention should also be made here of strained enones and their synthesis. In this class are the bridgehead enones wherein either the α- or β-carbon atom of the enone is at the bridgehead[286]. The synthetic study of enones with strained double bonds is largely the work of House and his group[287] who discovered that the reactive enone **528** can be generated by base-catalyzed dehalogenation of chloroenone **527**. However, they could not isolate **528** in a pure state as it underwent rapid addition reaction.



(527) (528)

Efforts were made to prepare the strained enones of the bicyclo[3.3.1] system. These included investigations[288,289] of the base-catalyzed elimination of **529** and the thermolysis of **530**–**532**. In each case **533** was produced but could not be isolated due to rapid further transformations, particularly self-dimerization. The finding, however, led to intensive *in situ* studies[290,291] of the [4 + 2]cycloaddition reactions of **533** with a variety of dienes to yield **534**.



(529) X = Br
(530) X = S(O)Ph
(531) X = Se(O)Ph
(532) X = OAc

(533)

(534)

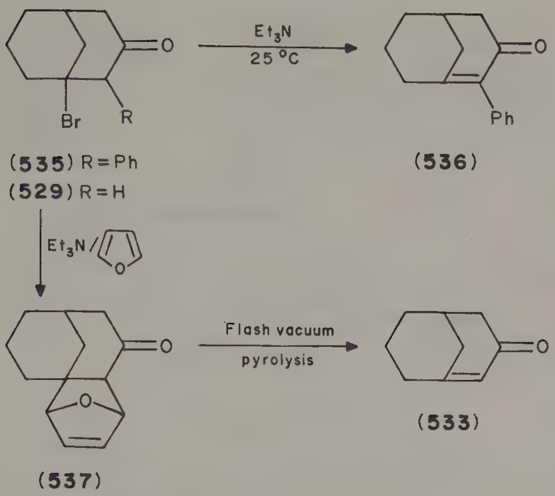
Interestingly, it was found that, by placing a bulky substituent at the α-position of the enone system, self-dimerization could be markedly retarded; hence **536** was obtained in a pure state from the base-catalyzed elimination of **535**. Although it reacts readily with nucleophiles, oxygen and dienes, **536** is stable and exhibits satisfactory spectroscopic data, e.g. it exhibits a conjugated carbonyl absorption at 1680 cm^{-1} in the IR spectrum. The $C{=}C$ deformation of **536** was also calculated[292] and the degree of average twisting deformation was found to be in the range of 25.

In the latest and most recent development, the parent strained enone **533** has been eventually obtained via flash-vacuum pyrolysis of the furan adduct **537** which, in turn, was prepared from **529**. Enone **533** can be collected in a cold trap and its spectroscopic properties successfully recorded at −78 °C to −40 °C. At temperatures above −40 °C **533** reacts with itself to give a mixture of three stereochemical isomers[293].

It should be pointed out that not only are strained enones of the type **533** theoretically important molecules, but the synthesis of certain complex natural products have also involved this type of compound as reactive intermediates[294,295].

VII. OPTICALLY ACTIVE CYCLOPENTENONES

Many biologically important natural products are cyclopentenone derivatives, for example the prostaglandins, pentenomycins and jasmones. Attempts to synthesize these



(535) R=Ph
(529) R=H
(536)
(537)
(533)

compounds have led to the discovery of many interesting and useful reactions[296-299]. More recently there has been a tendency to synthesize natural products in their optically active forms rather than as racemates, hence the need arose for methods for the preparation of optically active cyclopentenone precursors. Simple and efficient reactions which can effect this in high enantiomeric purity are discussed in the following final section of this chapter.

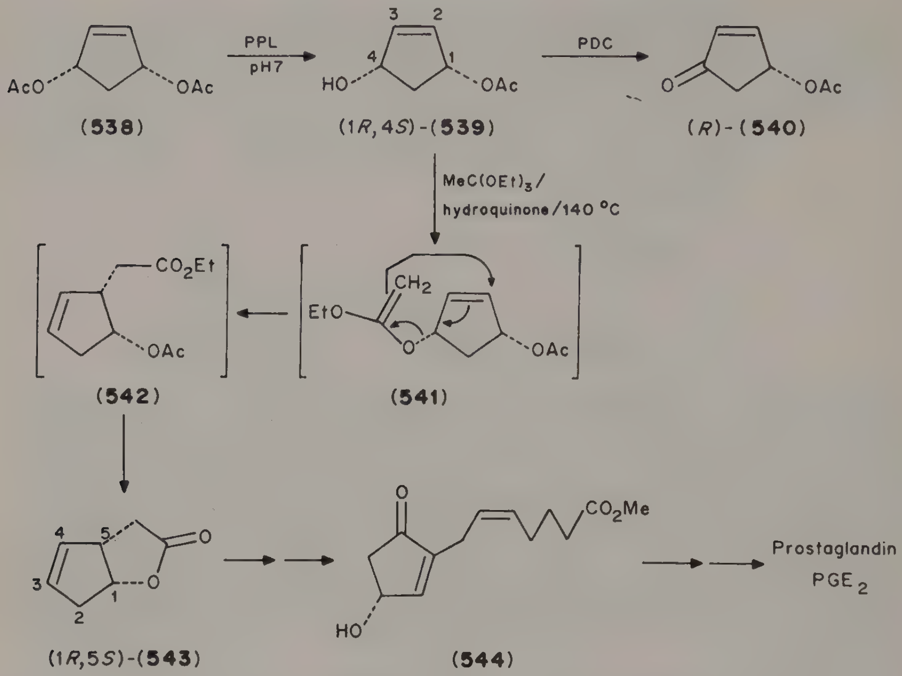
In the same manner as the selective (*S*)-ester hydrolysis of diacetate **524** to optically active **525** by lipase[284], the hydrolysis of prochiral **538** with commercially available and comparatively inexpensive porcine pancreatic lipase (PPL) provides (*1R*, *4S*)-**539** with hardly a trace of the other enantiomer. PDC oxidation of **539** gives (*R*)-acetylcyclopentenone **540** (85% yield)[300]. Moreover, the lipase hydrolysis product **539** can be converted into bicyclic lactone (*1R*, *5S*)-**543**, with 97% enantiomeric excess, via Claisen rearrangement[301]. Lactone **543** is an important intermediate in the synthesis of prostaglandin PGE_2, being a precursor of **544** on the route to PGE_2[302].

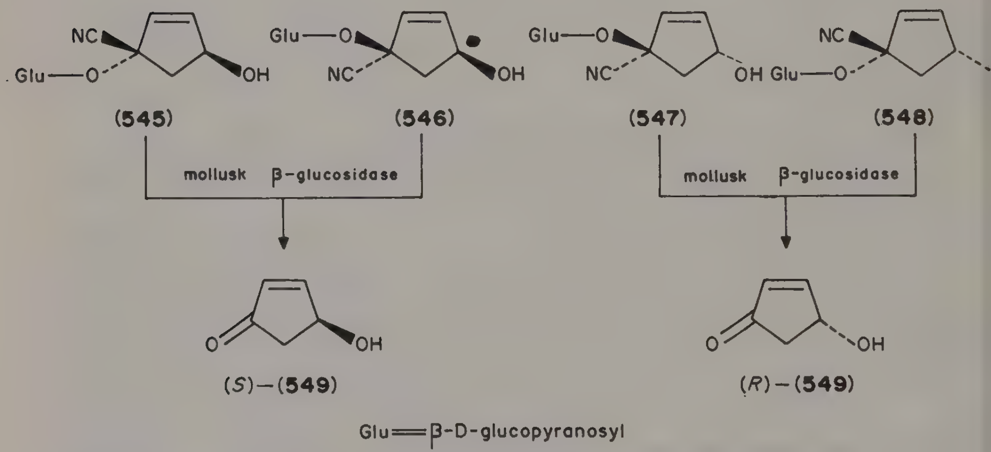
In likewise manner enantiomer (*1S*, *4R*)-**539**, the precursor of (*S*)-**540**, can be prepared by enzymatic hydrolysis, albeit with lower enantiomeric purity[303,304], using porcine liver esterase (PLE) instead of lipase (PPL).

In actual fact there is an alternative semi-synthetic approach to both the (*R*)- and (*S*)-enantiomers of 4-hydroxycyclopentenone. It has been found that plants in the Passifloraceae family[305] contain tetraphyllin B **545** and volkenin **547** while some in the Flacourtiaceae family[306] contain taraktophyllin **546** and epivolkenin **548**. When **545** and **546** are hydrolyzed with mollusk β-glucosidase, 4-hydroxycyclopentenone **549** with the (*S*)-configuration is obtained. Similarly (*R*)-**549** can be obtained from **547** and **548**[306].

A further example of enantiomeric synthesis utilizing the enzymatic process is the synthesis of optically active enedione **554**, a potential intermediate[307] for the synthesis of coriolin **276**. Racemic **554** had been synthesized by Trost and Curran[308] via palladium-catalyzed C-alkylation of pentanedione **550** and a mild and effective intramolecular Wittig reaction in the last step which could not be accomplished with the standard aldol condensation (**555** → **554**).

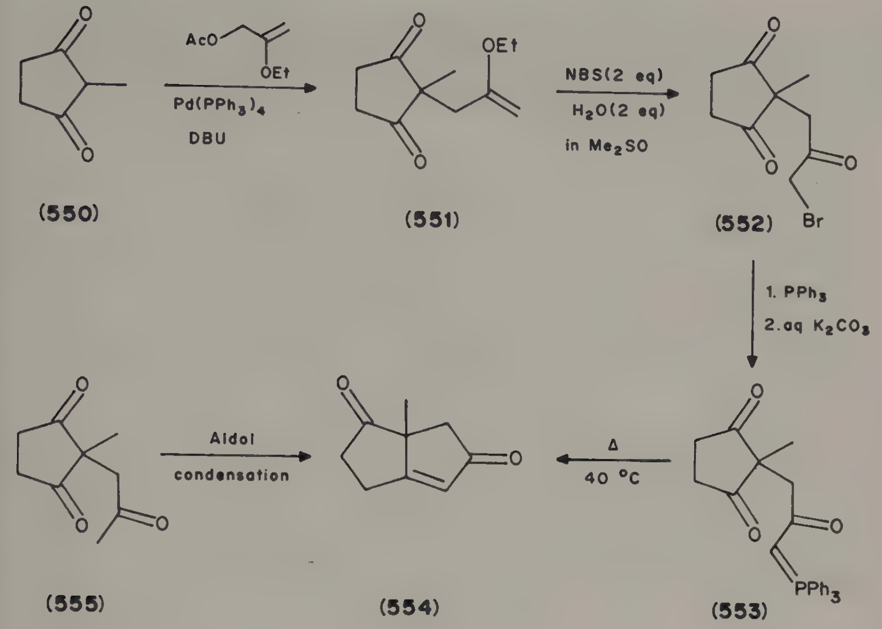
By employing optically active phosphine Trost was able to effect chirality transfer and **554** was obtained with up to 77% enantiomeric purity[309]. It is interesting to recall, at this point, that the optically active six-membered ring analog of **554** was synthesized by Robinson annelation using (*S*)-(−)-proline as catalyst (**41** → **42** → **43**).

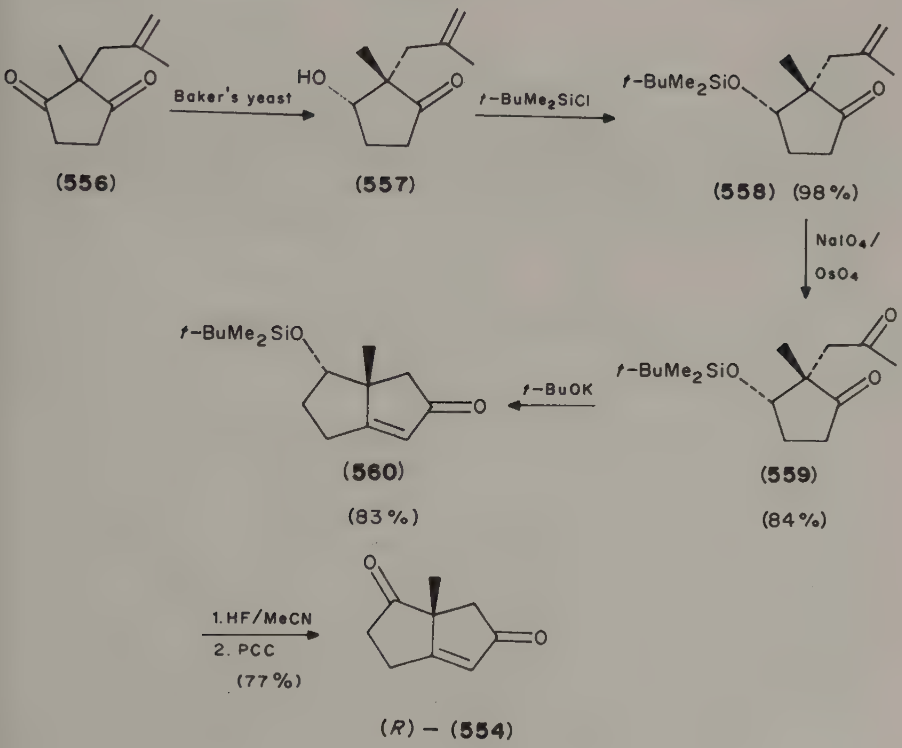




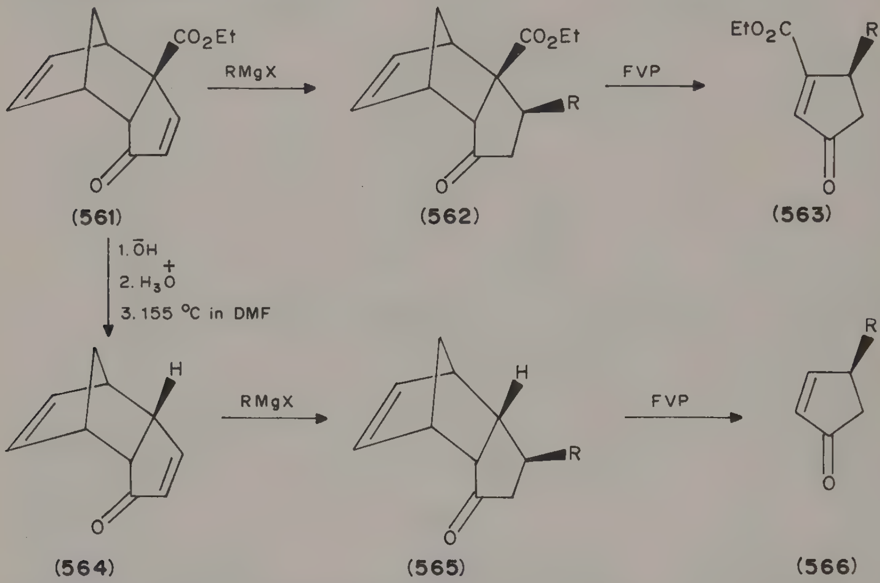
However, a more efficient enantioselective synthesis of **554** has since been achieved. Chiral ketol **557** can be produced in high yield, with more than 98% enantiomeric purity, by taking advantage of the asymmetric monoreduction of prochiral dione **556** with fermenting baker's yeast[310,311]. From there on the conversion of **557** into (*R*)-**554** is a straightforward process.

Optically active adduct **561** (cf. **436**) can be obtained by enzymatic resolution of the racemate using porcine liver esterase (PLE)[312]. The rigid *endo* configuration of **561**, whose


AcO
OEt
Pd(PPh$_3$)$_4$
DBU
OEt
NBS(2 eq)
H$_2$O(2 eq)
in Me$_2$SO
(550)
(551)
(552)
Br
1. PPh$_3$
2. aq K$_2$CO$_3$
Aldol
condensation
Δ
40 °C
PPh$_3$
(555)
(554)
(553)


Baker's yeast
HO
t-BuMe$_2$SiCl
t-BuMe$_2$SiO
(556)
(557)
(558) (98%)
NaIO$_4$/
OsO$_4$
t-BuMe$_2$SiO
t-BuOK
t-BuMe$_2$SiO
(560)
(83%)
(559)
(84%)
1. HF/MeCN
2. PCC
(77%)
(R) – (554)

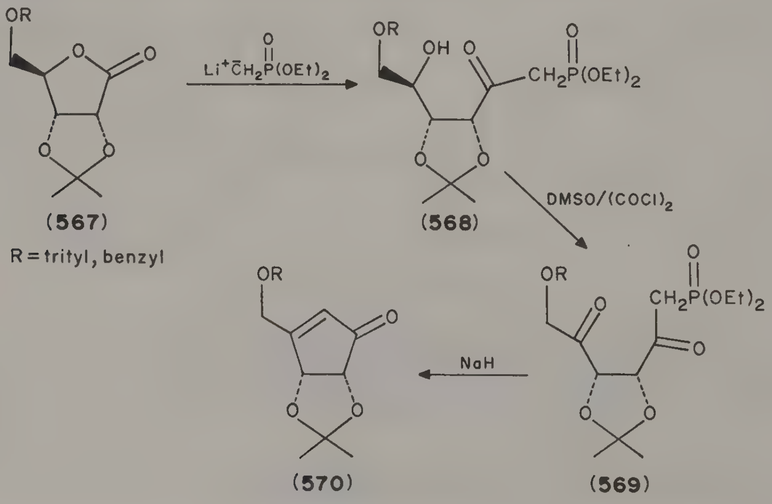
concave face is entirely blocked, controls the stereochemistry of Michael addition to the adduct. Flash-vacuum pyrolysis (FVP) of **562** proceeds quantitatively and yields optically active **563**. In addition, **561** can be converted into **564** by hydrolysis followed by decarboxylation, and leads to the synthesis[313,314] of optically active 4-substituted cyclopentenones **566**.



(561) (562) (563)

(564) (565) (566)

A partial synthesis of optically active **570** (a precursor of 3-substituted 4,5-dihydroxycyclopentenones) from *R*-ribolactone **567** has been described[315]. Reacting **567** with the lithium phosphonate salt followed by oxidizing the resulting ketol **568** with a mixture of dimethyl sulfoxide/oxalyl chloride the authors obtained 1,4-diketone **569** which, when subjected to the Horner–Wittig reaction, yielded **570**.

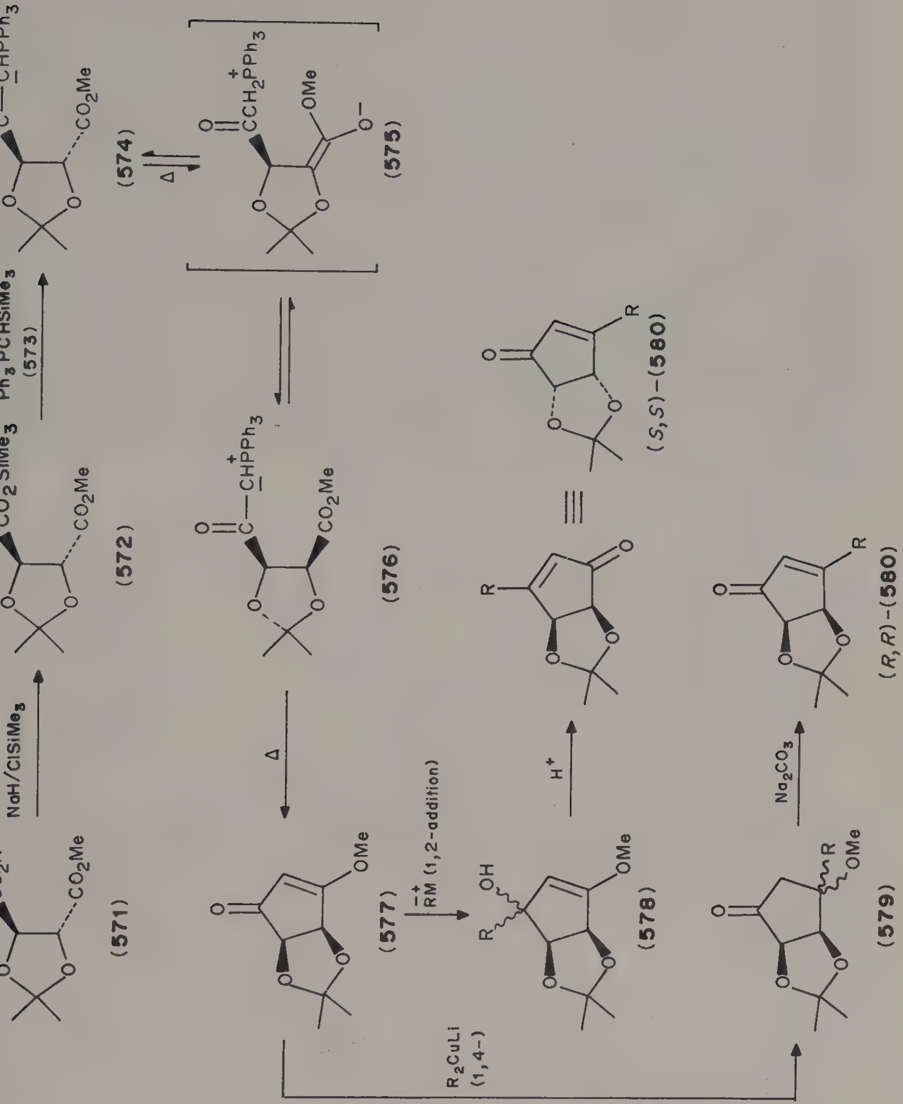


(567)

R = trityl, benzyl

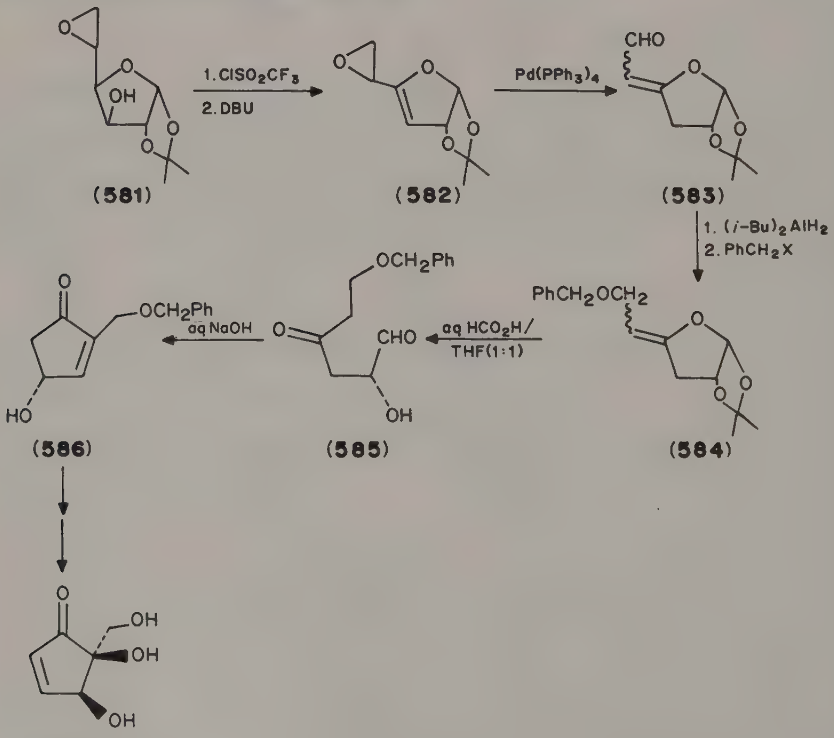
(568)

(570) (569)


(571)
NaH/ClSiMe$_3$
(572)
Ph$_3$PCHSiMe$_3$
(573)
(574)
Δ
(575)
(576)
Δ
(577)
RM (1,2-addition)
(578)
H$^+$
R$_2$CuLi
(1,4-)
(579)
Na$_2$CO$_3$
(R,R)-(580)
(S,S)-(580)

A similar method[316] which provides optically active cyclopentenones such as **570** in either the (*R*, *R*)- or (*S*, *S*)- form makes use of the readily available acetonide of (*R*, *R*)-tartaric acid monomethyl ester **571**. The reaction between phosphorane **573** and trimethylsilyl ester derivative **572** occurs with elimination of bis(trimethylsilyl) ether to give **574**. Upon refluxing in toluene for 8 days, this undergoes inversion at the carbon centre attached to the ester group followed by intramolecular Wittig reaction to yield (4*S*,5*R*)-methoxycyclopentenone **577**. The carbon inversion most likely involves an internal proton shift as shown in **575**, the strain of the *trans*-ring junction inhibiting cyclization prior to inversion. Subsequent 1,2- and 1,4-additions of nucleophiles to **577** lead to **578** and **579** respectively. Acid treatment of enol ether **578** accomplishes tandem hydrolysis and dehydration to (*S*, *S*)-**580**, while the corresponding (*R*, *R*)-enantiomer is obtained from **579** by treatment with sodium carbonate.

The synthesis of (*R*)-4-hydroxy-2-benzyloxymethylcyclopent-2-en-1-one **586**, the synthetic precursor of the antibiotic pentenomycin **587**[317], has been achieved[318,319] starting from glucose derivative **581**. The free hydroxy group in **581** was trifluoromethylsulfonated, then eliminated with DBU to give **582** in excellent yield. Palladium(0)-catalyzed rearrangement of vinyl epoxide **582** (cf. **497**→**500**), using tetrakis(triphenylphosphine)palladium in dichloromethane at 0 °C, furnished aldehyde **583**. Reduction with diisobutylaluminium hydride gave the corresponding alcohol (chromatographic separation of the *E*- and *Z*-isomers is possible but not essential) which was benzylated and then hydrolyzed with 80% aqueous formic acid: THF (1:1) at room temperature to yield ketoaldehyde **585**. Cyclization of **585** in aqueous sodium hydroxide yielded optically active cyclopentenone **586**.



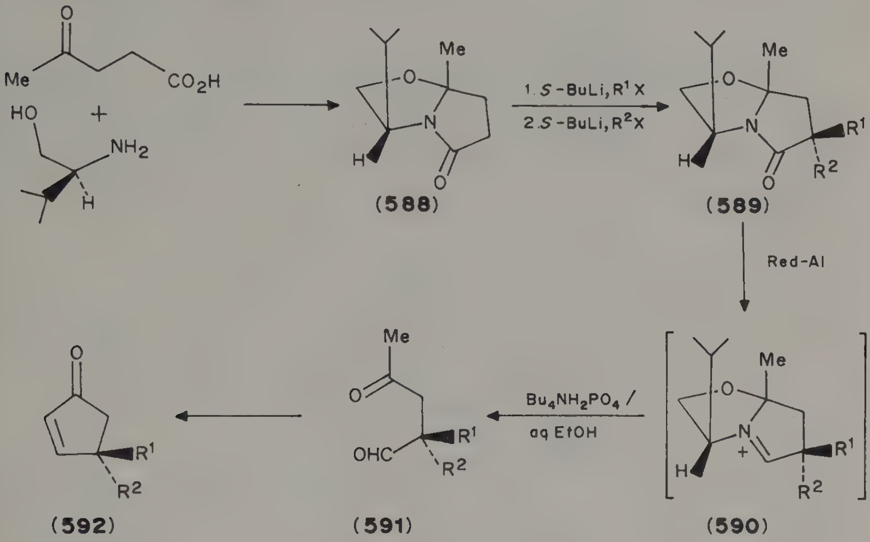
(581) (582) (583)

(586) (585) (584)

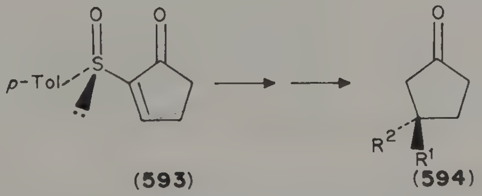
(587)

The use of chiral templates in asymmetric synthesis is fast growing in popularity, especially in the area of nucleophilic addition[320] and cycloaddition reactions[188], whilst in asymmetric alkylation it has already led to the synthesis of many optically active cyclopentenone and cyclohexenone derivatives[321–323].

Chiral template **588** [prepared from (*S*)-valinol and 3-acetylpropionic acid] can be manipulated to undergo successive alkylation reactions, with the electrophiles (R and R′) entering almost exclusively from the *endo* side because of the steric interference of substituents on the *exo* face. Product **589**, obtained in high yield with good to excellent selectivity, can be readily purified by chromatography. Reduction of this bicyclic lactam with bis(2-methoxyethoxy) aluminium hydride (Red-Al), followed by hydrolysis of the apparent intermediate **590** with tetrabutylammonium dihydrogen phosphate in aqueous ethanol, furnishes optically active ketoaldehyde **591** which can be converted to the chiral substituted cyclopentenone **592** in high yield.



The latest addition to the available methods for asymmetric synthesis of optically active cyclopentenones is the synthesis[324] of (*S*)-(+)-2-(*p*-toluenesulfonyl)-2-cyclopentenone **593**, a useful precursor in the enantioselective synthesis of 3-substituted cyclopentanones such as **594**.



In conclusion, we have presented an overview of the state of the art of enone synthesis, from improved classical methods to new methods of synthesis. Notwithstanding this array of available methods, however, it is expected that the importance of the enone functionality will continue to stimulate future development in this area.

IX. REFERENCES

1. B. P. Mundy, *J. Chem. Educ.*, **50**, 110 (1973).
2. M. E. Jung, *Tetrahedron*, **32**, 3 (1976).
3. R. E. Gawley, *Synthesis*, 777 (1976).
4. W. S. Rapson and R. Robinson, *J. Chem. Soc.*, 1285 (1935).
5. E. C. du Feu, F. J. McQuillin and R. Robinson, *J. Chem. Soc.*, 53 (1937).
6. J. W. Cornforth and R. Robinson, *J. Chem. Soc.*, 1855 (1949).
7. J. H. Brewster and E. L. Eliel, *Org. React.*, **7**, 99 (1953).
8. M. Pfau, G. Revial, A. Guingant and J. d'Angelo, *J. Am. Chem. Soc.*, **107**, 273 (1985); T. Volpe, G. Revial, M. Pfau and J. d'Angelo, *Tetrahedron Lett.*, **28**, 2367 (1987).
9. A. T. Nielsen and W. J. Houlihan, *Org. React.*, **16**, 1 (1968).
10. J. Muzart, *Synthesis*, 60 (1982).
11. H. Ishihara, K. Inomata and T. Mukaiyama, *Chem. Lett.*, 531 (1975); E. Kitazawa, T. Imamura, K. Saigo and T. Mukaiyama, *Chem. Lett.*, 569 (1975).
12. R. G. Kelleher, M. A. McKervey and P. Vibuljan, *J. Chem. Soc., Chem. Commun.*, 486 (1980).
13. W. H. Bunnelle, M. A. Rafferty and S. L. Hodges, *J. Org. Chem.*, **52**, 1603 (1987).
14. P. C. Wailes and H. Weigold, *J. Organomet. Chem.*, **24**, 405 (1970).
15. Y. Ishii, T. Nakano, A. Inada, Y. Kishigami, K. Sakurai and M. Ogawa, *J. Org. Chem.*, **51**, 240 (1986); T. Nakano, T. Terada, Y. Ishii and M. Ogawa, *Synthesis*, 774 (1986).
16. T. Nakano, S. Irifune, S. Umano, A. Inada, Y. Ishii and M. Ogawa, *J. Org. Chem.*, **52**, 2239 (1987).
17. D. Mead, R. Loh, A. E. Asato and R. S. H. Liu, *Tetrahedron Lett.*, **26**, 2873 (1985).
18. Y. Hanzawa, K. Kawagoe, N. Kobayashi, T. Oshima and Y. Kobayashi, *Tetrahedron Lett.*, **26**, 2877 (1985).
19. Y. Hanzawa, A. Yamada and Y. Kobayashi, *Tetrahedron Lett.*, **26**, 2881 (1985).
20. W. S. Wadsworth, Jr., *Org. React.*, **25**, 73 (1977).
21. P. Coutrot and A. Ghribi, *Synthesis*, 790 (1986).
22. J. Villieras and M. Rambaud, *Synthesis*, 300 (1983).
23. M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush and T. Sakai, *Tetrahedron Lett.*, **25**, 2183 (1984).
24. L. E. Overman, D. Lesuisse and M. Hashimoto, *J. Am. Chem. Soc.*, **105**, 5373 (1983).
25. G. Stork and B. Ganem, *J. Am. Chem. Soc.*, **95**, 6152 (1973).
26. R. K. Boeckman, *J. Am. Chem. Soc.*, **96**, 6179 (1974).
27. G. Stork and J. Singh, *J. Am. Chem. Soc.*, **96**, 6181 (1974).
28. R. V. Bonnert and P. R. Jenkins, *J. Chem. Soc., Chem. Commun.*, 6 (1987).
29. Z. G. Hajos and D. R. Parrish, *Org. Synth.*, **63**, 26 (1984); Z. G. Hajos and D. R. Parrish, *J. Org. Chem.*, **39**, 1615 (1974).
30. P. Buchschacher and A. Fürst, *Org. Synth.*, **63**, 37 (1984); J. Gutzwiller, P. Buchschacher and A. Fürst, *Synthesis*, 167 (1977).
31. K. L. Brown, L. Damm, J. D. Dunitz, A. Eschenmoser, R. Hobi and C. Kratky, *Helv. Chim. Acta*, **61**, 3108 (1978).
32. C. Agami, F. Meynier, C. Puchot, J. Guilhem and C. Pascard, *Tetrahedron*, **40**, 1031 (1984).
33. C. Agami, J. Levisalles and H. Sevestre, *J. Chem. Soc., Chem. Commun.*, 418 (1984).
34. W. Acklin, V. Prelog and A. P. Prieto, *Helv. Chim. Acta*, **41**, 1416 (1958).
35. V. Prelog and W. Acklin, *Helv. Chim. Acta*, **39**, 748 (1956).
36. Z. G. Hajos, D. R. Parrish and E. P. Oliveto, *Tetrahedron*, **24**, 2039 (1968).
37. G. R. Newkome, L. C. Roach, R. C. Montelaro and R. K. Hill, *J. Org. Chem.*, **37**, 2098 (1972).
38. W. L. Meyer, R. A. Manning, E. Schindler, R. S. Schroeder and D. C. Shew, *J. Org. Chem.*, **41**, 1005 (1976).
39. W. L. Meyer, C. G. Burgos, M. J. Brannon, T. E. Goodwin and R. W. Howard, *J. Org. Chem.*, **50**, 438 (1985).
40. K. Mori and H. Mori, *Tetrahedron*, **42**, 5531 (1986).
41. W. L. Meyer, M. J. Brannon, A. Merritt and D. Seebach, *Tetrahedron Lett.*, **27**, 1449 (1986).
42. J. C. Floyd, *Tetrahedron Lett.*, 2877 (1974).
43. B. M. Trost and R. A. Kunz, *J. Am. Chem. Soc.*, **97**, 7152 (1975).
44. G. Stork and L. Maldonado, *J. Am. Chem. Soc.*, **93**, 5286 (1971).
45. P. Tuchinda, V. Prapansiri, W. Naengchomnong and V. Reutrakul, *Chem. Lett.*, 1427 (1984).
46. C. E. Russell and L. S. Hegedus, *J. Am. Chem. Soc.*, **105**, 943 (1983).

47. H. Prinzbach and U. Fischer, *Helv. Chim. Acta*, **50**, 1669 (1967).
48. L. E. Friedrich and R. A. Cormier, *J. Org. Chem.*, **35**, 450 (1970).
49. J. Ciabattoni and J. P. Kocienski, *J. Am. Chem. Soc.*, **93**, 4902 (1971).
50. L. E. Friedrich and R. A. Fiato, *J. Org. Chem.*, **39**, 2267 (1974).
51. M. S. Baird and H. H. Hussain, *Tetrahedron Lett.*, **27**, 5143 (1986).
52. R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952).
53. B. Byrne and K. J. Wengenroth, *Synthesis*, 870 (1986).
54. I. Paterson and I. Fleming, *Tetrahedron Lett.*, 995 (1979).
55. A. J. Fatiadi, *Synthesis*, 65 (1976); 133 (1976).
56. E. J. Corey and G. Schmidt, *Tetrahedron Lett.*, 399 (1979).
57. J. Herscovici and K. Antonakis, *J. Chem. Soc., Chem. Commun.*, 561 (1980).
58. J. Defaye, A. Gadelle and S. J. Angyal, *Carbohydr. Res.*, **126**, 165 (1984).
59. S. Czernecki, C. Georgoulis, C. L. Stevens and K. Vijayakumaran, *Tetrahedron Lett.*, **26**, 1699 (1985).
60. E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 2647 (1975).
61. E. J. Corey and D. L. Boger, *Tetrahedron Lett.*, 2461 (1978).
62. K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).
63. J. C. Collins, W. W. Hess and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).
64. K. Nakagawa, R. Konaka and T. Nakata, *J. Org. Chem.*, **27**, 1597 (1962).
65. S. E. Denmark and T. K. Jones, *J. Am. Chem. Soc.*, **104**, 2642 (1982).
66. F. J. Kakis, M. Fetizon, N. Douchkine, M. Golfier, P. Mourgues and T. Prange, *J. Org. Chem.*, **39**, 523 (1974).
67. G. Cainelli and G. Cardillo, Eds. in *Chromium Oxidations in Organic Chemistry*, Springer-Verlag, Berlin (1984).
68. E. J. Corey and M. M. Mehrotra, *Tetrahedron Lett.*, **26**, 2411 (1985).
69. H. Kikuchi, Y. Tsukitani, K. Iguchi and Y. Yamada, *Tetrahedron Lett.*, **23**, 5171 (1982).
70. E. J. Corey and M. M. Mehrotra, *J. Am. Chem. Soc.*, **106**, 3384 (1984).
71. G. Piancatelli, A. Scettri and M. D'Auria, *Tetrahedron Lett.*, 2199 (1977).
72. G. Piancatelli, A. Scettri and M. D'Auria, *Tetrahedron*, **36**, 661 (1980).
73. R. Antonioletti, M. D'Auria, A. DeMico, G. Piancattelli and A. Scettri, *Synthesis*, 280 (1984).
74. W. G. Dauben and D. M. Michno, *J. Org. Chem.*, **42**, 682 (1977).
75. D. Liotta, D. Brown, W. Hoekstra and R. Monahan, III, *Tetrahedron Lett.*, **28**, 1069 (1987).
76. R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).
77. D. S. Fullerton and C.-M. Chen, *Synth. Commun.*, **6**, 217 (1976).
78. S. W. Kirtley, in *Comprehensive Organometallic Chemistry*, Vol. 3 (Eds. G. Wilkinson, F. G. A. Stone and E. W. Abel), Pergamon Press, 1982, p. 818.
79. A. J. Pearson, Y.-S. Chen, S.-Y. Hsu and T. Ray, *Tetrahedron Lett.*, **25**, 1235 (1984); A. J. Pearson, Y.-S. Chen, G. R. Han, S.-Y. Hsu and T. Ray, *J. Chem. Soc., Perkin Trans. 1*, 267 (1985).
80. R. J. Theissen, *J. Org. Chem.*, **36**, 752 (1971).
81. S. Wolff and W. C. Agosta, *Synthesis*, 240 (1976).
82. W. Ando, H. Hayakawa and N. Tokitoh, *Tetrahedron Lett.*, **27**, 6357 (1986).
83. T. H. Chan and B. S. Ong, *Tetrahedron*, **36**, 2269 (1980).
84. A. Padwa, D. N. Kline and J. Perumattam, *Tetrahedron Lett.*, **28**, 913 (1987).
85. T. Ohnuma, N. Hata, H. Fujiwara and Y. Ban, *J. Org. Chem.*, **47**, 4713 (1982).
86. H. Oediger, F. Möller and K. Eiter, *Synthesis*, 591 (1972).
87. P. P. Fu and R. G. Harvey, *Chem. Rev.*, **78**, 317 (1978).
88. K. B. Sharpless, R. F. Lauer and A. Y. Teranishi, *J. Am. Chem. Soc.*, **95**, 6137 (1973).
89. B. M. Trost, T. N. Salzmann and K. Hiroi, *J. Am. Chem. Soc.*, **98**, 4887 (1976).
90. D. Liotta, C. Barnum, R. Puleo, G. Zima, C. Bayer and H. S. Kezar, III, *J. Org. Chem.*, **46**, 2920 (1981).
91. L. Engman, *Tetrahedron Lett.*, **26**, 6385 (1985).
92. D. H. R. Barton, D. J. Lester and S. V. Ley, *J. Chem. Soc., Perkin Trans. 1*, 2209 (1980).
93. T. G. Back, *J. Org. Chem.*, **46**, 1442 (1981).
94. P. E. Eaton and W. H. Bunnelle, *Tetrahedron Lett.*, **25**, 23 (1984).
95. J. Schreiber, H. Maag, N. Hashimoto and A. Eschenmoser, *Angew. Chem., Int. Ed. Engl.*, **10**, 330 (1971).
96. S. Danishefsky, T. Kitahara, R. McKee and P. F. Schuda, *J. Am. Chem. Soc.*, **98**, 6715 (1976).

97. J. L. Roberts, P. S. Borromeo and C. D. Poulter, *Tetrahedron Lett.*, 1299 (1977); J. L. Roberts, P. S. Borromeo and C. D. Poulter, *Tetrahedron Lett.*, 1621 (1977).
98. T. A. Bryson, G. H. Bonitz, C. J. Reichel and R. E. Dardis, *J. Org. Chem.*, **45**, 524 (1980).
99. C. Rochin, O. Babot, J. Dunogues and F. Duboudin, *Synthesis*, 228 (1986).
100. V. Nair and C. S. Cooper, *J. Org. Chem.*, **46**, 4759 (1981).
101. V. Nair and T. S. Jahnke, *Synthesis*, 424 (1984).
102. H. Amri and J. Villieras, *Tetrahedron Lett.*, **27**, 4307 (1986).
103. I. Shimizu and J. Tsuji, *J. Am. Chem. Soc.*, **104**, 5844 (1982).
104. J. Tsuji, I. Minami, I. Shimizu and H. Kataoka, *Chem. Lett.*, 1133 (1984).
105. J. Tsuji, I. Minami and I. Shimizu, *Tetrahedron Lett.*, **24**, 5635 (1983).
106. R. L. Funk and K. P. C. Vollhardt, *Synthesis*, 118 (1980).
107. B. W. Disanayaka and A. C. Weedon, *Synthesis*, 952 (1983).
108. J. Tsuji, M. Nisar, I. Shimizu and I. Minami, *Synthesis*, 1009 (1984).
109. J. Tsuji, M. Nisar and I. Minami, *Tetrahedron Lett.*, **27**, 2483 (1986).
110. Y. Ito, T. Hirao and T. Saegusa, *J. Org. Chem.*, **43**, 1011 (1978).
111. Y. Ito, H. Aoyama, T. Hirao, A. Mochizuki and T. Saegusa, *J. Am. Chem. Soc.*, **101**, 494 (1979).
112. Y. Ito, H. Aoyama and T. Saegusa, *J. Am. Chem. Soc.*, **102**, 4519 (1980).
113. L. E. Torres and G. L. Larson, *Tetrahedron Lett.*, **27**, 2223 (1986).
114. T. Mitsudo, M. Kadokura and Y. Watanabe, *Tetrahedron Lett.*, **26**, 5143 (1985).
115. M. Kadokura, T. Mitsudo and Y. Watanabe, *J. Chem. Soc., Chem. Commun.*, 252 (1986).
116. T. Mitsudo, M. Kadokura and Y. Watanabe, *J. Org. Chem.*, **52**, 3186 (1987).
117. S. Hacini, R. Pardo and M. Santelli, *Tetrahedron Lett.*, 4553 (1979).
118. C. Santelli-Rouvier and M. Santelli, *Synthesis*, 429 (1983).
119. B. Tursch, J. C. Braekman, D. Daloze, P. Fritz, A. Kelecom, R. Karlsson and D. Losman, *Tetrahedron Lett.*, 747 (1974).
120. L. A. Paquette and W. H. Ham, *J. Am. Chem. Soc.*, **109**, 3025 (1987).
121. J. P. Pillot, J. Dunogues and R. Calas, *Bull. Soc. Chim. Fr.*, 2143 (1975).
122. I. Fleming and A. Pearce, *J. Chem. Soc., Chem. Commun.*, 633 (1975).
123. M. A. Cook, C. Eaborn and D. R. M. Walton, *J. Organomet. Chem.*, **24**, 301 (1970).
124. T. G. Traylor, H. J. Berwin, J. Jerkunica and M. L. Hall, *Pure Appl. Chem.*, **30**, 599 (1972).
125. F. Cooke, J. Schwindeman and P. Magnus, *Tetrahedron Lett.*, 1995 (1979).
126. W. E. Fristad, D. S. Dime, T. R. Bailey and L. A. Paquette, *Tetrahedron Lett.*, 1999 (1979).
127. T. H. Chan and I. Fleming, *Synthesis*, 761 (1979).
128. Z. N. Parnes and G. I. Bolestova, *Synthesis*, 991 (1984).
129. L. E. Overman and K. L. Bell, *J. Am. Chem. Soc.*, **103**, 1851 (1981).
130. S. D. Burke, C. W. Murtiashaw, M. S. Dike, S. M. S. Strickland and J. O. Saunders, *J. Org. Chem.*, **46**, 2400 (1981).
131. S. E. Denmark and J. P. Germanas, *Tetrahedron Lett.*, **25**, 1231 (1984).
132. M. E. Jung and K. M. Halweg, *Tetrahedron Lett.*, **22**, 3929 (1981).
133. K. Fukuzaki, E. Nakamura and I. Kuwajima, *Tetrahedron Lett.*, **25**, 3591 (1984).
134. R. L. Funk and K. P. C. Vollhardt, *Chem. Soc. Rev.*, **9**, 41 (1980).
135. H. Sawada, M. Webb, A. T. Stoll and E. Negishi, *Tetrahedron Lett.*, **27**, 775 (1986).
136. J. F. Normant and A. Alexakis, *Synthesis*, 841 (1981).
137. M. T. Reetz, B. Wenderoth and R. Urz, *Chem. Ber.*, **118**, 348 (1985).
138. D. Milstein and J. K. Stille, *J. Am. Chem. Soc.*, **100**, 3636 (1978).
139. J. A. Soderquist and W. W.-H. Leong, *Tetrahedron Lett.*, **24**, 2361 (1983).
140. M. W. Logue and K. Teng, *J. Org. Chem.*, **47**, 2549 (1982).
141. J. W. Labadie, D. Tueting and J. K. Stille, *J. Org. Chem.*, **48**, 4634 (1983).
142. F. K. Sheffy, J. P. Godschalx and J. K. Stille, *J. Am. Chem. Soc.*, **106**, 4833 (1984).
143. W. F. Goure, M. E. Wright, P. D. Davis, S. S. Labadie and J. K. Stille, *J. Am. Chem. Soc.*, **106**, 6417 (1984).
144. B. L. Chenard, C. M. Van Zyl and D. R. Sanderson, *Tetrahedron Lett.*, **27**, 2801 (1986).
145. E. Negishi, V. Bagheri, S. Chatterjee, F.-T. Luo, J. A. Miller and A. T. Stoll, *Tetrahedron Lett.*, **24**, 5181 (1983).
146. Y. Tamaru, H. Ochiai, F. Sanda and Z. Yoshida, *Tetrahedron Lett.*, **26**, 5529 (1985).
147. D. G. Batt and B. Ganem, *Tetrahedron Lett.*, 3323 (1978).
148. M. Franck-Neumann, M. Sedrati and M. Mokhi, *Tetrahedron Lett.*, **27**, 3861 (1986).
149. O. W. Lever, Jr., *Tetrahedron*, **32**, 1943 (1976).

150. E. J. Corey and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **4**, 1075 (1965); E. J. Corey and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **4**, 1077 (1965).
151. D. Seebach, *Synthesis*, 17 (1969).
152. D. Seebach and E. J. Corey, *J. Org. Chem.*, **40**, 231 (1975).
153. I. Degani, R. Fochi and V. Regondi, *Synthesis*, 51 (1981).
154. D. Seebach, M. Kolb and B.-Th. Gröbel, *Angew. Chem., Int. Ed. Engl.*, **12**, 69 (1973).
155. D. Seebach, M. Kolb and B.-Th. Gröbel, *Tetrahedron Lett.*, 3171 (1974).
156. E. J. Corey and A. P. Kozikowski, *Tetrahedron Lett.*, 925 (1975).
157. E. Guittet and S. Julia, *Tetrahedron Lett.*, 1155 (1978).
158. S. Yamada, T. Suzuki, H. Takayama, K. Miyamoto, I. Matsunaga and Y. Nawata, *J. Org. Chem.*, **48**, 3483 (1983).
159. S. Yamada, H. Suzuki, H. Naito, T. Nomoto and H. Takayama, *J. Chem. Soc., Chem. Commun.*, 332 (1987).
160. Y. Yamamoto, H. Yatagai, Y. Saito and K. Maruyama, *J. Org. Chem.*, **49**, 1096 (1984).
161. T. Mandai, T. Moriyama, Y. Nakayama, K. Sugino, M. Kawada and J. Otera, *Tetrahedron Lett.*, **25**, 5913 (1984).
162. T. Mandai, H. Arase, J. Otera and M. Kawada, *Tetrahedron Lett.*, **26**, 2677 (1985).
163. T. Mandai, K. Hara, T. Nakajima, M. Kawada and J. Otera, *Tetrahedron Lett.*, **24**, 4993 (1983).
164. I. U. Khand, G. R. Knox, P. L. Pauson, W. E. Watts and M. I. Foreman, *J. Chem. Soc., Perkin Trans. 1*, 977 (1973).
165. N. E. Schore, *Synth. Commun.*, **9**, 41 (1979).
166. N. E. Schore and M. C. Croudace, *J. Org. Chem.*, **46**, 5436 (1981).
167. C. Exon and P. Magnus, *J. Am. Chem. Soc.*, **105**, 2477 (1983).
168. T. Takeuchi, H. Iinuma, S. Takahashi and H. Umezawa, *J. Antibiot.*, **24**, 631 (1971).
169. P. Magnus and L. M. Principe, *Tetrahedron Lett.*, **26**, 4851 (1985).
170. J. M. Manriquez, D. R. McAlister, R. D. Sanner and J. E. Bercaw, *J. Am. Chem. Soc.*, **100**, 2716 (1978).
171. E. Negishi, S. J. Holmes, J. M. Tour and J. A. Miller, *J. Am. Chem. Soc.*, **107**, 2568 (1985).
172. E. Negishi, D. R. Swanson, F. E. Cederbaum and T. Takahashi, *Tetrahedron Lett.*, **28**, 917 (1987).
173. S. L. Buchwald, B. T. Watson and J. C. Huffman, *J. Am. Chem. Soc.*, **109**, 2544 (1987).
174. K. Doyama, T. Joh, S. Takahashi and T. Shiohara, *Tetrahedron Lett.*, **27**, 4497 (1986).
175. P. DeShong, G. A. Slough and A. L. Rheingold, *Tetrahedron Lett.*, **28**, 2229 (1987); P. DeShong, D. R. Sidler and G. A. Slough, *Tetrahedron Lett.*, **28**, 2233 (1987).
176. B. L. Booth and R. G. Hargreaves, *J. Chem. Soc. (A).*, 308 (1970).
177. B. M. Trost and L. N. Jungheim, *J. Am. Chem. Soc.*, **102**, 7910 (1980).
178. J. H. Byers and T. A. Spencer, *Tetrahedron Lett.*, **26**, 717 (1985).
179. D. A. Jackson, M. Rey and A. S. Dreiding, *Tetrahedron Lett.*, **24**, 4817 (1983).
180. J. R. Matz and T. Cohen, *Tetrahedron Lett.*, **22**, 2459 (1981).
181. C. Hoornaert, A. M. Frisque and L. Ghosez, *Angew. Chem., Int. Ed. Engl.*, **14**, 569 (1975).
182. C. Schmit, S. Sahraoui-Taleb, E. Differding, C. G. D. Lombaert and L. Ghosez, *Tetrahedron Lett.*, **25**, 5043 (1984).
183. D. Labar, J. L. Laboureur and A. Krief, *Tetrahedron Lett.*, **23**, 983 (1982); J. L. Laboureur and A. Krief, *Tetrahedron Lett.*, **25**, 2713 (1984).
184. R. A. Minns, *Org. Synth.*, **57**, 117 (1977).
185. A. E. Greene and J.-P. Deprès, *J. Am. Chem. Soc.*, **101**, 4003 (1979).
186. J.-P. Deprès and A. E. Greene, *J. Org. Chem.*, **45**, 2036 (1980).
187. A. E. Greene and F. Charbonnier, *Tetrahedron Lett.*, **26**, 5525 (1985).
188. A. E. Greene, F. Charbonnier, M.-J. Luche and A. Moyano, *J. Am. Chem. Soc.*, **109**, 4752 (1987).
189. G. L. Chetty and S. Dev, *Tetrahedron Lett.*, 73 (1964); T. Irie, T. Suzuki, S. Itô and E. Kurosawa, *Tetrahedron Lett.*, 3187 (1967).
190. R. L. Danheiser and D. M. Fink, *Tetrahedron Lett.*, **26**, 2513 (1985).
191. G. Barbarella, G. Pitacco, C. Russo and E. Valentin, *Tetrahedron Lett.*, **24**, 1621 (1983).
192. G. Barbarella, S. Bruckner, G. Pitacco and E. Valentin, *Tetrahedron*, **40**, 2441 (1984).
193. M. M. Cooper and J. W. Huffman, *J. Chem. Soc., Chem. Commun.*, 348 (1987).
194. N. Ono, H. Miyake and A. Kaji, *J. Org. Chem.*, **49**, 4997 (1984).
195. A. Yoshikoshi and M. Miyashita, *Acc. Chem. Res.*, **18**, 284 (1985).
196. R. A. Ellison, *Synthesis*, 397 (1973).

197. S. M. Kupchan, R. W. Britton, J. A. Lacadie, M. F. Ziegler and C. W. Sigel, *J. Org. Chem.*, **40**, 648 (1975).
198. D. M. Hedstrand, S. R. Byrn, A. T. McKenzie and P. L. Fuchs, *J. Org. Chem.*, **52**, 592 (1987).
199. A. J. Birch, L. F. Kelly and D. J. Thompson, *J. Chem. Soc., Perkin Trans. 1*, 1006 (1981).
200. L. F. Kelly, P. Dahler, A. S. Narula and A. J. Birch, *Tetrahedron Lett.*, **22**, 1433 (1981).
201. C. J. Moody and J. Toczek, *Tetrahedron Lett.*, **27**, 5253 (1986).
202. C. J. Moody, S. M. Roberts and J. Toczek, *J. Chem. Soc., Chem. Commun.*, 1292 (1986).
203. T. Ichikawa, M. Namikawa, K. Yamada, K. Sakai and K. Kondo, *Tetrahedron Lett.*, **24**, 3337 (1983).
204. A. Nishinaga, K. Watanabe and T. Matsuura, *Tetrahedron Lett.*, 1291 (1974).
205. A. Nishinaga, T. Itahara and T. Matsuura, *Bull. Chem. Soc. Jpn.*, **48**, 1683 (1975).
206. A. McKillop, D. H. Perry, M. Edwards, S. Antus, L. Farkas, M. Nógrádi and E. C. Taylor, *J. Org. Chem.*, **41**, 282 (1976).
207. D. T. Coxon, K. R. Price, B. Howard, S. F. Osman, E. B. Kalan and R. M. Zacharius, *Tetrahedron Lett.*, 2921 (1974).
208. T. Fujimori, R. Kasuga, H. Kaneko and M. Noguchi, *Phytochemistry*, **16**, 392 (1977).
209. C. Iwata, T. Fusaka, T. Fujiwara, K. Tomita and M. Yamada, *J. Chem. Soc., Chem. Commun.*, 463 (1981).
210. C. Iwata, M. Yamada, Y. Shinoo, K. Kobayashi and H. Okada, *J. Chem. Soc., Chem. Commun.*, 888 (1977).
211. C. Iwata, K. Miyashita, Y. Ida and M. Yamada, *J. Chem. Soc., Chem. Commun.*, 461 (1981).
212. J. C. Bottaro, R. N. Hanson and D. E. Seitz, *J. Org. Chem.*, **46**, 5221 (1981).
213. M. R. Peel and C. R. Johnson, *Tetrahedron Lett.*, **27**, 5947 (1986).
214. E. Wada, I. Fujiwara, S. Kanemasa and O. Tsuge, *Bull. Chem. Soc. Jpn.*, **60**, 325 (1987).
215. B. A. Vick and D. C. Zimmerman, *Biochem. Biophys. Res. Commun.*, **111**, 470 (1983).
216. E. J. Corey, P. T. Lansbury, Jr. and Y. Yamada, *Tetrahedron Lett.*, **26**, 4171 (1985).
217. E. J. Corey, M. d'Alarcao, S. P. T. Matsuda and P. T. Lansbury, Jr., *J. Am. Chem. Soc.*, **109**, 289 (1987).
218. E. J. Corey, K. Ritter, M. Yus and C. Nájera, *Tetrahedron Lett.*, **28**, 3547 (1987).
219. G. Mehta, D. S. Reddy and A. N. Murty, *J. Chem. Soc., Chem. Commun.*, 824 (1983).
220. E. Ayanoglu, T. Gebreyesus, C. M. Beechan, C. Djerassi and M. Kaisin, *Tetrahedron Lett.*, 1671 (1978).
221. G. Mehta, A. N. Murthy, D. S. Reddy and A. V. Reddy, *J. Am. Chem. Soc.*, **108**, 3443 (1986).
222. S. Nozoe, J. Furukawa, U. Sankawa and S. Shibata, *Tetrahedron Lett.*, 195 (1976).
223. R. L. Danheiser, S. K. Gee and H. Sard, *J. Am. Chem. Soc.*, **104**, 7670 (1982).
224. A. Jellal and M. Santelli, *Tetrahedron Lett.*, **21**, 4487 (1980).
225. D. El-Abed, A. Jellal and M. Santelli, *Tetrahedron Lett.*, **25**, 1463 (1984).
226. M.-C. Lasne and J.-L. Ripoll, *Synthesis*, 121 (1985).
227. A. Ichihara, *Synthesis*, 207 (1987).
228. G. Stork, G. L. Nelson, F. Rouessac and O. Gringore, *J. Am. Chem. Soc.*, **93**, 3091 (1971).
229. P. Ducos and F. Rouessac, *Tetrahedron*, **29**, 3233 (1973).
230. H. Raistrick and G. Smith, *Biochem. J.*, **29**, 606 (1935).
231. J. Auerbach and S. M. Weinreb, *J. Chem. Soc., Chem. Commun.*, 298 (1974).
232. D. H. R. Barton and L. A. Hulshof, *J. Chem. Soc., Perkin Trans. 1*, 1103 (1977).
233. A. J. H. Klunder, W. Bos, J. M. M. Verlaak and B. Zwanenburg, *Tetrahedron Lett.*, **22**, 4553 (1981).
234. A. J. H. Klunder, W. Bos and B. Zwanenburg, *Tetrahedron Lett.*, **22**, 4557 (1981).
235. Y. Jenkitkasemwong, Y. Thebtaranonth and N. Wajirum, *Tetrahedron Lett.*, 1615 (1979).
236. P. Prempree, T. Siwapinyoyos, C. Thebtaranonth and Y. Thebtaranonth, *Tetrahedron Lett.*, **21**, 1169 (1980).
237. T. Siwapinyoyos and Y. Thebtaranonth, *J. Org. Chem.*, **47**, 598 (1982).
238. R. M. Scarborough, Jr., B. H. Toder and A. B. Smith, III, *J. Am. Chem. Soc.*, **102**, 3904 (1980).
239. T. Haneishi, N. Kitihara, Y. Takiguchi, M. Arai and S. Sugawara, *J. Antibiot.*, **27**, 386 (1974).
240. J. Jernow, W. Tautz, P. Rosen and T. H. Williams, *J. Org. Chem.*, **44**, 4212 (1979).
241. Y. Takahashi, H. Kosugi and H. Uda, *J. Chem. Soc., Chem. Commun.*, 496 (1982).
242. M. Mikołajczyk, W. Midura and S. Grzejszczak, *Tetrahedron Lett.*, **25**, 2489 (1984).
243. M. Koller, M. Karpf and A. S. Dreiding, *Tetrahedron Lett.*, **27**, 19 (1986).
244. M. Pohmakotr and S. Chancharunee, *Tetrahedron Lett.*, **25**, 4141 (1984).

245. H. Umezawa, T. Takeuchi, K. Nitta, Y. Yamamoto and S. Yamaoka, *J. Antibiot.*, **6**, 101 (1953).
246. J. N. Marx and G. Minaskanian, *Tetrahedron Lett.*, 4175 (1979).
247. R. K. Boeckman, Jr., P. C. Naegely and S. D. Arthur, *J. Org. Chem.*, **45**, 752 (1980).
248. Y. Kobayashi and J. Tsuji, *Tetrahedron Lett.*, **22**, 4295 (1981).
249. E. J. Barreiro, *Tetrahedron Lett.*, **23**, 3605 (1982).
250. J. N. Marx and G. Minaskanian, *J. Org. Chem.*, **47**, 3306 (1982).
251. B. A. Wexler, B. H. Toder, G. Minaskanian and A. B. Smith, III, *J. Org. Chem.*, **47**, 3333 (1982).
252. A. T. Hewson and D. T. MacPherson, *Tetrahedron Lett.*, **24**, 647 (1983).
253. S. V. Govindan, T. Hudlicky and F. J. Koszyk, *J. Org. Chem.*, **48**, 3581 (1983).
254. P. G. Baraldi, A. Barco, S. Benetti, G. P. Pollini, E. Polo and D. Simoni, *J. Chem. Soc., Chem. Commun.*, 1049 (1984).
255. T. Cohen, Z. Kosarych, K. Suzuki and L.-C. Yu, *J. Org. Chem.*, **50**, 2965 (1985).
256. Y. Thebtaranonth, *Pure Appl. Chem.*, **58**, 781 (1986).
257. M. Kodpinid, T. Siwapinyoyos and Y. Thebtaranonth, *J. Am. Chem. Soc.*, **106**, 4862 (1984).
258. A. Ichihara, R. Kimura, K. Oda, K. Moriyasu and S. Sakamura, *Agric. Biol. Chem.*, **46**, 1879 (1982).
259. S. Danishefsky and J. F. Kerwin, Jr., *J. Org. Chem.*, **47**, 3183 (1982).
260. P. Nanjappan and A. W. Czarnik, *J. Org. Chem.*, **51**, 2851 (1986).
261. W. H. Bunnelle and W. R. Shangraw, *Tetrahedron*, **43**, 2005 (1987).
262. P. Gosselin, *Tetrahedron Lett.*, **27**, 5495 (1986).
263. P. N. Confalone, E. Baggiolini, B. Hennessy, G. Pizzolato and M. R. Uskoković, *J. Org. Chem.*, **46**, 4923 (1981).
264. P. G. Biraldi, A. Barco, S. Benetti, G. P. Pollini and V. Zanirato, *Tetrahedron Lett.*, **25**, 4291 (1984).
265. A. B. Smith, III, S. J. Branca, N. N. Pilla and M. A. Guaciaro, *J. Org. Chem.*, **47**, 1855 (1982).
266. F. W. Lichtenthaler, *Chem. Rev.*, **61**, 607 (1961).
267. S. C. Welch, J.-M. Assercq and J.-P. Loh, *Tetrahedron Lett.*, **27**, 1115 (1986).
268. S. C. Welch, J.-M. Assercq, J.-P. Loh and S. A. Glase, *J. Org. Chem.*, **52**, 1440 (1987).
269. J. Moskal and A. M. van Leusen, *Tetrahedron Lett.*, **25**, 2585 (1984).
270. S. Sato, I. Matsuda and Y. Izumi, *Tetrahedron Lett.*, **26**, 1527 (1985).
271. E. J. Corey, W. Su and I. N. Houpis, *Tetrahedron Lett.*, **27**, 5951 (1986).
272. J. Villieras and M. Rambaud, *Synthesis*, 924 (1982).
273. J. P. Gillet, R. Sauvêtre and J. F. Normant, *Synthesis*, 297 (1982).
274. P. Albert and J. Cousseau, *J. Chem. Soc., Chem. Commun.*, 961 (1985).
275. G. Berthiaume, J.-F. Lavallée and P. Deslongchamps, *Tetrahedron Lett.*, **27**, 5451 (1986).
276. J.-F. Lavallée, G. Berthiaume, P. Deslongchamps and F. Grein, *Tetrahedron Lett.*, **27**, 5455 (1986).
277. J.-F. Lavallée and P. Deslongchamps, *Tetrahedron Lett.*, **28**, 3457 (1987).
278. N. Furukawa, T. Inoue, T. Aida and S. Oae, *J. Chem. Soc., Chem. Commun.*, 212 (1973).
279. G. A. Olah, Y. D. Vankar, M. Arvanaghi and G. K. S. Prakash, *Synthesis*, 720 (1979).
280. G. A. Olah, M. Arvanaghi and Y. D. Vankar, *Synthesis*, 721 (1979).
281. Y. L. Chow and B. H. Bakker, *Can. J. Chem.*, **60**, 2268 (1982).
282. C. H. Foster and G. A. Berchtold, *J. Org. Chem.*, **40**, 3743 (1975).
283. A. J. Pearson, S. L. Kole and T. Ray, *J. Am. Chem. Soc.*, **106**, 6060 (1984).
284. A. J. Pearson and H. S. Bansal, *Tetrahedron Lett.*, **27**, 283 (1986).
285. A. J. Pearson, H. S. Bansal and Y.-S. Lai, *J. Chem. Soc., Chem. Commun.*, 519 (1987).
286. K. J. Shea, *Tetrahedron*, **36**, 1683 (1980).
287. J. A. Bertrand, D. Cheung, A. D. Hammerich, H. O. House, W. T. Reichle, D. Vanderveer and E. J. Zaiko, *J. Org. Chem.*, **42**, 1600 (1977).
288. H. O. House, W. A. Kleschick and E. J. Zaiko, *J. Org. Chem.*, **43**, 3653 (1978).
289. H. O. House and T. V. Lee, *J. Org. Chem.*, **44**, 2819 (1979).
290. H. O. House, M. B. DeTar and D. VanDerveer, *J. Org. Chem.*, **44**, 3793 (1979).
291. G. A. Kraus and Y.-S. Hon, *J. Org. Chem.*, **51**, 116 (1986).
292. H. O. House, R. J. Outcalt, J. L. Haack and D. VanDerveer, *J. Org. Chem.*, **48**, 1654 (1983).
293. K. A. Campbell, H. O. House, B. W. Surber and W. S. Trahanovsky, *J. Org. Chem.*, **52**, 2474 (1987).
294. P. Magnus, T. Gallagher, P. Brown and J. C. Huffman, *J. Am. Chem. Soc.*, **106**, 2105 (1984).
295. G. A. Kraus and Y.-S. Hon, *J. Am. Chem. Soc.*, **107**, 4341 (1985).

296. A. Mitra, *The Synthesis of Prostaglandins*, Wiley, New York, 1977.
297. M. P. L. Caton, *Tetrahedron*, **35**, 2705 (1979).
298. M. Harre, P. Raddatz, R. Walenta and E. Winterfeldt, *Angew. Chem., Int. Ed. Engl.*, **21**, 480 (1982).
299. I. Tömösközi, in *Chemistry and Biotechnology of Biologically Active Natural Products* (Ed. Cs. Szäntay), Elsevier, Amsterdam, 1984.
300. K. Laumen and M. P. Schneider, *J. Chem. Soc., Chem. Commun.*, 1298 (1986).
301. K. Kondo, M. Matsumoto and F. Mori, *Angew. Chem., Int. Ed. Engl.*, **14**, 103 (1975).
302. C. J. Sih, P. Price, R. Sood, R. G. Salomon, G. Peruzzotti and M. Casey, *J. Am. Chem. Soc.*, **94**, 3643 (1972).
303. K. Laumen and M. Schneider, *Tetrahedron Lett.*, **25**, 5875 (1984).
304. Y.-F. Wang, C.-S. Chen, G. Girdaukas and C. J. Sih, *J. Am. Chem. Soc.*, **106**, 3695 (1984).
305. J. W. Jaroszewski and E. S. Ólafsdóttir, *Tetrahedron Lett.*, **27**, 5297 (1986).
306. J. W. Jaroszewski, J. V. Andersen and I. Billeskov, *Tetrahedron*, **43**, 2349 (1987).
307. B. M. Trost and D. P. Curran, *J. Am. Chem. Soc.*, **103**, 7380 (1981).
308. B. M. Trost and D. P. Curran, *J. Am. Chem. Soc.*, **102**, 5699 (1980).
309. B. M. Trost and D. P. Curran, *Tetrahedron Lett.*, **22**, 4929 (1981).
310. D. W. Brooks, P. G. Grothaus and W. L. Irwin, *J. Org. Chem.*, **47**, 2820 (1982).
311. D. W. Brooks and K. W. Woods, *J. Org. Chem.*, **52**, 2036 (1987).
312. A. J. H. Klunder, W. B. Huizinga, A. J. M. Hulshof and B. Zwanenburg, *Tetrahedron Lett.*, **27**, 2543 (1986).
313. A. J. H. Klunder, W. B. Huizinga, P. J. M. Sessink and B. Zwanenburg, *Tetrahedron Lett.*, **28**, 357 (1987).
314. A. J. H. Klunder, J. H. M. Lange and B. Zwanenburg, *Tetrahedron Lett.*, **28**, 3027 (1987).
315. H.-J. Altenbach, W. Holzapfel, G. Smerat and S. H. Finkler, *Tetrahedron Lett.*, **26**, 6329 (1985).
316. H. J. Bestmann and T. Moenius, *Angew. Chem., Int. Ed. Engl.*, **25**, 994 (1986).
317. J. D. Elliott, M. Hetmanski, M. N. Palfreyman, N. Purcell and R. J. Stoodley, *Tetrahedron Lett.*, **24**, 965 (1983).
318. S. Achab, J.-P. Cosson and B. C. Das, *J. Chem. Soc., Chem. Commun.*, 1040 (1984).
319. M. Capobianco, E. Mezzina, D. Sovoia, E. Tagliavini, C. Trombini and A. U. Ronchi, *Tetrahedron Lett.*, **27**, 1387 (1986).
320. W. Oppolzer, R. Moretti and G. Bernardinelli, *Tetrahedron Lett.*, **27**, 4713 (1986).
321. A. I. Meyers and K. Th. Wanner, *Tetrahedron Lett.*, **26**, 2047 (1985).
322. A. I. Meyers, B. A. Lefker, K. Th. Wanner and R. A. Aitken, *J. Org. Chem.*, **51**, 1936 (1986).
323. A. I. Meyers and B. A. Lefker, *Tetrahedron Lett.*, **28**, 1745 (1987).
324. M. Hulce, J. P. Mallamo, L. L. Frye, T. P. Kogan and G. H. Posner, *Org. Synth.*, **64**, 196 (1986).

The Chemistry of Enones
Edited by S. Patai and Z. Rappoport

CHAPTER 8

Synthetic uses of enones

GERHARD V. BOYD
Department of Organic Chemistry, The Hebrew University of Jerusalem, Jerusalem, Israel

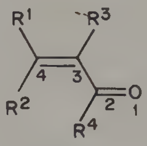
---

I. INTRODUCTION

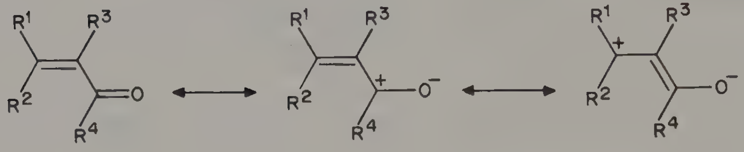
In this chapter syntheses starting with enones are described. The term 'enone' is interpreted rather broadly to include unsaturated aldehydes, the enals. We shall deal mainly with α,β-unsaturated aldehydes and ketones; other olefinic carbonyl compounds will be mentioned occasionally if their chemistry reflects an interaction between the carbonyl group and the remote double bond. The emphasis will be on recent work. General reviews are in References 1–4. A special section is devoted to synthetic uses of cyclopropenones and cyclobutenones.

The atoms in the enone structure are labelled by Greek letters, as in **1**, or by numerals, as in **2**. The reactivity of enones is explained by the polarisation shown in the resonance hybrid **3**. A nucleophilic reagent Nu^- can thus attack $C_{(2)}$, leading to 1,2-addition, or $C_{(4)}$, so-called 'conjugate addition', giving a 1,4-adduct **4**, which can tautomerise to **5** (equation 1).

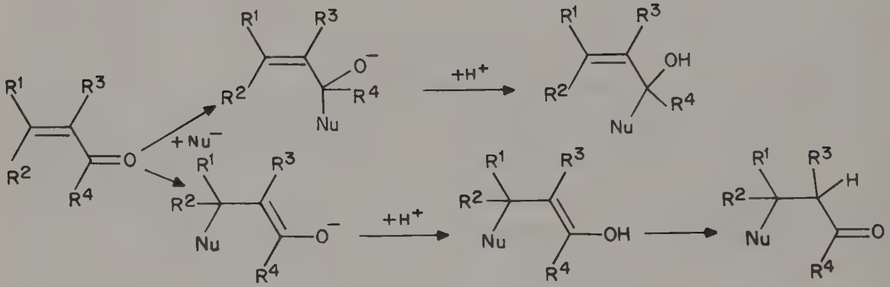
(1)



(2)



(3)



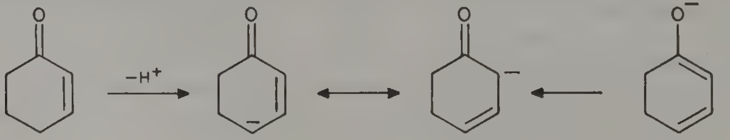
(1)

The question of 1,2- versus 1,4-addition is one of the most important features of the chemistry of enones[5].

II. REACTIONS WITH NUCLEOPHILES

A. Formation of Dienolate Anions and Enol Ethers

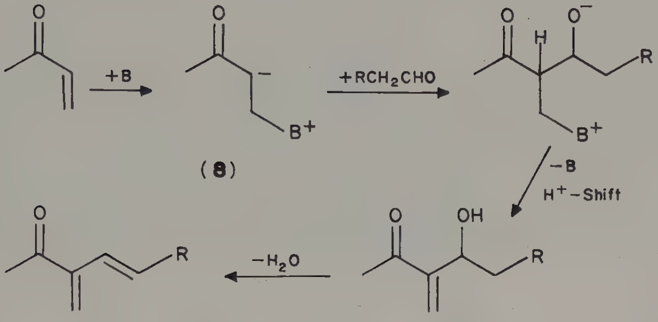
In the presence of strong bases enones form dienolate anions by abstraction of a proton from the γ-carbon atom, e.g. equation 2. Such anions react with various electrophiles, the position of attack depending on the nature of the reagent and on conditions. Alkylation is solvent-dependent; thus treatment of the enone **6** with $EtMe_2CO^-\ K^+$ in benzene, followed by methyl iodide, yields the α-methylated product **7** (equation 3)[6], whereas in polar solvents γ-methylation occurs. 1,4-Diazabicyclo[2.2.2]octane (B) is a unique catalyst for promoting attack by aldehydes on vinyl ketones at the α-carbon atom, presumably by way of the betaine **8**. Methyl vinyl ketone affords[7] the aldol products **9**, which can be dehydrated[8] to unstable 3-methylene-4-alken-2-ones **10** (equation 4).



(2)

(6) (7)

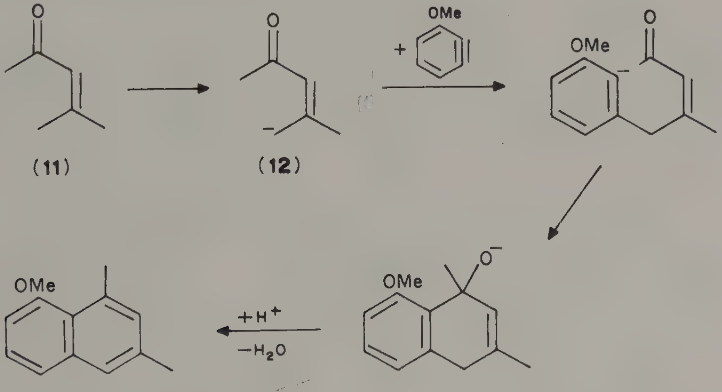
(3)



(8) (10) (9)

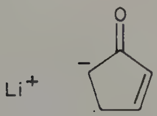
(4)

Treatment of mesityl oxide (**11**) with lithium diisopropylamide gives the anion **12**, which reacts with 3-methoxybenzyne, generated from either 2- or 3-bromoanisole, to yield 1-methoxy-6,8-dimethylnaphthalene (equation 5)[9]. The lithium dienolate **13**, derived from cyclopent-2-enone, is formed by deprotonation at the α′-position. It reacts with aldehydes RCHO to form a mixture of *threo*- and *erythro*-aldol products, **14** and **15**, respectively, with a preference for the former. In contrast, the corresponding zirconium dienolate gives the reverse diastereoselectivity[10].

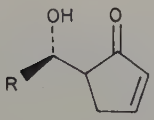


(11) (12)

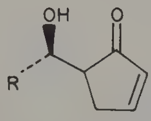
(5)



(13)

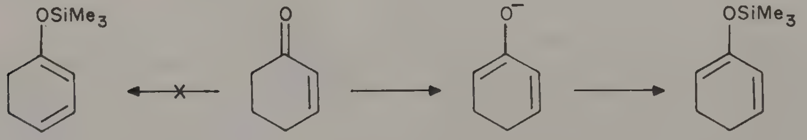


(14)



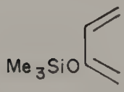
(15)

Numerous enones have been converted into trimethylsilyl ethers by the action of trimethylsilyl chloride in the presence of triethylamine or lithium diisopropylamide. Cyclohex-2-enone affords solely the ether (**17**) via the dienolate (**16**) (equation 6), and methyl vinyl ketone yields 2-trimethylsilyloxy-1,3-butadiene **18**[11]. Silyloxydienes such as **17**–**20** readily undergo Diels–Alder reactions with various olefins, and even aldehydes, and have been used for the synthesis of numerous complex compounds[12]. The trimethylsilyloxycyclohexadiene **17** reacts with maleic anhydride to form mainly the *endo*-adduct **21** (equation 7)[13]. The adduct of the ether **18** to methyl vinyl ketone is readily hydrolysed to 4-acetylcyclohexanone (equation 8)[14]. The silyl ether **22**, derived from 1-acetylcyclohexene, adds *trans*-β-nitrostyrene to afford a mixture of adducts, which on acidic work-up yields the decalones **23** and **24** (equation 9)[15]. 'Phosphoniosilylation' of cyclopentenone, cyclohexenone and cycloheptenone yields ethers, such as **25**, which undergo a Wittig reaction on treatment with butyllithium, followed by an aliphatic or aromatic aldehyde RCHO. The products **26** yield the substituted enones **27** on hydrolysis with aqueous hydrofluoric acid (equation 10)[16]. Alkoxyalkyl groups can be introduced at the α-position of enones by treatment with trimethylsilyl phenyl selenide in the presence of catalytic amounts of trimethylsilyl trifluoromethanesulphonate, followed by an *ortho* ester or an acetal. The whole sequence is conducted as a 'one-pot reaction'; it is exemplified by equation 11[17].

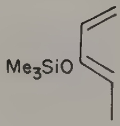


(16) (17)

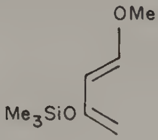
(6)



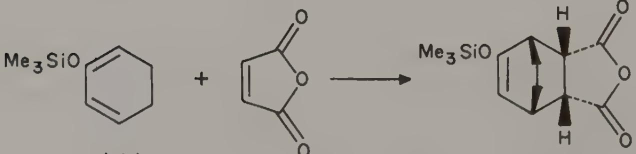
(18)



(19)

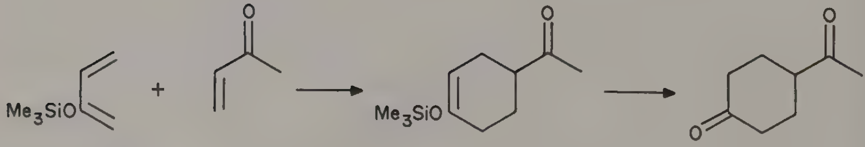


(20)



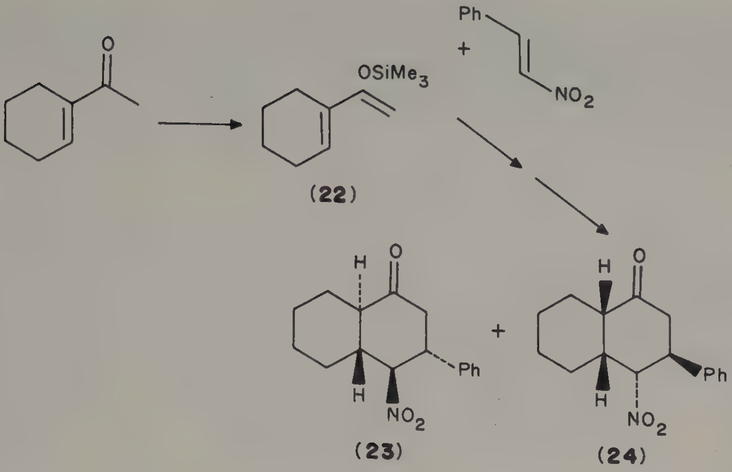
(17) (21)

(7)

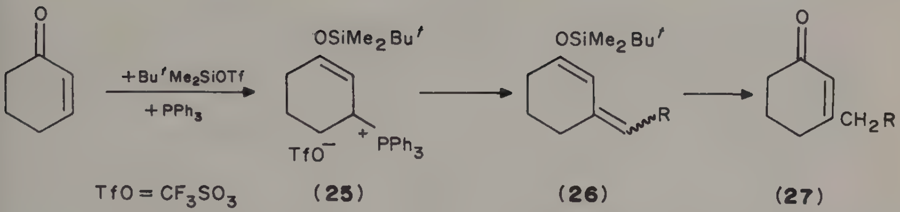


(18)

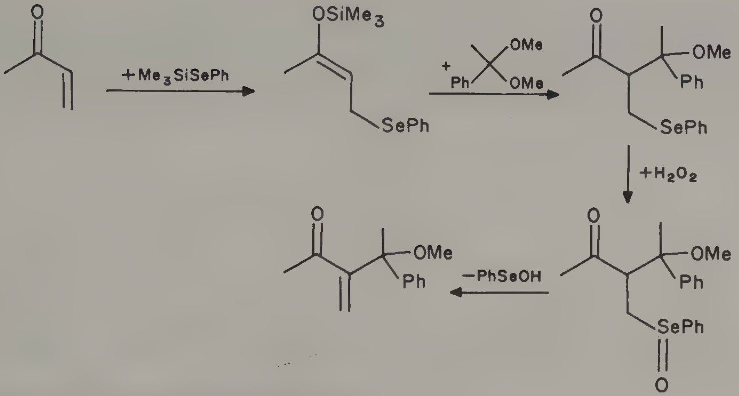
(8)



(9)



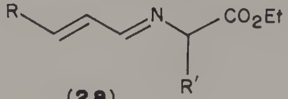
(10)



(11)

B. Reactions at the Carbonyl Carbon Atom

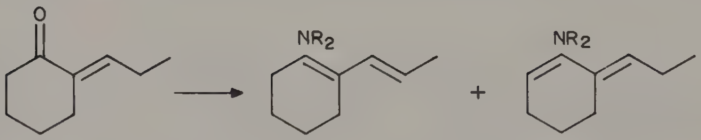
Unsaturated aldehydes RCH=CHCHO condense with primary amines to yield Schiff's bases, as in the formation of the imines **28** with esters of primary amino acids[18]. Secondary amines, such as pyrrolidine or morpholine, react with enones to form dienamines by dehydration of initial 1,2-adducts. The formation of linear dienamines from transoid enones is favoured; the octalenone **29**, for instance, yields a mixture of the linear dienamines **30** and **31**, and none of the 'cross-conjugated' isomer **32** (equation 12), whereas the cisoid 2-propylidenecyclohexanone **33** gives comparable amounts of linear (**34**) and 'cross-conjugated' (**35**) dienamines (equation 13)[19]. Dienamines such as **31** readily undergo Diels–Alder reactions with the usual dienophiles.



(28)

(32) (29) (30) (31)

(12)

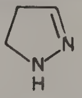


(13)

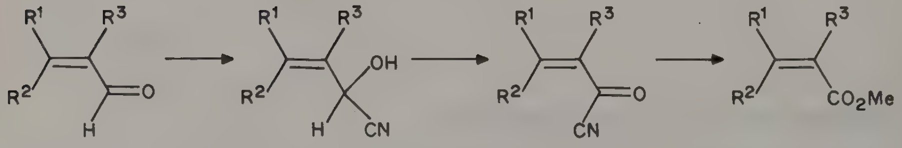
(33) (34) (35)

NR_2 = pyrrolidino

Acrolein (propenal), $CH_2{=}CHCHO$, forms a normal hydrazone with 2,4-dinitrophenylhydrazine; with hydrazine itself, however, the reaction goes further, yielding the pyrazoline **36**[1]. Unsaturated aldehydes add hydrogen cyanide at the carbonyl group; the resulting cyanohydrins can be oxidised by manganese(IV) oxide to acyl cyanides. The latter react with methanol to yield esters of α,β-olefinic acids, in which the original geometry round the double bond is preserved (equation 14)[20]. This method for obtaining unsaturated acids is preferable to the direct oxidation of alkenals with silver oxide.

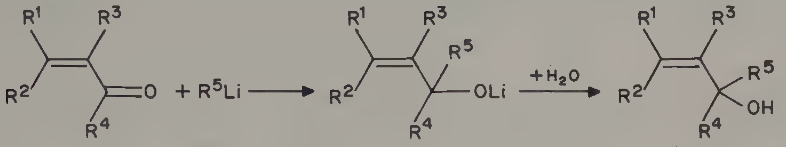


(**36**)

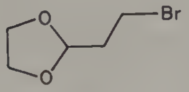


(14)

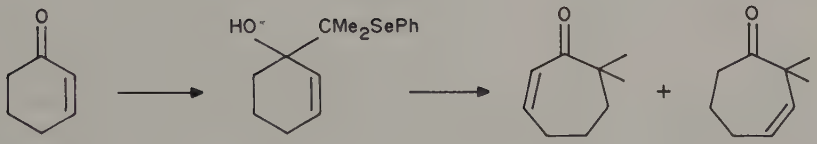
Alkyl- and aryl-lithium compounds react with enals and enones exclusively by 1,2-addition to give allyl alcohols (equation 15), while Grignard reagents usually give mixtures of products formed by 1,2- and 1,4-addition, with the former predominating[21]. However, the Grignard reagent derived from the acetal **37** adds to cyclopentenone and cyclohexenone at low temperatures to give mainly 1,4-adducts[22]. Metal derivatives of allyl ethers add exclusively to the carbonyl group of enones[23]. The action of the selenide $Me_2C(SePh)Li$ on cyclohex-2-enone produces an allyl alcohol, which undergoes ring expansion under the influence of thallium(I) ethoxide to yield a mixture of two cycloheptenones (equation 16)[24].



(15)



(**37**)

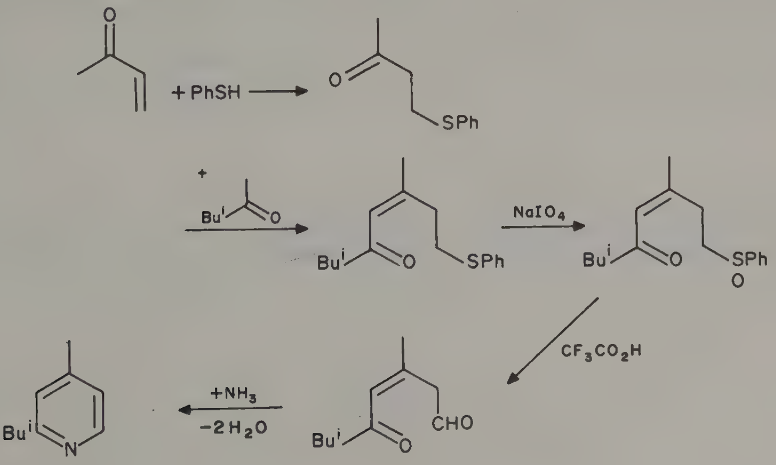


(16)

C. Reactions at the β-Carbon Atom (Conjugate Additions)

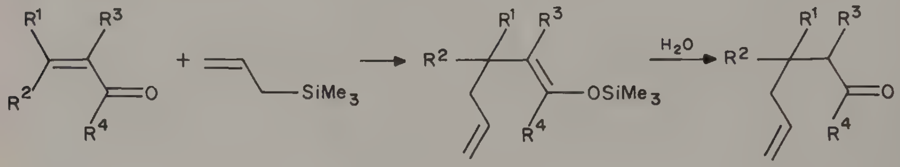
1. *With various nucleophiles*

Thiols react with enones to yield saturated ketones. This reaction is the basis of a new pyridine synthesis (equation 17). A variety of 2,3-, 2,4-, 2,3,4-, 2,3,5- and 2,4,5-substituted

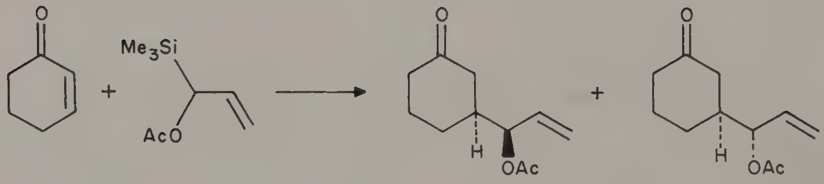


(17)

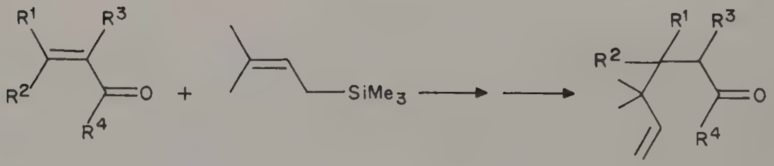
pyridines has been obtained by this method[25]. The conjugate addition of allyltrimethylsilane to enones is promoted by Lewis acids or fluoride ion (equation 18)[26]. (1-Acetoxy-2-propenyl)trimethylsilane reacts with enones, such as cyclohexenone, in the presence of tetrabutylammonium fluoride to yield a mixture of diastereoisomeric products (equation 19)[27]. The titanium(IV) chloride-catalysed reaction of allylsilanes with enones produces δ,ε-enones, in which the allyl group has been transposed (equation 20). An angular allyl substituent is introduced stereoselectively into the octalenone **37** (equation 21)[28].



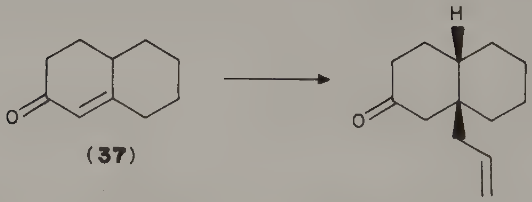
(18)



(19)



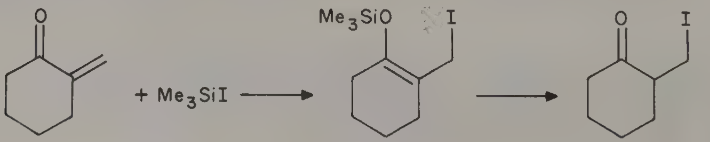
(20)



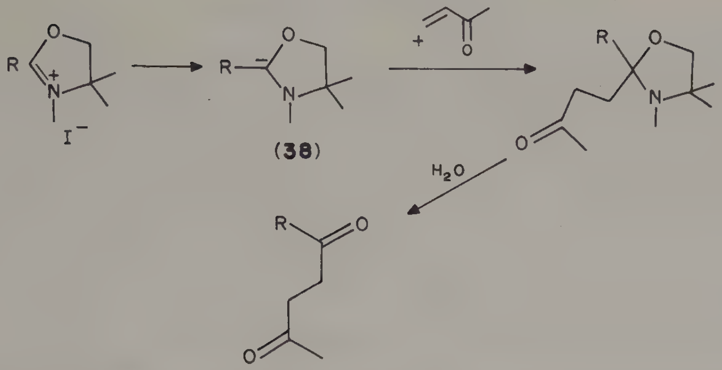
(37)

(21)

Useful highly reactive β-iodo ketones are obtained in good yields from trimethylsilyl iodide and enones, e.g. equation 22[29]. Electrolytic reduction of oxazolinium salts in the presence of trimethylsilyl chloride and enones yields, after hydrolysis, 1,4-diketones, the intermediate **38** having functioned as an acyl anion equivalent (equation 23)[30].

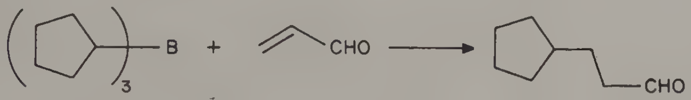


(22)



(23)

β-Alkylation of enals and enones can be achieved by using trialkylboranes, followed by hydrolysis, as in the cyclopentylation of acrolein (equation 24)[31].

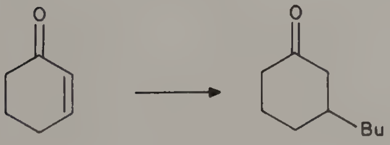


(24)

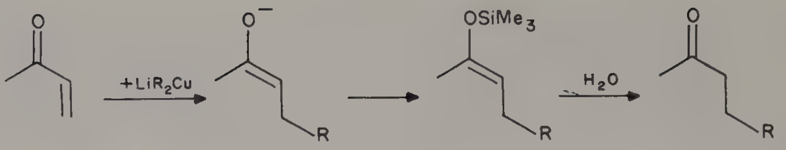
2. *With organometallic reagents*

In contrast to the reaction of organolithium and Grignard reagents with α,β-unsaturated carbonyl compounds, discussed in Section II.B, clean conjugate addition is brought about by the use of organocopper reagents, which are produced from lithium or Grignard compounds and copper(I) salts[32]. Thus 2-isopropylidenecyclohexanone and lithium dimethylcuprate, $LiMe_2Cu$, give *t*-butylcyclohexanone (equation 25)[33] and lithium dibutylcuprate and cyclohexenone yield 3-butylcyclohexanone (equation 26). A comparison of various sources of copper for the latter reaction showed that the combination butyllithium and copper(I) cyanide gave the highest yield, surpassing copper(I) bromide—dimethyl sulphide and copper(I) iodide[34]. The organocopper reaction of enals and enones proceeds particularly well in the presence of trimethylsilyl chloride and hexamethylphosphoric triamide, e.g. equation 27. The function of the trimethylsilyl chloride is not merely to trap the initially formed enolate anion but it appears to accelerate the addition reaction[35]. The organocopper reagent may be quite complex, as in the following example of an α-alkoxyalkyl cuprate (equation 28). Hydrolysis of the products affords 'homoaldol' derivatives of cyclic ketones, e.g. **39**[36].

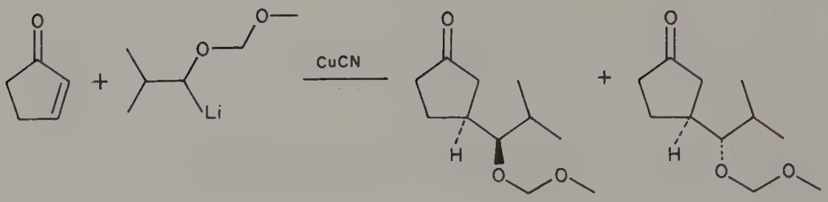
(25)



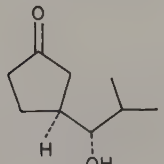
(26)



(27)

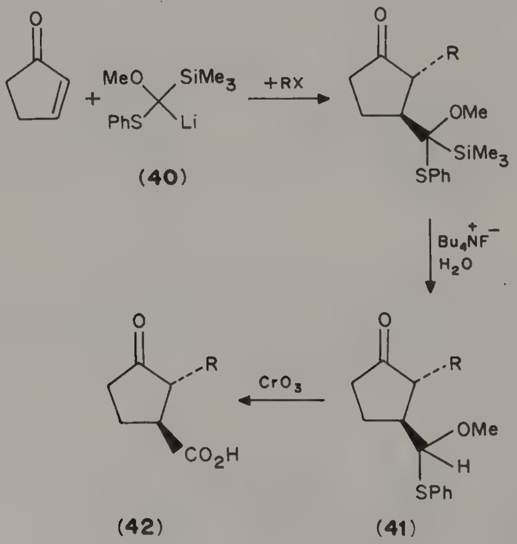


(28)



(39)

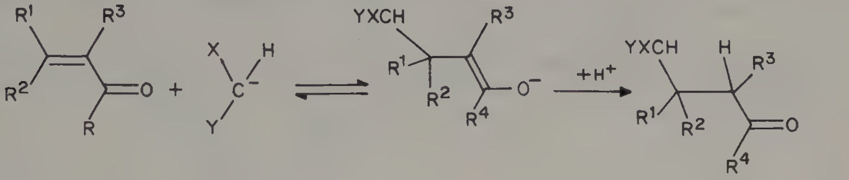
α,β-Dialkylation of enones is achieved by treating, for example, cyclopentenone with the lithium reagent **40**, followed by an alkyl halide RX. The product **41** can be oxidised to yield a β-alkyl γ-keto acid **42** (equation 29)[37].



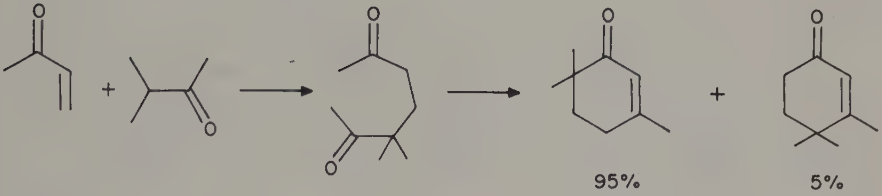
(29)

3. *With carbanions—Michael additions and Robinson annulation*

Carbanions derived from reactive methylene compounds H_2CXY, the 'donors', undergo reversible conjugate addition to enals and enones, the 'acceptors', to yield the products of a Michael reaction (equation 30). The reaction is of very wide scope: the donors may be esters of malonic, cyanoacetic, or a β-keto acid, acetic or arylacetic or higher acids, they may be anhydrides or ketones, nitriles, nitroalkanes, sulphones or acidic hydrocarbons, such as cyclopentadiene, indene or fluorene[38]. If the donor is a ketone, a 1,5-diketone is produced which frequently cyclises under the basic conditions of the reaction to yield a cyclohexenone, e.g. equation 31[19].



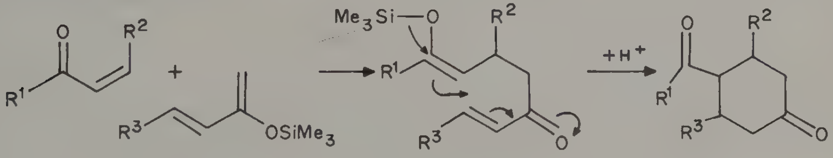
(30)



(31)

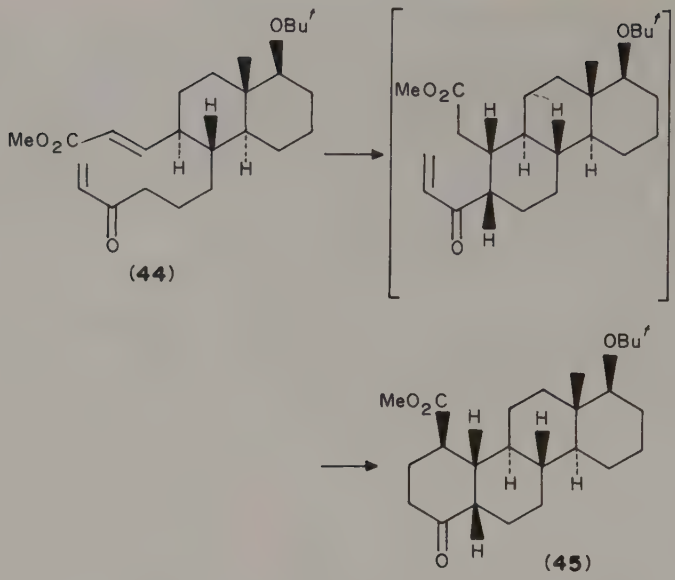
Triphenylmethyl perchlorate catalyses the addition of trimethylsilyloxybutadienes to enones; the products **43**, in which the trimethylsilyloxy group has been transferred, undergo an intramolecular Michael reaction to give 4-acylcyclohexanones in good yield (equation 32)[40]. A twofold Michael reaction of the complex enone **44** in equation 33 in the presence of trimethylsilyl chloride, triethylamine and zinc chloride affords *inter alia* the œstrane derivative **45**[41]. The dimerisation of methyl vinyl ketone in the presence of 1,4-diazabicyclo[2.2.2]octane involves a Michael addition of the betaine **8** (equation 34)[42].

Wittig reagents undergo conjugate addition to enones. This type of reaction is particularly fruitful if (triphenyl)propylidenephosphorane (**46**) is employed. Its Michael adduct **47** to 4-methyl-3-penten-2-one undergoes a proton shift, followed by an intramolecular Wittig reaction, to yield a cyclohexadiene (equation 35). Similarly, **46** reacts with cycloheptenone and cyclooctenone to yield, respectively, bicyclo[4.3.1]deca-6,8-diene (**48**) and bicyclo[5.3.1]undeca-7,9-diene (**49**). Cyclohexenone gives rise to the highly strained bridgehead olefin **50**, which was trapped as the Diels–Alder adduct with diphenylisobenzofuran[43].

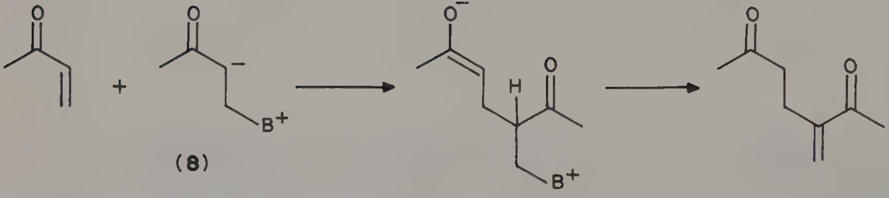


(43)

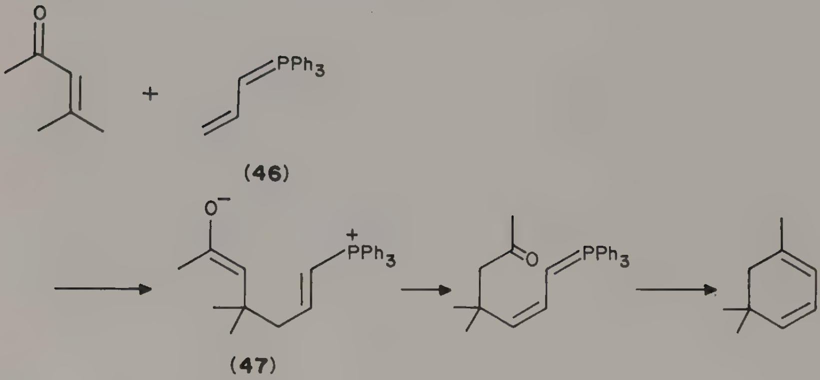
(32)



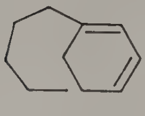
(33)



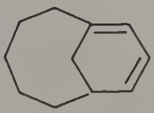
(34)



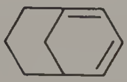
(35)



(48)

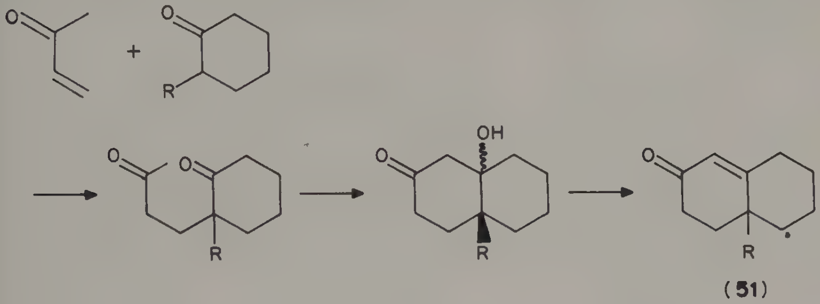


(49)

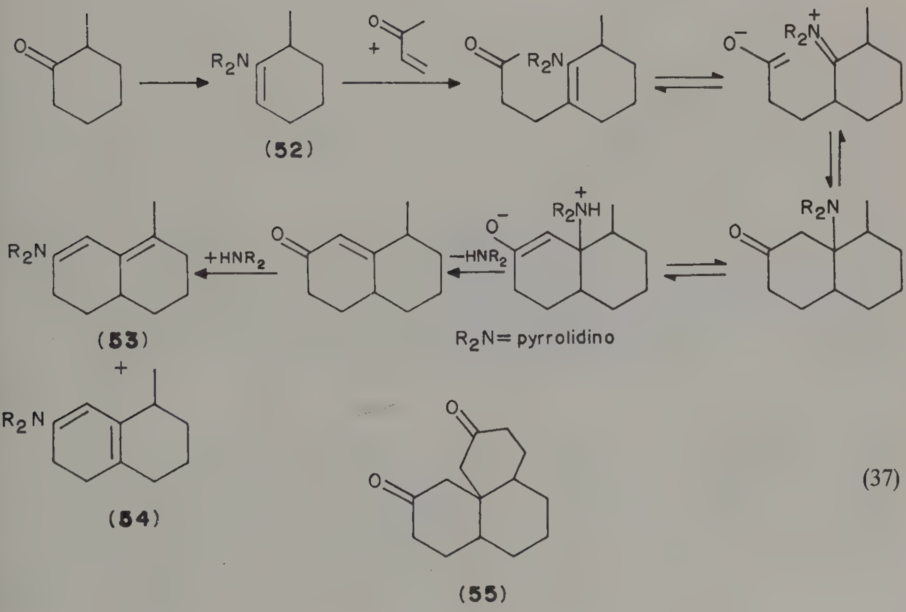


(50)

The formation and cyclisation of 1,5-diketones shown in equation **31** is the basis of the Robinson annulation[44]; that is, the construction of a ring onto an existing one[45]. A cyclic ketone is treated with a vinyl ketone under basic conditions (triethylamine, sodium methoxide or a basic ion exchange resin), as in the formation of the octalenones **51** from a 2-alkylcyclohexanone and methyl vinyl ketone (equation 36). It is possible to isolate all the intermediates in this sequence[46]. Since 2-alkylcyclohexanones react at the more substituted carbon atom, the products possess angular alkyl groups. Several modifications of the original procedure have been introduced. Since alkyl vinyl ketones $RCH_2COCH{=}CH_2$ tend to polymerise in the presence of bases, it is advantageous to replace them by the Mannich bases $RCH_2COCH_2CH_2NEt_2$ or the salts $RCH_2COCH_2CH_2\overset{+}{N}Et_2MeI^-$. A further improvement results from the use of enamines of cyclic ketones[47] as no catalyst is required for their reaction with vinyl ketones. 2-Alkylcyclohexanones form the enamines **52**, so that the Michael reaction takes place at the less substituted carbon atom of the ketone. Hence, in contrast to the previous reaction (equation 36), the enamines **53**, **54** of 8-alkyloctalenones are produced (equation 37)[48]. From the reaction of pyrrolidinocyclo-

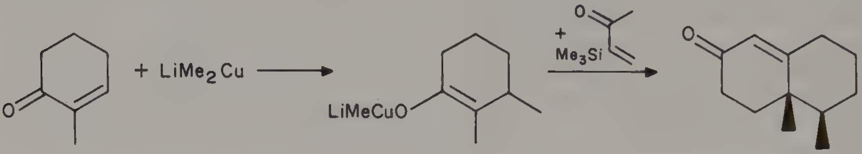


(36)

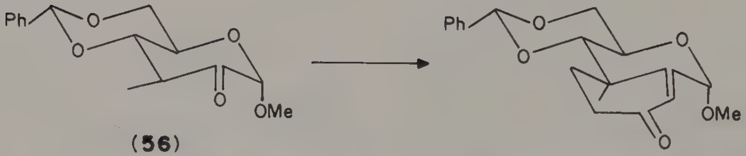


(37)

hexene with methyl vinyl ketone the 'bis-adduct' **55** was isolated, in addition to enamines analogous to **53** and **54**[49]. Annulation at the more substituted carbon atom of 2,3-dimethylcyclohexanone and 2,3-dimethylcyclopentanone is accomplished by the use of 3-trimethylsilyl-3-buten-2-one as Michael acceptor, as shown in equation 38[50]. Methyl vinyl ketone can be replaced by its complex with cyclopentadiene iron dicarbonyl in the reaction with the lithium enolate of cyclohexanone or its trimethylsilyl enol ether[51]. A carbohydrate derivative, compound **56**, has been subjected to the Robinson annulation with 3-trimethylsilyl-3-buten-2-one[52].

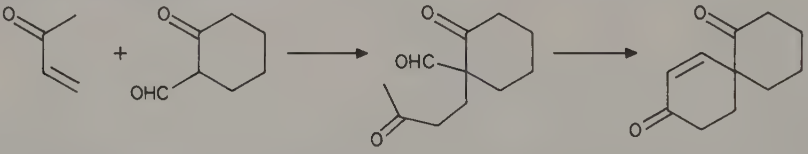


(38)



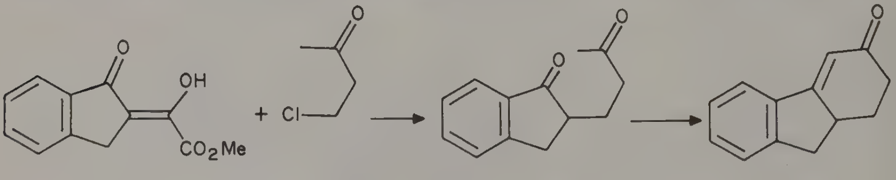
(56)

When 2-formylcycloalkanones are the donors in the Robinson reaction spiro-compounds result (equation 39)[53].



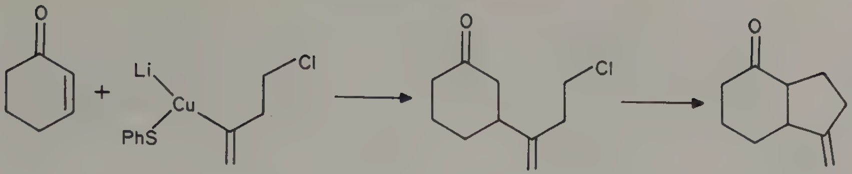
(39)

We conclude this section with some examples of annulation by alkylation of enones and one of a threefold conjugate addition. The hydroxymethylene ketone **57** reacts with 4-chlorobutan-2-one in the presence of sodium methoxide to give the diketone **58**, which cyclises to the tricyclic ketone **59** under basic or acidic catalysis (equation 40)[54]. 'Methylenecyclopentane annulation' is brought about by conjugate addition of the cuprate **60** to various cyclopentenones and cyclohexenones. The products, e.g. **61**, cyclise under the influence of potassium hydride (equation 41)[55]. A similar sequence, using the homologue of **60**, gives fused methylenecyclohexanes, e.g. a mixture of *E*- and *Z*-**63** from isophorone (**62**) (equation 42)[56]. The methylenecyclopentenone **64** adds phenylthiolate anion, followed by methyl acrylate, to yield the bicycloheptanone **65** (equation 43)[57].



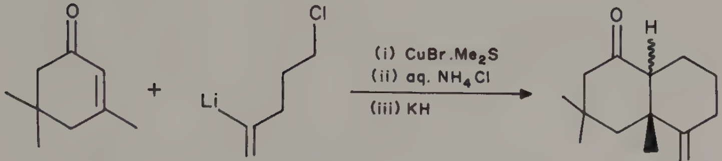
(57) **(58)** **(59)**

(40)



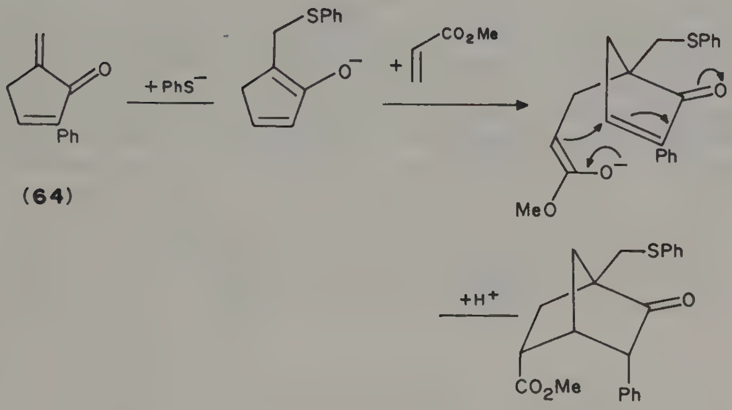
(60) (61)

(41)



(62) (63)

(42)



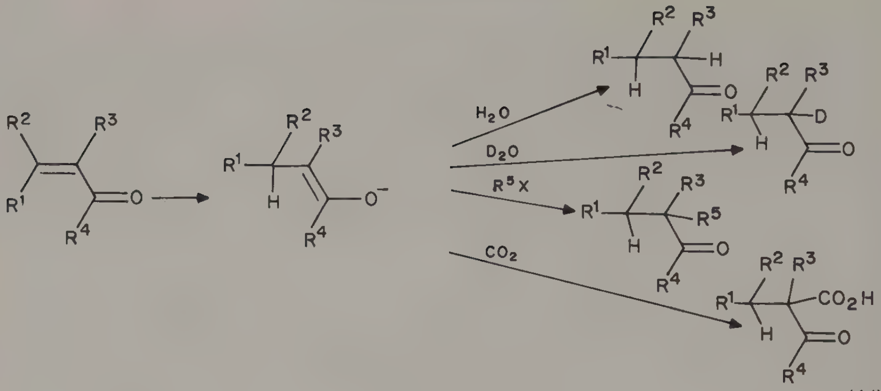
(64)

(65)

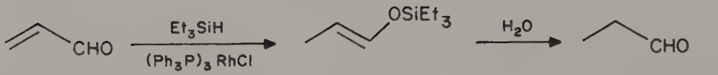
(43)

III. REDUCTION[58]

α,β-Unsaturated aldehydes and ketones are reduced cleanly to allyl alcohols by lithium aluminium hydride in ether or by sodium borohydride in aqueous ethanol[59]. Selective reduction of the carbonyl group also occurs by catalytic hydrogenation in the presence of *cis*-$[H_2Ir(PEt_2Ph)_4]^+$ under rather severe conditions[60]. On the other hand, the double bond is reduced by metals in liquid ammonia. The enolate ion formed initially can be trapped by water, deuterium oxide, reactive alkyl halides R^5X or carbon dioxide to give saturated ketones, α-deuteriated ketones, α-alkyl ketones, or β-keto acids, respectively (equation 44)[61]. Enones are also reduced to saturated ketones by lithium aluminium hydride in the presence of copper(I) iodide[62] or by the combination zinc dust–nickel(II) chloride in aqueous 2-methoxyethanol; the reaction is speeded up by ultrasonic irradiation[63]. Hydrosilylation of unsaturated aldehydes affords silyl ethers of saturated aldehydes, which are readily hydrolysed (equation 45)[64].

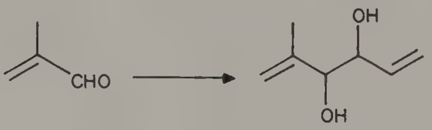


(44)

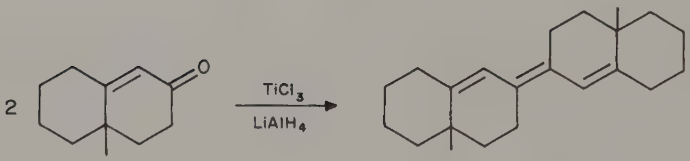


(45)

Electrochemical reduction of acrolein gives the coupled product $OHC(CH_2)_4CHO$[65]. Enals give pinacols as mixtures of *meso*- and (±)-isomers by the action of zinc and acetic acid (equation 46)[66]. The reductive coupling of carbonyl compounds in the presence of titanium(III) chloride to give olefins[67] was discovered for the case of the octalenone **66** (equation 47). An intramolecular variant of the reaction is shown in equation 48[68]. Chalcones yield mixtures of hydrodimers on electrolytic reduction (equation 49)[69]. δ,ε-Unsaturated ketones undergo reductive cyclisation on irradiation (equations 50 and 51)[70].

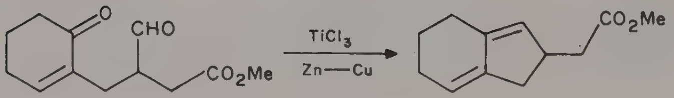


(46)

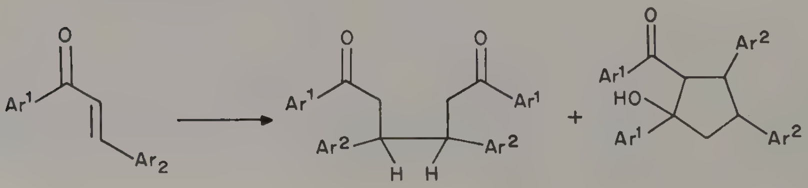


(47)

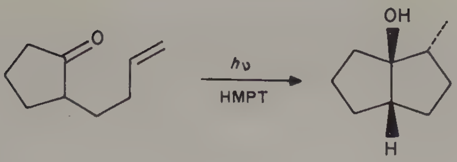
(66)



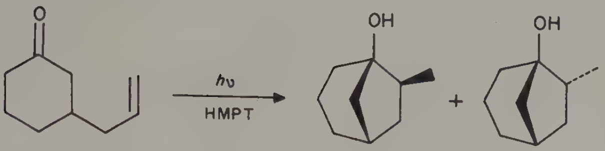
(48)



(49)



(50)

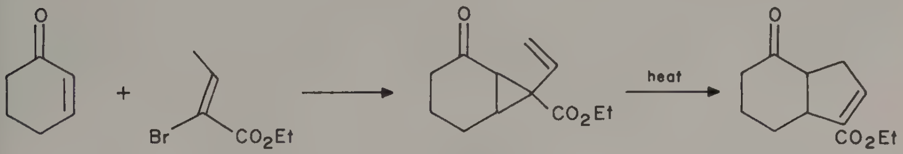


(51)

IV. CYCLOADDITION REACTIONS

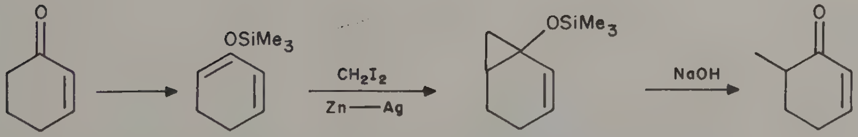
A. Formation of Three-membered Rings

Alkenals can be epoxidised with alkaline hydrogen peroxide[71]. Treatment of ethyl α-bromocrotonate with lithium diisopropylamide, followed by cyclohexenone, yields compound **67**, which undergoes the vinylcyclopropane → cyclopentene rearrangement (equation 52)[72]. The trimethylsilyl ether derived from cyclohexenone (see Section II.A) undergoes the Simmons–Smith reaction with a carbenoid reagent to yield the cyclopropane derivative **68**; hydrolysis gives 6-methylcyclohex-2-enone (equation 53)[73]. Methyl vinyl ketone similarly affords the vinylcyclopropane **69**, which undergoes hydrolytic ring-expansion to 2-methylcyclobutanone and thermal rearrangement to 1-trimethylsilyloxycyclopentene; the latter can be hydrolysed to cyclopentanone (equation 54). 1-Acetylcyclohexene similarly gives the spiro-compound **70** and the annulated ketone **71** (equation 55)[74]. Treatment of trimethylsilyloxydienes with an excess of the carbenoid reagent results in double cyclopropanation (equations 56–58)[75].



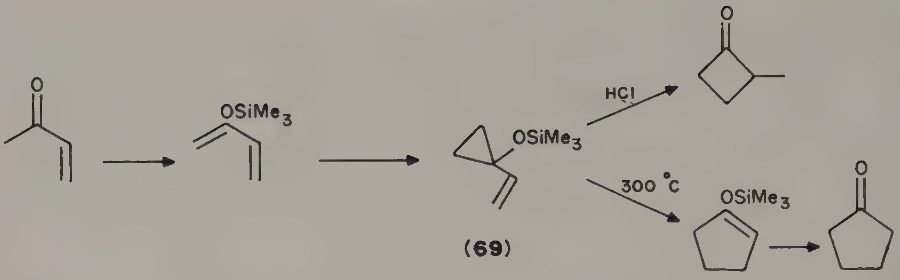
(67)

(52)

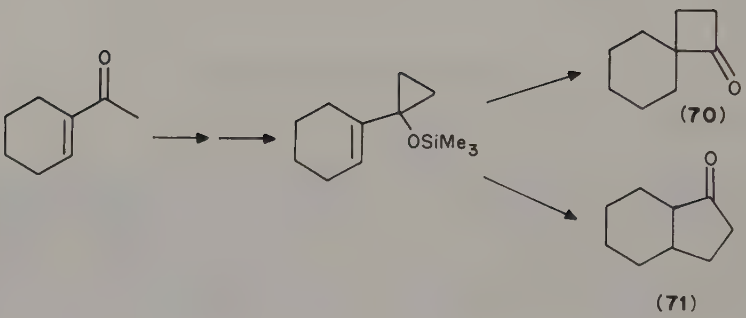


(68)

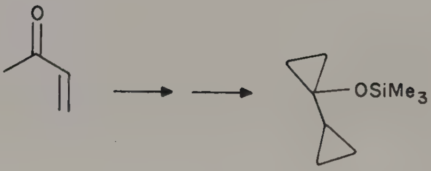
(53)



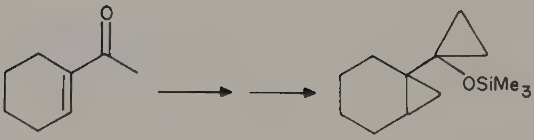
(54)



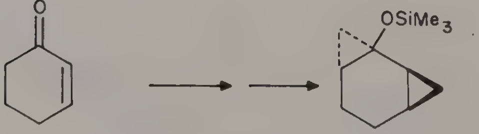
(55)



(56)



(57)

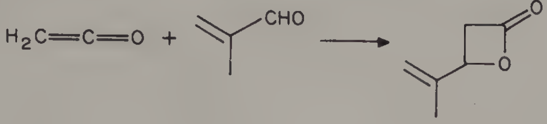


(58)

B. Formation of Four-membered Rings

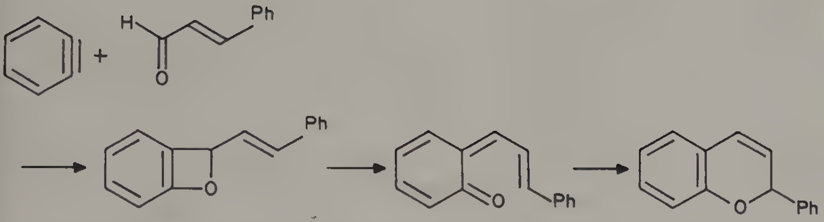
The boron trifluoride-catalysed reaction of ketene with methacrolein leads to the β-lactone **72** by addition to the carbonyl group of the aldehyde (equation 59)[76]; similarly, benzyne and cinnamaldehyde form the cyclic ether **73**, which rearranges to the benzopyran

74 by two consecutive electrocyclic reactions (equation 60)[77]. When a mixture of crotonaldehyde and 2-methyl-2-butene is irradiated two products are obtained, one of which arises from addition of the olefin to the carbonyl group of the aldehyde and the other from addition to the double bond (equation 61)[78].



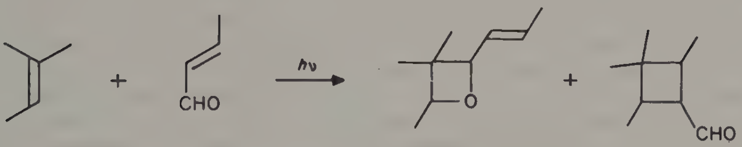
(59)

(72)



(60)

(73) **(74)**

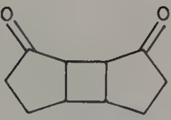


(61)

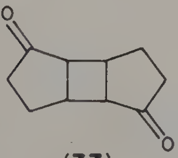
The photochemical addition of olefins to cyclic enones results in cyclobutanes[79]. Thus cyclopentene and cyclopentenone yield the adduct **75** (equation 62). Photodimerisation of cyclopentenone gives both the head-to-head (**76**) and head-to-tail dimer **77**; cyclohexenone and methyl vinyl ether, on the other hand, afford solely compound **78**. The regiochemistry of the cycloaddition reaction is still not well understood[80].

(62)

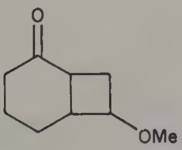
(75)



(76)

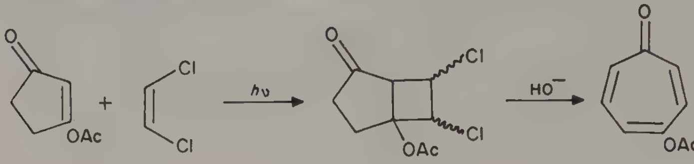


(77)

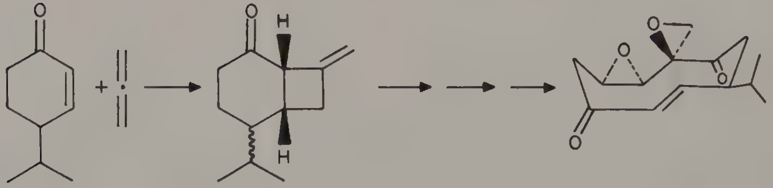


(78)

The photoaddition reaction has been applied to the synthesis of γ-tropolone acetate (equation 63)[81] and numerous complex natural products. For example, the photoadducts **79** of allene to 4-isopropyl-2-cyclohexen-1-one have been elaborated into the cockroach pheromone periplanone-B (**80**) (equation 64)[82].



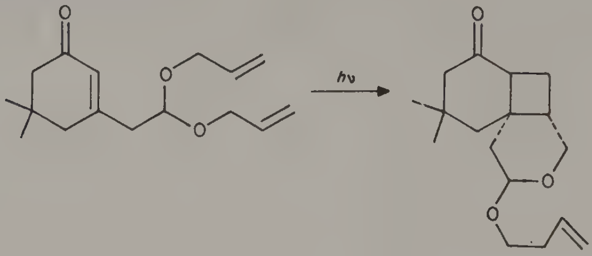
(63)



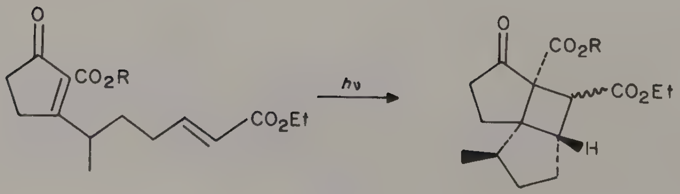
(**79**) (**80**)

(64)

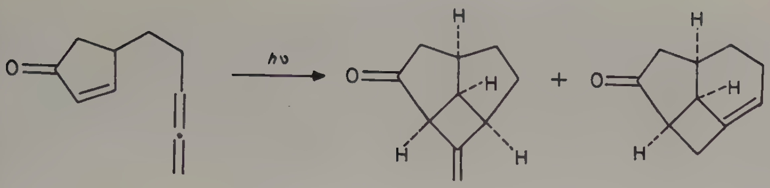
Intramolecular[2 + 2]cycloadditions of enones are exemplified by equation 65[83] and by the reaction depicted in equation 66 as a route to angularly substituted triquinanes[84]. The effect of ring size and chain length on the course of the intramolecular photocyclisation of various cycloalkenones containing terminal allene groups has been investigated; the results are summarised in equations 67–70[85]. Some quite complex bridged polycyclic molecules are readily obtained by intramolecular photocycloaddition, e.g. the tricyclic compound shown in equation 71[86] and the sterically congested fenestrane of equation 72[87]. Irradiation of the enol acetate **81** gives the fused cyclobutane **82**, which is converted into the cyclopentanooctane **83** by the action of potassium hydroxide (equation 73). The sequence amounts to a ring-expansion and the formation of a 1,5-diketone from a 1,3-diketone[88].



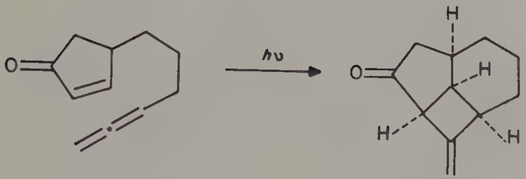
(65)



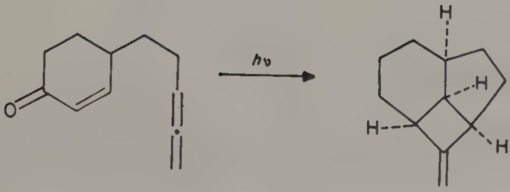
(66)



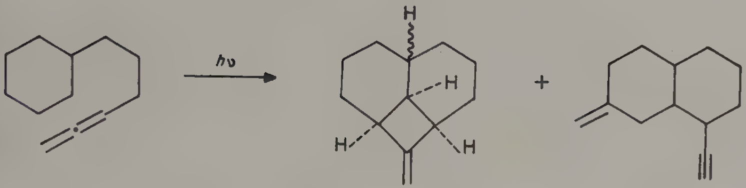
(67)



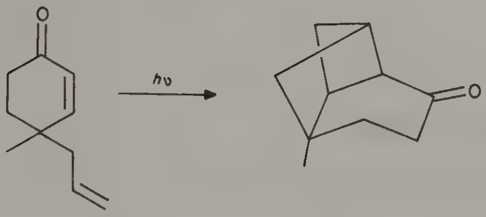
(68)



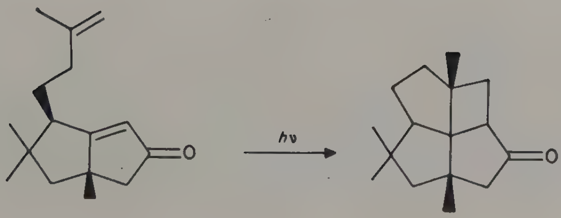
(69)



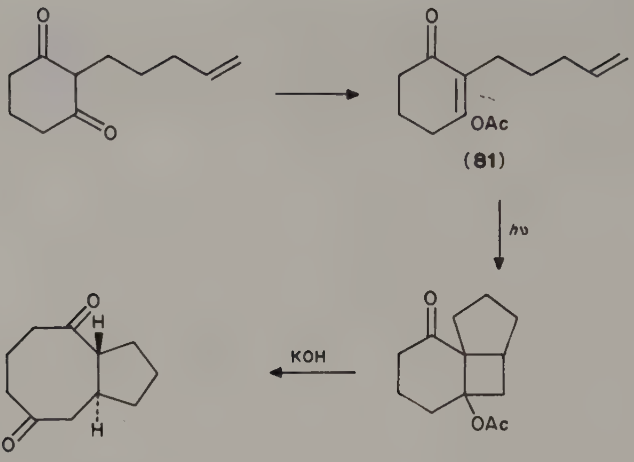
(70)



(71)



(72)



(81)

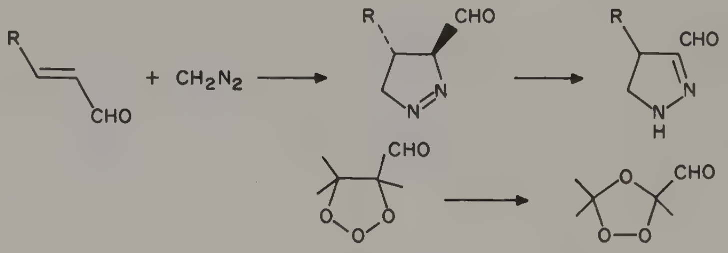
(82)

(83)

(73)

C. Formation of Five-membered Rings

Alkenals function as dipolarophiles in 1,3-dipolar cycloaddition reactions[89]. Addition of diazomethane yields pyrazolines (equation 74) and ozone reacts with 2,3-dimethyl-2-butenal to give initially a 1,2,3-trioxolan **84A** which rearranges to the ozonide **84B**.



(74)

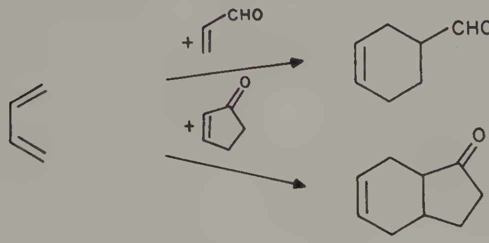
(84A) **(84B)**

D. Formation of Six-membered Rings

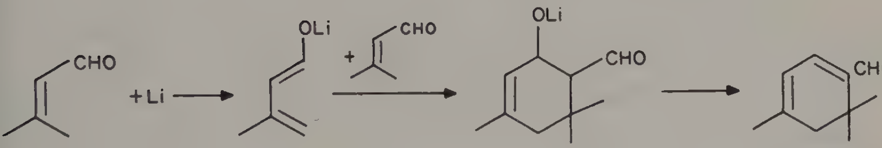
Enones and enals can function as dienophiles or as dienes in Diels–Alder reactions; these two modes are discussed separately.

1. *Reactions of enones as dienophiles*

Numerous Diels–Alder additions of dienes to enals and enones are known (equation 75)[90]. The formation of the cyclohexadiene aldehyde **85** when 3-methyl-2-butenal is treated with lithium has been formulated as a Diels–Alder reaction (equation 76)[91]. Whereas furan gives a mixture of Michael addition products, **86** and **87**, with acrolein[92], intramolecular Diels–Alder reactions of the γ'-furyl-enones **88** (R^1, $R^2 = H$ or Me) to yield the adducts **89** have been reported (equation 77)[93]. A synthesis of Δ^3-carene (**91**) is based on the formation of cyclopropanes from γ-stannyl tertiary alcohols by the action of thionyl chloride. The mixture of the Diels–Alder adducts of isoprene with the stannyl-enone **90** was treated with methyllithium, followed by thionyl chloride, to yield Δ^3-carene (equation 78)[94]. Derivatives of bicyclo[3.2.1]octane have been obtained from Diels–Alder adducts of 2-trimethylsilyloxybutadiene (see Section II.A) and alkenals or alkenones. The product **92** from acrolein, for example, was treated with the benzodithiole derivative **93** to yield compound **94**, which cyclised in the presence of trifluoroacetic acid; hydrolysis then afforded the bicyclic diketone **95** (equation 79)[95].

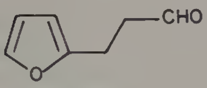


(75)

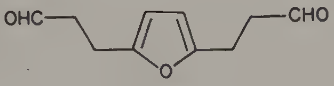


(85)

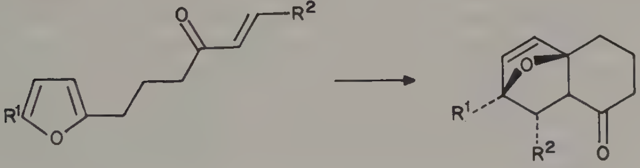
(76)



(86)

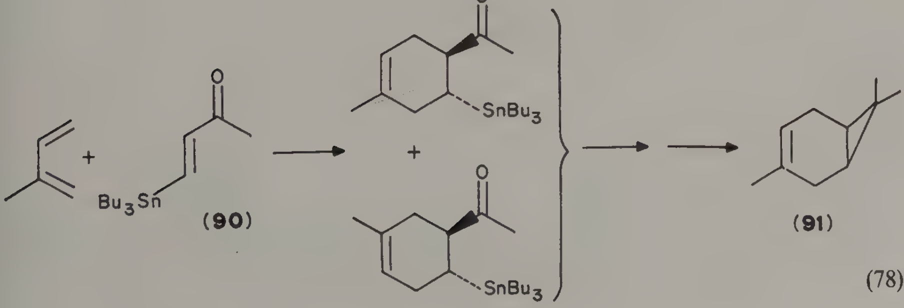


(87)



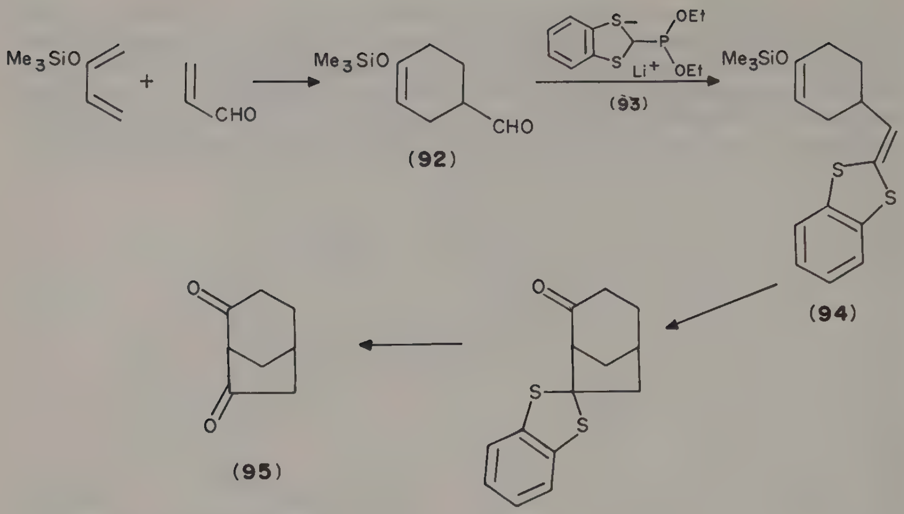
(88) **(89)**

(77)



(90) **(91)**

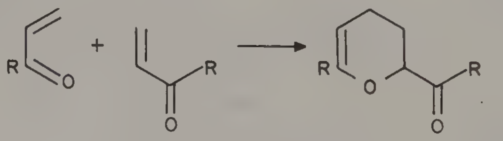
(78)



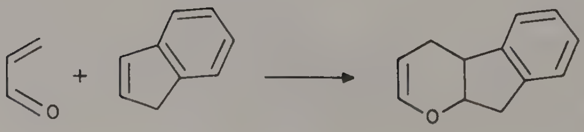
(79)

2. *Reactions of enones as dienes*[96]

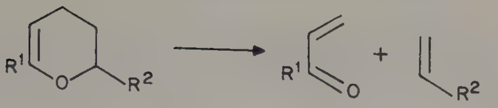
Enones and enals dimerise on heating to yield dihydropyrans, which are formed in a Diels–Alder reaction in which one molecule acts as a diene and the other as a dienophile (equation 80). Diels–Alder reactions of unsaturated aldehydes and ketones with numerous olefins have been described, e.g. the addition of indene to acrolein (equation 81)[97]. Retro-Diels–Alder reactions, the thermal decomposition of dihydropyrans to enones and olefins, have been observed (equation 82)[98]. Since enals and enones are electron-poor, the cycloaddition proceeds well with electron-rich olefins, such as vinyl ethers (equations 83[99] and 84[100]). Molybdenum acetylacetonate catalyses the Diels–Alder reaction of methacrolein with 1-benzyloxypropene; the addition is stereoselective, affording mainly the *cis*-adduct (equation 85)[101]. Enamines have frequently been employed as electron-rich dienophiles; see equations 86[102] and 87[103]. When ynamines, e.g. **96**, add to enones, mixtures of cycloadducts **97** and dienamides **99** are obtained; the latter are thought to be formed by way of oxetenes **98** (equation 88)[104]. The cycloadducts **97** are enamines and may add a second molecule of the enone to yield bis-adducts **100** (equation 89)[105].



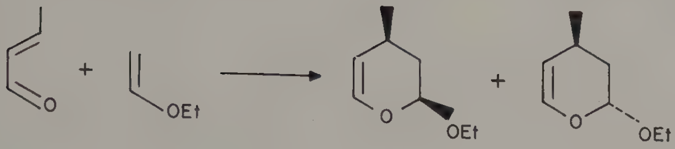
(80)



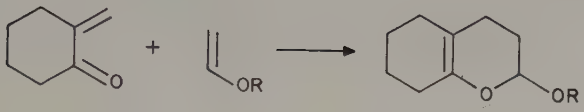
(81)



(82)

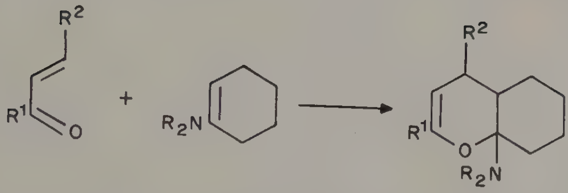


(83)

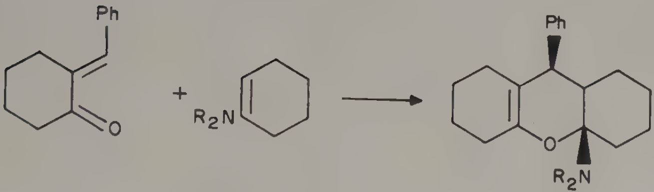


(84)

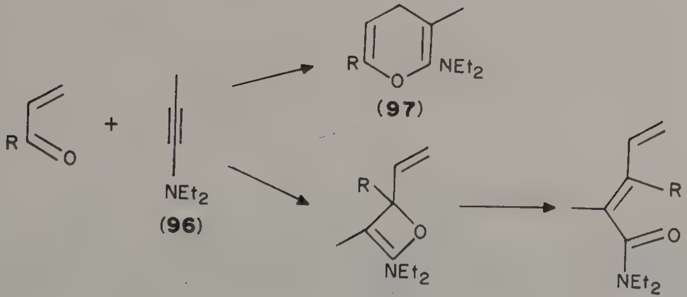
(85)



(86)

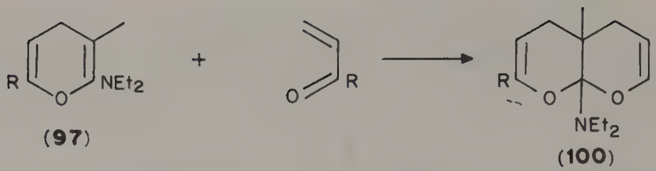


(87)



(96) (97) (98) (99)

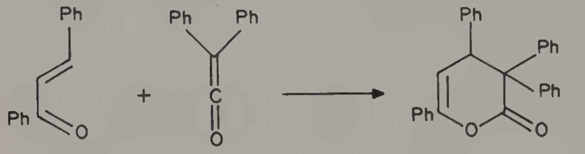
(88)



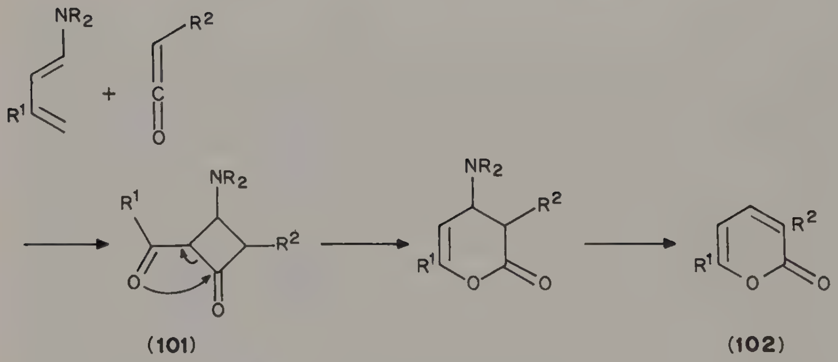
(97) **(100)**

(89)

The addition of ketenes to enones was discovered by Staudinger in 1913 (equation 90)[106]. Enaminoketones are particularly reactive towards ketenes[107]. The formation of the adducts is thought to proceed by way of the cyclobutanones **101**; the products often eliminate dialkylamine to produce α-pyrones **102** (equation 91). Sulphene, which contains a bond system similar to that of ketene, is generated by the action of triethylamine on methanesulphonyl chloride; in the presence of an enaminoketone the sulphene is trapped as a δ-sultone, (**103**, equation 92)[108].

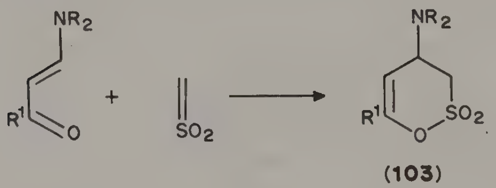


(90)



(101) **(102)**

(91)

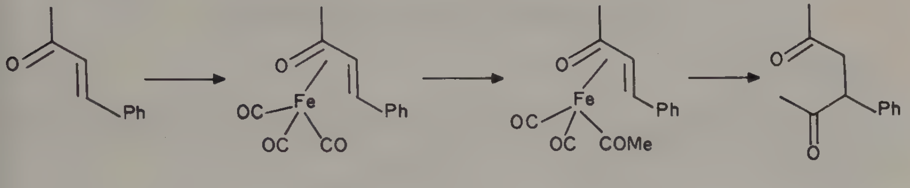


(103)

(92)

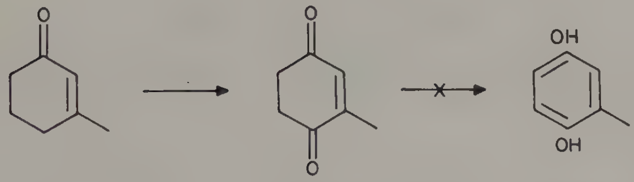
V. MISCELLANEOUS REACTIONS

α,β-Unsaturated ketones form iron tricarbonyl complexes, e.g. **104** from benzylideneacetone and diiron enneacarbonyl[109], which reacts with methylmagnesium bromide to yield the 1,4-diketone **106**, possibly via the intermediate **105** (equation 93)[110]. 3-Methylcyclohex-2-enone is oxidised by 2,3,5-triphenyltetrazolium chloride to the cyclohexenedione **107**, which has little tendency to tautomerise to the hydroquinone **108** (equation 94)[111]. A number of cyclic acetals has been obtained by treatment of ketones containing two isolated double bonds with phenylselenyl chloride in aqueous acetonitrile; some examples are shown in equations 95–97[112]. The cyclopropane derivative **109** was converted into the silyl ether **110**, which underwent a Cope rearrangement at 110 °C to yield the cycloheptadiene **111** (equation 98)[113].



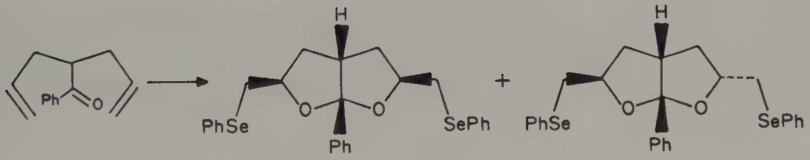
(104) (105) (106)

(93)

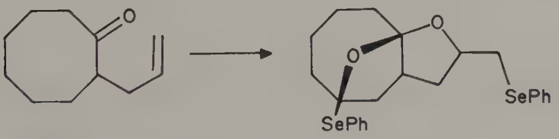


(107) (108)

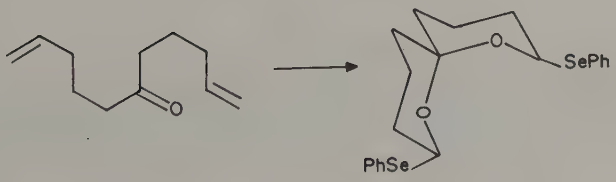
(94)



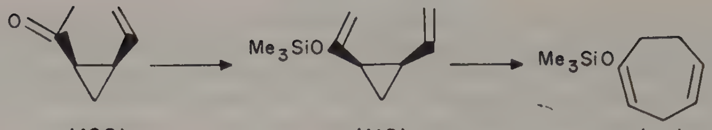
(95)



(96)



(97)

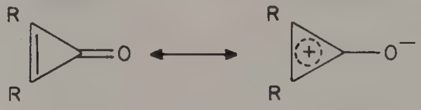


(109) (110) (111) (98)

VI. SYNTHESES WITH SMALL-RING ENONES

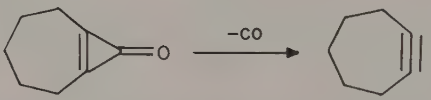
A. Cyclopropenones[114]

The chemistry of cyclopropenones **112** is dominated by their tendency to polarise to the aromatic cyclopropenylium oxide structure (**112A**) and by the propensity of the three-membered ring to open in reactions with nucleophiles.



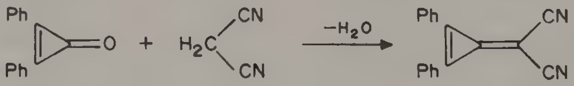
(112) (112A)

On pyrolysis, cyclopropenones form acetylenes by extrusion of carbon monoxide. Thus cycloheptenocyclopropenone gives rise to the highly strained cycloheptyne as a transient species (equation 99)[115].

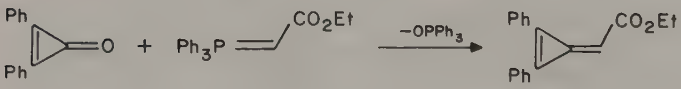


(99)

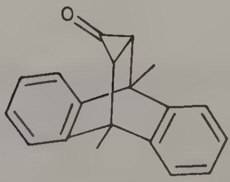
Only a few reactions of cyclopropenone are known in which the cyclopropene structure is preserved: diphenylcyclopropenone condenses with malononitrile under the influence of acetic anhydride to yield the methylenecyclopropene **113** (equation 100)[116] and its Wittig reaction with ethoxycarbonylmethylenetriphenylphosphorane affords compound **114** (equation 101)[117].



(113) (100)

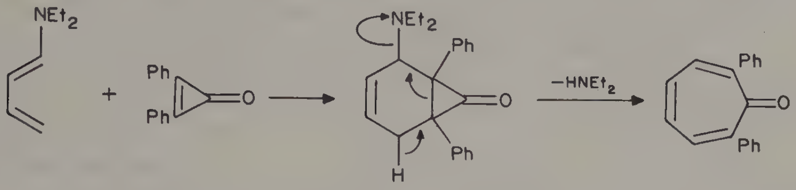


(114) (101)

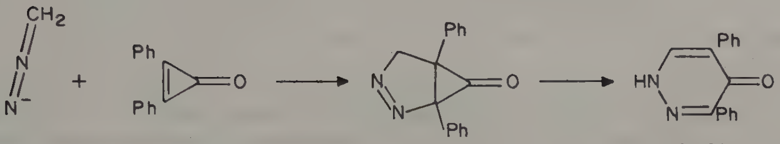


(115)

Cyclopropenone functions as a dienophile in the Diels–Alder reaction with 9,10-dimethylanthracene, giving the adduct **115**[118]; more typical is the reaction of diphenylcyclopropenone with 1-diethylamino-1,3-butadiene, in which the initial adduct suffers fission of the cyclopropane ring (equation 102)[119]. Similarly, 1,3-dipolar cycloaddition of diazomethane to diphenylcyclopropenone gives the pyridazinone **116** (equation 103)[120].



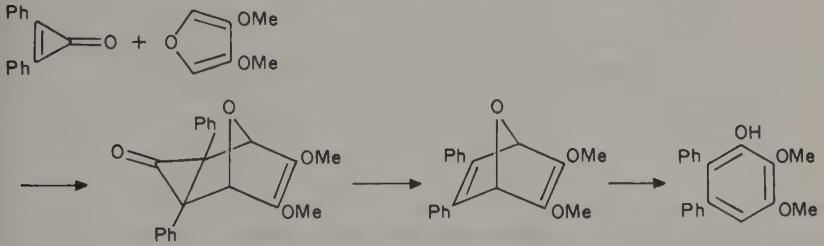
(102)



(116)

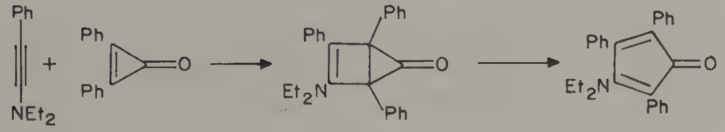
(103)

Diphenylcyclopropenone and 3,4-dimethoxyfuran afford the phenol **117** by loss of carbon monoxide from the initial Diels–Alder adduct (equation 104)[121]. The ynamine **118** adds diphenylcyclopropenone to yield a cyclopentadienone by rearrangement of the primary [2 + 2]adduct (equation 105)[122].



(117)

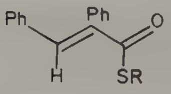
(104)



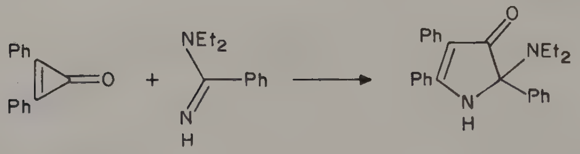
(118)

(105)

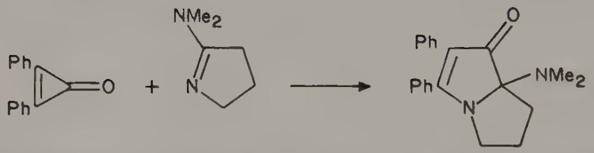
The action of nucleophilic reagents on diphenylcyclopropenone usually leads to products in which the unit —CPh=CPh—CO— has been inserted. Thus aliphatic and aromatic thiols RSH afford the thioesters **119**[123] and amidines yield pyrrolinones (equations 106[124] and 107[125]).



(119)

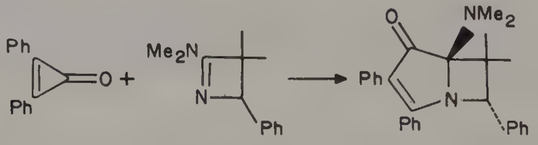


(106)



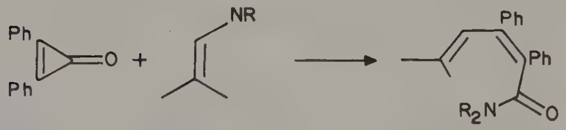
(107)

The azetine **120** adds diphenylcyclopropenone in an analogous manner (equation 108)[126]. Pyridine and diphenylcyclopropenone afford the 1-indolizinol (**121**)[127]. The literature on the reactions of cyclopropenones with enamines is contradictory; it appears that wrong structures have often been assigned to the products. It is probable that insertion products (cf. equation 109) are formed in most cases[128].



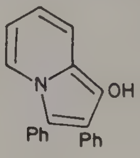
(120)

(108)

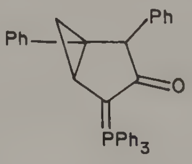


(109)

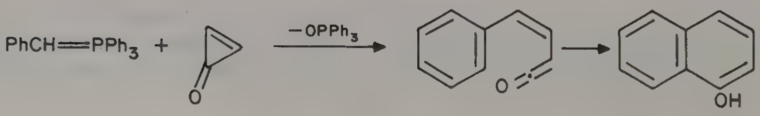
Cyclopropenone reacts with benzylidenetriphenylphosphorane to yield 1-naphthol (equation 110)[129]. The complex phosphorus derivative **122** results from the action of the Wittig reagent $H_2C{=}CHCH{=}PPh_3$ on diphenylcyclopropenone[130].



(121)

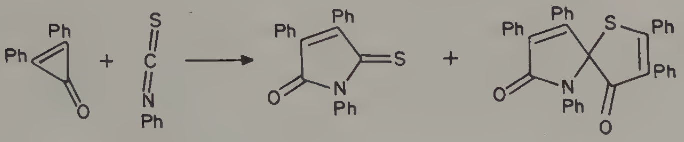


(122)



(110)

Diphenylcyclopropenone adds phenyl isothiocyanate in the presence of nickel tetracarbonyl to give a mixture containing the mono-adduct **123** and major amounts of the bis-adduct **124** (equation 111)[131].



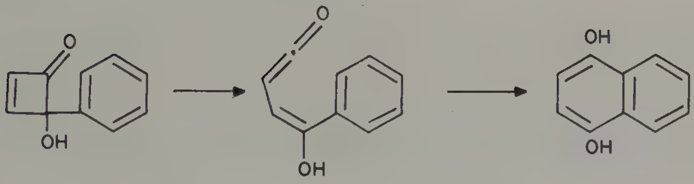
(111)

(123) **(124)**

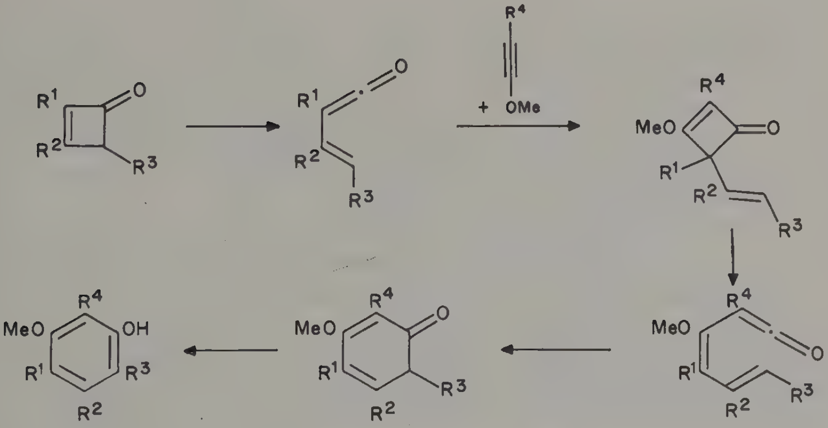
B. Cyclobutenones

Cyclobutenones are in equilibrium with vinyl ketenes (equation 112), which is the basis for their synthetic utility. Heating 4-hydroxy-4-phenyl-2-cyclobuten-1-one in xylene gives 1,4-dihydroxynaphthalene (equation 113)[132]. Cyclobutenones add electron-rich acetylenes, such as acetylenic ethers, to yield vinylcyclobutenones, which open to dienylketenes; electrocyclisation of the latter leads to phenols (equation 114)[133]. This reaction has been applied to the construction of the benzene ring of mycophenolic acid (**125**) (equation 115)[134]. Cyclobutenones react with 1,3-dienes to yield cyclooctadienones by a sequence of pericyclic reactions: ring-opening, [2 + 2]cycloaddition and Cope rearrangement (equation 116)[135].

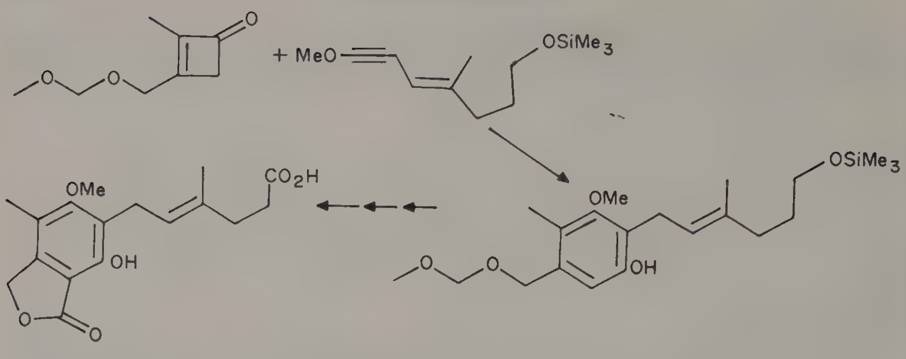
(112)



(113)

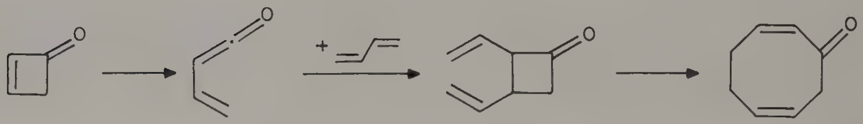


(114)



(125)

(115)



(116)

VII. REFERENCES

1. P. Brettle, in *Comprehensive Organic Chemistry*, Vol. 1 (Ed. J. F. Stoddart), Pergamon Press, Oxford, 1979, p. 943.
2. A. J. Waring, in *Comprehensive Organic Chemistry*, Vol. 1 (Ed. J. F. Stoddart), Pergamon Press, Oxford, 1979, p. 1017.
3. H. O. House, *Modern Synthetic Reactions*, 2nd edn., Benjamin, Menlo Park, 1972.
4. D. N. Kirk and M. P. Hartshorn, *Steroid Reaction Mechanism*, Elsevier, Amsterdam, 1968.
5. (a) O. Eisenstein, J. M. Lefour, C. Minot, N. T. Anh and G. Soussan, *Compt. rend.*, **274C**, 1310 (1972).
   (b) G. Stork and L. Maldonado, *J. Am. Chem. Soc.*, **96**, 5272 (1974).
6. Y. Nakadaira, J. Hayashi, H. Sato and K. Nakanishi, *J. Chem. Soc., Chem. Commun.*, 282 (1972).
7. D. Basavaiah and V. V. L. Gowriswari, *Tetrahedron Lett.*, **27**, 2031 (1986).
8. H. M. R. Hoffmann, U. Eggert and W. Poly, *Angew. Chem., Int. Ed. Engl.*, **26**, 1015 (1987).
9. P. G. Sammes and T. W. Wallace, *J. Chem. Soc., Perkin Trans. 1*, 1377 (1975).
10. D. W. Brown, M. M. Campbell, A. P. Taylor and X. Zhang, *Tetrahedron Lett.*, **28**, 985 (1987).
11. M. E. Jung and C. A. McCombs, *Tetrahedron Lett.*, 2935 (1976).
12. Review: S. Danishefsky, *Acc. Chem. Res.*, **14**, 400 (1981).
13. G. M. Rubottom and S. S. Krueger, *Tetrahedron Lett.*, 611 (1977).
14. M. E. Jung, C. A. McCombs, Y. Takeda and Y. G. Pan, *J. Am. Chem. Soc.*, **103**, 6677 (1981).
15. F. Richter and H. H. Otto, *Tetrahedron Lett.*, **28**, 2945 (1987).
16. A. P. Kozikowski and S. H. Jung, *J. Org. Chem.*, **51**, 3400 (1986).
17. M. Suzuki, T. Kawagishi and R. Noyori, *Tetrahedron Lett.*, **22**, 1809 (1981).
18. S. I. Hashimoto, S. I. Yamada and K. Koga, *J. Am. Chem. Soc.*, **98**, 7450 (1976).
19. Review: P. W. Hickmott, *Tetrahedron*, **40**, 2989 (1984).
20. E. J. Corey, N. W. Gilman and B. E. Ganem, *J. Am. Chem. Soc.*, **90**, 5616 (1968).
21. Reviews: (a) E. A. Braude, *Prog. Org. Chem.*, **3**, 172 (1955).
   (b) K. Nützel, in *Houben-Weyl Methoden der Organischen Chemie*, Vol. 13/2a (Ed. E. Müller) Thieme, Stuttgart, 1973, p. 401.

22. M. Sworin and W. L. Neumann, *Tetrahedron Lett.*, **28**, 3217 (1987).
23. (a) W. C. Still and T. L. Macdonald, *J. Am. Chem. Soc.*, **96**, 5561 (1974).
    (b) D. A. Evans, G. C. Andrews and B. Buckwalter, *J. Am. Chem. Soc.*, **96**, 5560 (1974).
24. A. Krief and J. L. Laboureur, *J. Chem. Soc., Chem. Commun.*, 702 (1986).
25. K. Konno, K. Hashimoto, H. Shirahama and T. Matsumoto, *Tetrahedron Lett.*, **27**, 3865 (1986).
26. (a) G. Majetich, A. Casares, D. Chapman and M. Behnke, *J. Org. Chem.*, **51**, 1745 (1986).
    (b) G. Majetich, R. W. Desmond and J. J. Soria, *J. Org. Chem.*, **51**, 1753 (1986).
27. J. S. Panek and M. A. Sparks, *Tetrahedron Lett.*, **28**, 4649 (1987).
28. A. Hosomi and H. Sakurai, *J. Am. Chem. Soc.*, **99**, 1673 (1977).
29. R. D. Miller and D. R. McKean, *Tetrahedron Lett.*, 2305 (1979).
30. T. Shono, S. Kashimura, Y. Yamaguchi and F. Kuwata, *Tetrahedron Lett.*, **28**, 4411 (1987).
31. (a) H. C. Brown, *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, 1972.
    (b) J. A. Sinclair, G. A. Molander and H. C. Brown, *J. Am. Chem. Soc.*, **99**, 954 (1977).
32. Reviews: (a) D. Seebach and K. H. Geisse, in *New Applications of Organometallic Reagents in Organic Synthesis* (Ed. D. Seyferth), Elsevier, Amsterdam, 1976, p. 1.
    (b) J. F. Normant, in *New Applications of Organometallic Reagents in Organic Synthesis* (Ed. D. Seyferth), Elsevier, Amsterdam, 1976, p. 219.
    (c) G. H. Posner, *Org. React.*, **19**, 1 (1972).
33. (a) E. J. Corey and R. H. K. Chen, *Tetrahedron Lett.*, 3817 (1973).
    (b) I. Shahak and Y. Sasson, *Tetrahedron Lett.*, 4207 (1973).
34. S. H. Bertz, C. P. Gibson and G. Dabbagh, *Tetrahedron Lett.*, **28**, 4251 (1987).
35. Y. Horiguchi, S. Matsuzawa, E. Nakamura and I. Kuwajima, *Tetrahedron Lett.*, **27**, 4025, 4029 (1986).
36. R. J. Linderman, A. Godfrey and K. Horne, *Tetrahedron Lett.*, **28**, 3911 (1987).
37. J. Otera, Y. Niibo and H. Aikawa, *Tetrahedron Lett.*, **28**, 2147 (1987).
38. Review: E. D. Bergmann, D. Ginsburg and R. Pappo, *Org. React.*, **10**, 179 (1959).
39. H. A. Smith, B. J. L. Huff, W. J. Powers and D. Caine, *J. Org. Chem.*, **32**, 2851 (1967).
40. T. Mukaiyama, Y. Sagawa and S. Kobayashi, *Chem. Lett.*, 1821 (1986).
41. M. Ihara, T. Takahashi, N. Shimizu, Y. Ishida, I. Sudow, F. Fukumoto and T. Kametani, *J. Chem. Soc., Chem. Commun.*, 1467 (1987).
42. D. Basavaiah, V. V. L. Gowriswari and T. K. Bharathi, *Tetrahedron Lett.*, **28**, 4591 (1987).
43. Review: K. B. Becker, *Tetrahedron*, **36**, 1717 (1980).
44. W. S. Rapson and R. Robinson, *J. Chem. Soc.*, 1285 (1935).
45. Review: M. E. Jung, *Tetrahedron*, **32**, 3 (1976).
46. J. A. Marshall and W. I. Fanta, *J. Org. Chem.*, **29**, 2501 (1964).
47. (a) A. G. Cook, *Enamines, Synthesis, Structure and Reactions*, Dekker, New York, 1969.
    (b) S. F. Dyke, *Chemistry of Enamines*, Cambridge University Press, Cambridge, 1973.
    (c) P. W. Hickmott, *Tetrahedron*, **38**, 1975, 3363 (1982).
    (d) J. E. Telschow and W. Reusch, *J. Org. Chem.*, **40**, 862 (1975).
48. G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).
49. H. O. House, B. M. Trost, R. W. Magin, R. G. Carlson, R. W. Franck and G. H. Rasmusson, *J. Org. Chem.*, **30**, 2513 (1965).
50. R. K. Boeckman, Jr., D. M. Blum and B. Ganem, *Org. Synth.*, **58**, 158 (1978).
51. A. Rosan and M. Rosenblum, *J. Org. Chem.*, **40**, 3621 (1975).
52. R. V. Bonnert and P. R. Jenkins, *J. Chem. Soc., Chem. Commun.*, 6 (1987).
53. V. Dave and J. S. Whitehurst, *J. Chem. Soc., Perkin Trans. 1*, 393 (1973).
54. E. Brown, M. Ragault and J. Touet, *Tetrahedron Lett.*, 1043 (1971).
55. E. Piers and V. Karunaratne, *J. Chem. Soc., Chem. Commun.*, 935 (1983).
56. E. Piers and B. W. A. Yeung, *J. Org. Chem.*, **49**, 4569 (1984).
57. C. Thanupran, C. Thebtaranonth and Y. Thebtaranonth, *Tetrahedron Lett.*, **27**, 2295 (1986).
58. Ref. 2, pp. 1077, 1078.
59. (a) M. R. Johnson and B. Rickborn, *J. Org. Chem.*, **35**, 1041 (1970).
    (b) I. Ghilezan, E. R. H. Jones, G. D. Meakins and J. O. Miners, *J. Chem. Soc., Perkin Trans. 1*, 1350 (1976).
60. E. Farnetti, M. Pesce, S. Kašpar, R. Spogliarich and M. Graziani, *J. Chem. Soc., Chem. Commun.*, 746 (1986).
61. Review: D. Caine, *Org. React.*, **23**, 1 (1976).

62. E. C. Ashby, J. J. Lin, and R. Kovar, *J. Org. Chem.*, **41**, 1939 (1976).
63. C. Petrier and J. L. Luche, *Tetrahedron Lett.*, **28**, 2347 (1987).
64. I. Ojima and T. Kogure, *Tetrahedron Lett.*, 5035 (1972).
65. J. Wiemann, M. Dedieu and D. Delandais, Fr. Pat. 1 591 372 (1968); *Chem. Abstr.*, **74**, 70 990 (1971).
66. J. Wiemann and Le Thi-Thuan, *Bull. Soc. Chim. Fr.*, 95 (1955).
67. Review: J. E. McMurry, *Acc. Chem. Res.*, **16**, 405 (1983).
68. U. Berlage, J. Schmidt, U. Peters and P. Welzel, *Tetrahedron Lett.*, **28**, 3091 (1987).
69. J. Berthelot, C. Guette, F. Fournier and D. Davoust, *Tetrahedron Lett.*, **28**, 1881 (1987).
70. D. Belotti, J. Cossy, J. P. Pete and C. Portella, *J. Org. Chem.*, **51**, 4196 (1986).
71. G. B. Payne, *J. Org. Chem.*, **26**, 250 (1961).
72. T. Hudlicky, L. Radesca, H. Luna and F. E. Anderson III, *J. Org. Chem.*, **51**, 4746 (1986).
73. C. Girard and J. M. Conia, *Tetrahedron Lett.*, 3327 (1974).
74. C. Girard, P. Amice, J. P. Barnier and J. M. Conia, *Tetrahedron Lett.*, 3329 (1974).
75. C. Girard and J. M. Conia, *Tetrahedron Lett.*, 3333 (1974).
76. Review: H. E. Zaugg, *Org. React.*, **8**, 305 (1954).
77. H. Heaney, J. M. Jablonski and C. T. Mc Carty, *J. Chem. Soc., Perkin Trans. 1*, 2903 (1972).
78. Review: D. R. Arnold, *Adv. Photochem.*, **6**, 301 (1968).
79. (a) P. E. Eaton, *J. Am. Chem. Soc.*, **84**, 2454 (1962).
    (b) Review: P. E. Eaton, *Acc. Chem. Res.*, **1**, 50 (1968).
80. Review: P. de Mayo, *Acc. Chem. Res.*, **4**, 41 (1971).
81. B. D. Challand, H. Hikino, G. Kornis, G. Lange and P. de Mayo, *J. Org. Chem.*, **34**, 794 (1969).
82. S. L. Schreiber and C. Santini, *J. Am. Chem. Soc.*, **106**, 4038 (1984).
83. M. C. Pirrung and S. A. Thomson, *Tetrahedron Lett.*, **27**, 2703 (1986).
84. M. T. Crimmins and J. A. DeLoach, *J. Amer. Chem. Soc.*, **108**, 800 (1986).
85. W. G. Dauben, G. Shapiro and L. Luders, *Tetrahedron Lett.*, **26**, 1429 (1985).
86. I. D. Cunningham and T. B. H. Mc Murry, *J. Chem. Res., Synop.*, 222 (1984).
87. M. T. Crimmins, S. W. Mascarella and L. D. Bredon, *Tetrahedron Lett.*, **26**, 997 (1985).
88. Review: W. Oppolzer, *Acc. Chem. Res.*, **15**, 135 (1982).
89. Reviews: (a) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 565, 633 (1963).
    (b) *1,3-Dipolar Cycloaddition Chemistry* (Ed. A. Padwa), Wiley–Interscience, New York, 1984.
90. Reviews: (a) H. L. Holmes, *Org. React.*, **4**, 60 (1948).
    (b) L. W. Butz and A. W. Rytina, *Org. React.*, **5**, 137 (1949).
    (c) H. Wollweber, *Diels–Alder-Reaktion*, G. Thieme, Stuttgart, 1972.
91. E. A. Braude, B. F. Gofton, G. Lowe and E. S. Waight, *J. Chem. Soc.*, 4054 (1956).
92. I. Webb and G. Borcherdt, *J. Am. Chem. Soc.*, **73**, 752 (1951).
93. B. A. Keay, *J. Chem. Soc., Chem. Commun.*, 419 (1987).
94. C. R. Johnson and J. F. Kadow, *J. Org. Chem.*, **52**, 1493 (1987).
95. J. H. Rigby and A. S. Kotnis, *Tetrahedron Lett.*, **28**, 4943 (1987).
96. Review: G. Desimoni and G. Tacconi, *Chem. Rev.*, **75**, 651 (1975).
97. G. Descotes and A. Jullien, *Tetrahedron Lett.*, 3395 (1969).
98. H. M. Frey, R. G. Hopkins and N. S. Isaacs, *J. Chem. Soc., Perkin Trans. 2*, 2082 (1972).
99. J. Castells, F. Camps and F. Sanchez Ferrando, *An. Real. Soc. Esp. Fis. Quim., Ser. B*, **66**, 175 (1970).
100. H. Mühlstädt and G. Müller, *Tetrahedron Lett.*, 1811 (1968).
101. Y. Yamamoto, H. Suzuki and Y. Moro-Oka, *Chem. Lett.*, 73 (1986).
102. (a) G. Opitz and H. Holtmann, *Annalen*, **684**, 79 (1965).
    (b) I. Fleming and M. H. Karger, *J. Chem. Soc.* (*C*), 226 (1967).
    (c) F. P. Colonna, S. Fatutta, A. Risaliti and C. Russo, *J. Chem. Soc.* (*C*), 2377 (1970).
    (d) J. W. Lewis, P. L. Myers, J. A. Ormerod and I. A. Selby, *J. Chem. Soc., Perkin Trans. 1*, 1549 (1972).
103. J. W. Lewis, P. L. Myers and M. J. Redhead, *J. Chem. Soc.* (*C*), 771 (1970).
104. J. Ficini and A. Krief, *Tetrahedron Lett.*, 1427 (1969).
105. J. Ficini, J. Bisseyre, J. D'Angelo and C. Barbara, *C.R. Acad. Sci., Ser. C*, **271**, 468 (1970).
106. H. Staudinger and P. Endle, *Annalen*, **401**, 263 (1913).
107. (a) J. C. Martin, K. R. Barton, P. G. Gott and R. H. Meen, *J. Org. Chem.*, **31**, 943 (1966).
    (b) G. Bignardi, F. Evangelisti, P. Schenone and A. Bargagna, *J. Heterocycl. Chem.*, **9**, 1071 (1972).

108. G. Opitz and E. Tempel, *Annalen*, **699**, 68 (1966).
109. A. N. Nesmeyanov, L. V. Rybin, N. T. Gubenko, M. I. Rybinskaya and P. V. Petrovskii, *J. Organomet. Chem.*, **71**, 271 (1974).
110. S. E. Thomas, *J. Chem. Soc., Chem. Commun.*, 226 (1987).
111. J. Jasiczak, *Tetrahedron Lett.*, **28**, 4323 (1987).
112. G. Mehta, H. S. P. Rao and K. R. Reddy, *J. Chem. Soc., Chem. Commun.*, 78 (1987).
113. E. Piers, M. S. Burmeister and H. V. Reissig, *Can. J. Chem.*, **64**, 180 (1986).
114. Reviews: (a) K. T. Potts and J. S. Baum, *Chem. Rev.*, **74**, 189 (1974).
    (b) T. Eicher and J. L. Weber, *Top. Curr. Chem.*, **57**, 1 (1975).
    (c) *The Chemistry of the Cyclopropyl Group* (Ed. Z. Rappoport), Wiley, Chichester, 1987, pp. 1241–1245, 1300–1312, 1543–1559.
115. R. Breslow, J. Posner and A. Krebs, *J. Am. Chem. Soc.*, **85**, 234 (1963).
116. E. D. Bergmann and I. Agranat, *J. Am. Chem. Soc.*, **86**, 3587 (1964).
117. M. H. Battiste, *J. Am. Chem. Soc.*, **86**, 942 (1964).
118. R. Breslow and M. Oda, *J. Am. Chem. Soc.*, **94**, 4787 (1972).
119. C. Cicibattoni and G. A. Berchtold, *J. Am. Chem. Soc.*, **87**, 1404 (1965).
120. R. Breslow, T. Eicher, A. Krebs, R. A. Peterson and J. Posner, *J. Am. Chem. Soc.*, **87**, 1320 (1965).
121. K. Matsumoto, Y. Ikemi, S. Hashimoto, H. S. Lee and Y. Okamoto, *J. Org. Chem.*, **51**, 3729 (1986).
122. M. Franck-Neumann, *Tetrahedron Lett.*, 341 (1966).
123. H. Yoshida and T. Ogata, *Nippon Kogaku Kaishi*, 534 (1982); *Chem. Abstr.*, **97**, 6 263 (1982).
124. T. Eicher, F. Abdesaken, G. Franke and J. L. Weber, *Tetrahedron Lett.*, 3915 (1975).
125. T. Eicher and R. Rohde, *Synthesis*, 619 (1985).
126. F. Stierli, R. Prewo, J. H. Bieri and H. Heimgartner, *Helv. Chim. Acta*, **66**, 1366 (1983).
127. D. H. Wadsworth, S. L. Bender, D. L. Smith and H. R. Luss, *Tetrahedron Lett.*, **22**, 3569 (1981).
128. V. Bilinski and A. S. Dreiding, *Helv. Chim. Acta*, **55**, 1271 (1972).
129. R. Breslow, M. Oda and J. Pecoraro, *Tetrahedron Lett.*, 4415 (1972).
130. J. Ipaktschi and A. Saasatmandi, *Justus Liebigs Annalen Chem.*, 1989 (1984).
131. Y. Oshiro, H. Nanimoto, H. Tanaka, M. Komatsu, T. Agawa, N. Yasuoka, Y. Kai and N. Kasai, *Tetrahedron Lett.*, **26**, 3015 (1985).
132. S. T. Perri and H. W. Moore, *Tetrahedron Lett.*, **28**, 4507 (1987).
133. R. L. Dannheiser, S. K. Gee and J. J. Perez, *J. Org. Chem.*, **49**, 1672 (1984).
134. R. L. Dannheiser, S. K. Gee and J. J. Perez, *J. Am. Chem. Soc.*, **108**, 806 (1986).
135. R. L. Dannheiser, S. K. Gee and H. Sard, *J. Am. Chem. Soc.*, **104**, 7670 (1982).

The Chemistry of Enones
Edited by S. Patai and Z. Rappoport

CHAPTER 9

Acid–base behaviour of enones

ROMUALD I. ZALEWSKI
Department of General Chemistry, Academy of Economy, Poznań, Poland

---

I. INTRODUCTION

Most organic compounds are weak bases and/or weak acids. Among the many chemical reactions and equilibria, that of proton transfer continues to attract a great deal of attention. The main reasons for this interest are the following:

(i) The unique role of the proton in chemistry and in acid-base catalysis.

(ii) The wide occurrence and relative simplicity of these reactions.

(iii) The existence of three isotopes (^1H, ^2D and ^3T) with relatively large mass differences provides good objects for studying kinetic hydrogen isotope effects.

(iv) The relationships existing between kinetic and/or equilibrium data for families of similar compounds.

(v) The relationships between reactivity and structure of reacting species.

(vi) The effect of solvents (H_2O, D_2O and others, as well as mixtures) on proton-transfer reactions.

The rates of proton-transfer reactions allow the somewhat arbitrary classification of these reactions as fast, slow and very slow. The reactions which will occupy our attention belong to slow reactions, for which appropriate equilibrium constants can be defined.

The definition of weak bases or weak acids used throughout this chapter is that of Brønsted[1]; thus a weak organic acid is a compound which liberates a proton from a given molecule. The anion formed may be a carboxylate, $RCOO^-$, an alcoholate RO^- or an enolate $R—C{=}C—O^-$. If a C—H bond in an organic molecule dissociates, a carbanion $R^1R^2R^3C^-$ is the product.

Any compound that contains a carbon–hydrogen bond is a potential acid. For aqueous media we can compare relative acid strengths by examination of equilibrium constants in a given dissociation (equations 1 and 2). If reaction 1 proceeds almost to completion, we can say that the acid is much stronger than water (solvent). The larger the value of pK_a ($= -\log K_a$), the weaker the acid. The equilibrium lies far to the left for many varieties of organic compounds and their weak acidic properties cannot be observed and detected in water. A number of acidic compounds ionize in dilute alkaline media so effectively that the concentration of anion $[A^-]$ can be measured, and pK_a can be calculated. The terms *weak acids* or *pseudoacids*[2] are usually applied.

$$AH + H_2O \rightleftharpoons A^- + H_3O^+ \tag{1}$$

$$K_a = \frac{[A]^-][H_3O^+]}{[AH][H_2O]} \tag{2}$$

On the other hand, a weak organic base is a compound having a lone electron pair to which a solvated proton can be attached and a positive ion thus formed (equation 3). In aqueous media we can compare relative base strengths by examination of equilibrium constants for reaction 3 (equation 4). If reaction 3 proceeds almost to completion, the base is much stronger than water (solvent). However, the equilibrium lies far over to the left for many organic compounds, and their weak basic properties cannot be observed and detected in water. A number of organic compounds ionize in acidic media of various concentrations so effectively that the concentration of the cation BH^+ can be measured and pK_b ($= -\log K_b$) can be calculated. The term *weak base* is commonly used. The atoms having lone electron pairs are most frequently nitrogen and oxygen. Nitrogen bases are stronger than similar oxygen bases due to the higher electronegativity of oxygen. The structure of the resulting organic cations is very varied, and often a carbonium ion is formed as the final structure.

$$B + H_3O^+ \rightleftharpoons BH^+ + HOH \tag{3}$$

$$K_b = \frac{[BH^+][HOH]}{[B][H_3O^+]} \tag{4}$$

There is no doubt that the strength and structure of weak bases have been investigated and reviewed to a greater extent than that of weak acids. Structural investigations of weak bases have been mainly conducted in superacids in which further reactions of cationic species are arrested. Identification and structural elucidation of a variety of species became known through the studies of Olah and others[3-6]. Equilibrium constants of protonation reactions, pK_b or more frequently pK_{BH^+}, were investigated for various classes of organic compounds including aldehydes[7], carboxylic acids[8], ketones[9], alcohols and ethers[10], amides[11] and anilines[12]. The media for these studies have normally been aqueous solutions of perchloric acid (0–72%) or sulphuric acid (0–96%), in which the capacity of the solution to protonate a weak base may exceed that of the formal concentration of $[H^+]$ as a result of medium effects. In general, two approaches to describing medium effects in strong acid solutions have been developed. One of them—introduced by Hammett[13]—established the *acidity function concept* as an extension of the pH scale. It was believed that acidity functions as in equation 5, where H_0 is the acidity function, C_{H^+} is the acid concentration and the fs are the activity coefficients, provide a quantitative measure of the tendency of the medium to protonate the organic base. However, it was found later that the acidity of the medium depends also on the nature of the base[14].

$$H_0 = -\log c_{H^+} - \log(\bar{f}_B f_{H^+}/f_{BH^+}) \quad (5)$$

For various classes of organic bases different acidity functions have been introduced and reviewed[15]. The impression created was of a great complexity of the acidity function concept[16]. New results derived from characteristic vector analysis of numerous acidity functions for various strong acids indicate linearity among them[17]. In another type of work the medium effect upon a pK_{BH^+} is separated from the changes in $[H^+]$ to define 'excess acidity function'[18–20]. The concept of acidity function stressed water as a standard state for equilibrium measurements and the extrapolation of aqueous pK_{BH^+} data from ionization measurements in highly non-aqueous acidic media.

The second approach was developed by Bunnett and Olsen[21] on the basis of *linear free-energy relationships*, and leads to the fundamental equation 6, where ϕ describes the solvation of a base and H_0 and C_{H^+} have the same meaning as in equation 5. In a recent study Bagno, Scorrano and More O'Ferrall[22] have reviewed the previous works and tend to explain acidity dependences in terms of LFER medium effects. In strongly acidic solutions the basicity depends on two factors, reflecting stabilization of the cation by internal charge delocalization and solvation (most frequently hydration). There is competition between the organic cation BH^+ and H_3O^+ for finding appropriate numbers of water molecules for hydration. Stabilization of the positive charge of the hydrogen ion is excessively solvent-dependent and increasing the concentration of acid decreases the number of water molecules available to solvate the H_3O^+. Concentration profiles of various species present in sulphuric acid were investigated and are of help in understanding the role of water[23–25]. Despite the important role of water in solvating both H_3O^+ and BH^+, its concentration is omitted in the thermodynamic pK_{BH^+} equation.

$$\log K/K_0 = (1-\phi)(H_0 + \log c_{H^+}) \quad (6)$$

In contrast to numerous and varied studies carried out in concentrated solutions of strong mineral acids, relatively few investigations dealing with the cleavage of carbon–hydrogen bonds have been reported in highly basic media[26]. The highly basic media can be prepared as solutions of sodium hydroxide (up to 12 M) in water or in non-aqueous solutions[15,27], and by addition of dipolar aprotic solvents[15,28]. Hydroxide ion is the strongest base that can exist in water. The number of water molecules usually hydrating each OH^- ion is between 3 and 6[29,30]. A dipolar aprotic solvent, such as DMSO, added to aqueous alkaline medium, will increase the basicity by desolvating OH^- ions[31]. Other solvents of this type are sulpholane and hexamethylphosphoramide (HMPA).

This method of producing highly basic media is superior to other methods, in particular, since basicity can be varied continuously over a wide range, ion association is reduced or is absent, and the concentration of base remains constant.

The acidity function concept has been adapted to describe the basicity of media. The acidity function H_- for an electrically neutral weak acid AH in reaction 7 is defined in equation 8. In this equation f_{A^-} and f_{AH} are the activity coefficients of the anion and acid, respectively, and $K_w = \alpha_{H^+}\alpha_{OH^-}/\alpha_{H_2O}$ where the αs are the activities; H_- data and activity coefficients for various systems and temperatures were reported[32]. Amines and unsaturated hydrocarbons were used as indicators. Other acidic compounds include nitro derivatives, ketones, sulphones and nitriles[33].

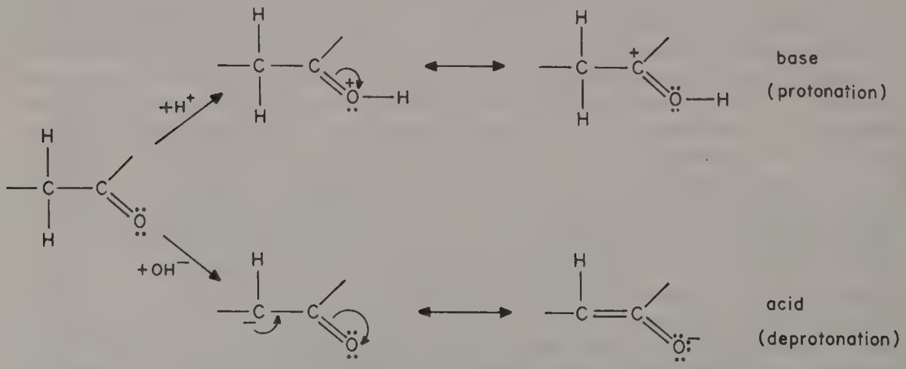
$$AH + OH^- \rightleftharpoons A^- + H_2O \tag{7}$$

$$H_- = -\log \alpha_{H^+}\frac{f_{A^-}}{f_{AH}} = -\log \frac{K_w \alpha_{H_2O}}{\alpha_{OH^-}} \cdot \frac{f_{A^-}}{f_{AH}} \tag{8}$$

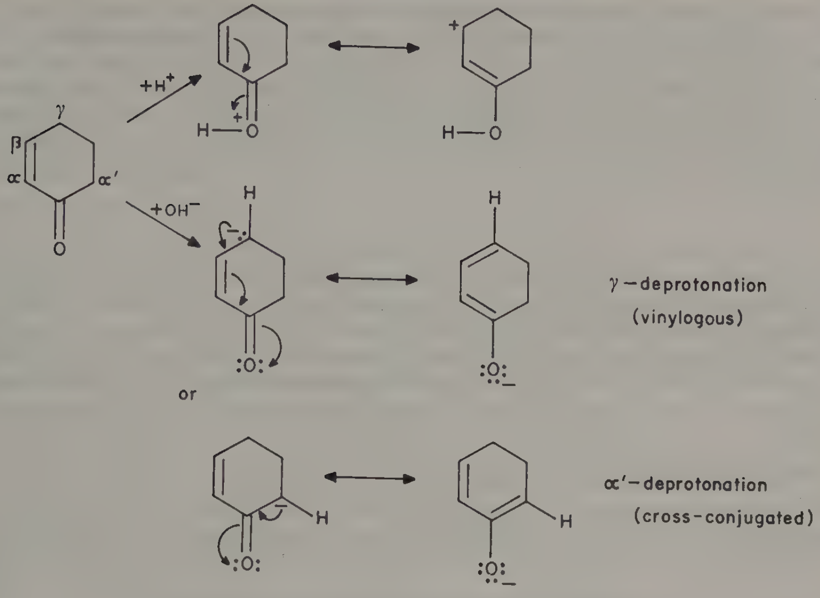
II. KETONES AS WEAK ACIDS AND BASES

The chemical and physicochemical properties of ketones depend on the carbonyl group and on the nature of neighbouring carbons. The carbonyl group consists of two atoms of different electronegativity, with the oxygen being more electronegative. This leads to charge distribution with the negative charge at the oxygen and the positive charge at the carbon atom[34]. The α and α′ substituents can increase or decrease the localization of the charge[35]. For example, in α,β-unsaturated ketones the additional conjugated C=C double bond stabilizes the dipolar structure and increases the electron density on oxygen. To a first approximation, the basicity of a given group depends on its electronegativity and hence oxygen bases such as ketones are weaker than similar nitrogen bases. Indeed, it is difficult to detect protonation on a carbonyl group in water, unless the substrate is a relatively strong base. As a rule, significant protonation occurs only in media of high acidity, and proceeds according to Scheme 1 for an isolated carbonyl group or according to Scheme 2 in case of an α,β-unsaturated carbonyl group. The attack of hydrated protons takes place on the carbonyl oxygen (for more details see Section IV.B.2). The resulting oxonium ion is stabilized by mesomerism involving a carbocation hybrid and by solvation (hydration). Quantitative evaluation of the protonation reaction is possible due to the different properties of the carbonyl base and its conjugate acid. The protonation of a strong base, such as cyclohexan-1,3-dione ($pK_{BH^+} = -0.7$), is achieved in very dilute sulphuric acid[36]. However, the protonation of a weak base, such as 3-cyano-2-cyclohexen-1-one ($pK_{BH^+} = -5.29$), is not complete even in concentrated sulphuric or perchloric acid[37].

In media of high basicity it is possible to observe the other mode of dissociation which leads to α carbanion. Hydroxide ion deprotonates ketones in the α-position and the resulting carbanion is stabilized by mesomerism with a structure in which the negative charge is located on the oxygen of the carbonyl group (Scheme 1).



SCHEME 1. Acid-base properties of the carbonyl group.



SCHEME 2. Acid-base properties of a cyclic enone.

In an α, β-unsaturated ketone such as 2-cyclohexen-1-one there are two sites for deprotonation by the basic media: at the γ site leading to a vinylogous enolate, and at the α′ site leading to a 'cross-conjugated' enolate (Scheme 2). Selection of the deprotonation site in solution depends on the nature of the attacking base, the solvent, and on the concentration and nature of the reactant[38–40]. However, prediction of this site is almost impossible. The situation is clear only when the α′ or γ position is substituted. For stereoelectronic reasons the α′ site will be of lower acid strength in cyclic enones, since the α, β double bond cannot be involved in π delocalization. The separation of the roles of intrinsic structure of the acid from external solvent and other effects can be achieved by gas-phase studies[41].

III. pK_a CALCULATIONS FROM EXPERIMENTAL DATA SETS

Measurements of acid-base behaviour of organic compounds in media of various acidities allow evaluation of pK_a values. For the simplest analysis of titration-like curves (response vs. medium acidity) there are two general strategies of pK_{BH^+}calculation from the ionization ratio $I = C_{BH^+}/C_B$: an acidity function strategy and a free-energy strategy. There are also kinetic strategies.

A. Acidity Function Strategy

The acidity function strategy applies equation 9 to calculate equilibrium constants for protonation reactions. The $\log(C_B/C_{BH^+})$ values can be obtained from experimental measurements in a set of solvents of various acidity, which is described by the acidity function. Equation 9 is solved either graphically or computationally. A plot of $\log(C_B/C_{BH^+})$ vs. the acidity function is a straight line, and when $C_B = C_{BH^+}$, $\log Q = 0$, and thus $\mathrm{p}K_{\mathrm{BH}^+} = H_0$. One must be aware that this is true only when the slope of the above plot is unity. If not, it gives only information on the value of H_0 at half-protonation. The acidity function concept was introduced by Hammett[13] for non-charged bases. Subsequently it was discovered that its general applicability is restricted to a given class of bases, and that each class of bases follows its own acidity function[14,15,17]. The best acidity function which is applicable for the protonation of ketones is the amide acidity function[42] H_A, introduced by Yates and coworkers[11b]. The slope of the log Q vs. H_A plot is very close to unity.

$$\mathrm{p}K_{\mathrm{BH}^+} = H_0 - \log(C_{\mathrm{B}}/C_{\mathrm{BH}^+}) = H_0 - \log Q \tag{9}$$

$\mathrm{p}K_{\mathrm{BH}^+}$ values calculated from equation 9 are constant within the experimental error only if the appropriate acidity function is applied. In other cases the computed $\mathrm{p}K_{\mathrm{BH}^+}$ values vary systematically with the acidity. However, finding the appropriate acidity function is not easy, since many different sets are available. The 1983 papers by Zalewski and coworkers[17] and by Cox and Yates[15] give the most complete set of references to more than 400 various acidity functions for various combinations of acids and solvents.

B. Free-energy Strategy

This stratigy was developed by Bunnett and Olsen[21] and has been applied widely by Scorrano and his colleagues[22]. The LFER character of the fundamental equation 10 is not easily recognized.

$$\log K = (1-\phi)(H_0 + \log C_{\mathrm{H}^+}) + \log K_0 \tag{10}$$

Substitution for K yields equation 11 or 12:

$$\log\frac{C_{\mathrm{H}^+}C_{\mathrm{B}}}{C_{\mathrm{BH}^+}} = (1-\phi)(H_0 + \log C_{\mathrm{H}^+}) + \log K_0 \tag{11}$$

$$-\log C_{\mathrm{H}^+} + \log\frac{C_{\mathrm{BH}^+}}{C_{\mathrm{B}}} = (1-\phi)(H_0 + \log C_{\mathrm{H}^+}) + \mathrm{p}K_0 \tag{12}$$

and after rearranging:

$$H_0 + \log\frac{C_{\mathrm{BH}^+}}{C_{\mathrm{B}}} = \phi(H_0 + \log C_{\mathrm{H}^+}) + \mathrm{p}K_0 \tag{13}$$

The value of $\mathrm{p}K_0$ (or $\mathrm{p}K_{\mathrm{BH}^+}$) can be found as the intercept of the plot of $[H_0 + \log(C_{\mathrm{BH}^+}/C_{\mathrm{B}})]$ vs. $(H_0 + \log C_{\mathrm{H}^+})$, while ϕ is the slope. This strategy is particularly important with the many acid systems for which only H_0 has been determined.

Recent development of the Bunnett–Olsen model supported by the excess acidity[12b,20] function leads to equation 14:

$$-\log C_{\mathrm{H}^+} + \log\frac{C_{\mathrm{BH}^+}}{C_{\mathrm{B}}} = m^*X + \mathrm{p}K_{\mathrm{BH}^+} \tag{14}$$

where $\mathrm{p}K_{\mathrm{BH}^+}$ is the intercept of the plot of $[\log(C_{\mathrm{BH}^+}/C_{\mathrm{B}}) - \log C_{\mathrm{H}^+}]$ vs. excess acidity function X, m^* being the slope[22].

The Bunnett–Olsen treatment of equilibria in mineral acids has been compared with the 'excess acidity function' procedure. The two methods lead to the same results and conclusions[44]. The importance and necessity of describing the protonation properties of weak bases with two parameters ($\mathrm{p}K_{\mathrm{BH}^+}$ and ϕ or m^*) is also emphasized[22]. Acidity function strategies provided by H_0 and X acidity functions have been compared[45]. In some cases nearly correct thermodynamic quantities are available from H_0. The excess acidity function method has been compared with the target testing procedure[46].

Both strategies apply to acidic and basic media, as a general rule. The acidity function strategy has been applied more frequently in basic media; however, the Bunnett–Olsen method also has been accepted[47,48]. The excess acidity function procedure in basic media, e.g. DMSO/water[47] and aqueous KOH[49], has been used with good results.

C. Kinetic Strategies

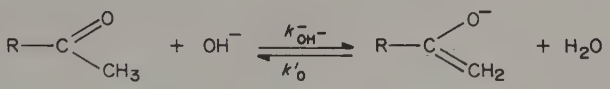
Besides the above-described two strategies, thermodynamic properties of ketones in alkaline media may be evaluated from kinetic measurements. The relations between ketone, enol and enolate are presented in Scheme 3. In general, the equilibrium between a ketone and its corresponding enol is usually shifted so far towards the keto form (K) that the concentration of enol (E) cannot be detected by spectroscopic methods. Various conditions for existence of 'kinetically stable' enols and methods used for determining enol content were reviewed by Toullec[50] and by Hart[51]. The values of the keto–enol equilibrium constant K_{KE} depend on the experimental methods used and were summarized for various ketones[50]. Besides the keto–enol equilibrium, both the ketone (K) and enol (E) forms may be in equilibrium with the enolate (E^-).

Enol acidity constants K_E have been determined by halogen titration and from variation of the $[E]+[E^-]$ plot as a function of acidity[52] or by indirect treatment[53,54]. At present the most powerful method for evaluating K_E is that proposed by Haspra and coworkers[55] (flash photolysis in weakly basic media).

Keto-form acidity constants K_K may be evaluated by classical spectrophotometric procedures or from equation 15[56]:

$$K_K = K_{KE}K_E \tag{15}$$

An additional possibility is provided by keto-enolate kinetics in alkaline media:



$$R{-}C({=}O)CH_3 + OH^- \underset{k'_0}{\overset{k_{OH^-}}{\rightleftharpoons}} R{-}C(O^-){=}CH_2 + H_2O \tag{16}$$

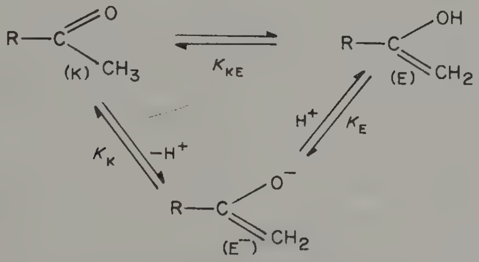
for which

$$k'_0/k^0_{OH^-} = K_w/(K_{KE}K_E) \tag{17}$$

and

$$K_K = K_w k^0_{OH^-}/k'_0 \tag{18}$$

where $k^0_{OH^-}$ is the rate constant of the formation of the enolate ion in alkaline media, k'_0 is that of the ketonisation and K_w is the dissociation constant of water.



SCHEME 3

Substituting equation 17 into 18 gives equation 15. The value of K_k of acetophenone thus obtained equals 18.24[57] and is similar to other results[58] referring to water as a standard state. In DMSO, however, acetophenone is a weaker acid with $pK_k = 24.7$[59].

IV. EXPERIMENTAL TECHNIQUES

Experimental methods for determining the basicity constant of a weak base in acidic media are in general similar to those for determining pK_a values. Usually UV-VIS or NMR measurements are applied to calculate ratios of concentrations of unprotonated to protonated base over the acid concentration range of interest. In some cases circular dichroism, Raman spectroscopy, solvent partitioning, cryoscopy, electrochemical measurements or other methods are used[60,61].

A. UV-VIS Spectroscopy

An organic base may be considered to exist as the free base, B, in water or dilute acid solutions, while in strongly acidic solution it is protonated to its conjugate acid, BH^+. The spectral transitions that are responsible for the light absorption of carbonyl compounds are $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$. The location of the absorption band maximum depends on structural and electronic factors. Isolated carbonyl groups absorb in a region which is not convenient for measurements. α,β-unsaturated carbonyl groups absorb the radiation above 210 nm (in non-polar solvents) and aromatic carbonyl compounds at still longer wavelengths. The $n \rightarrow \pi^*$ band is less intensive than $\pi \rightarrow \pi^*$ and located at a longer wavelength. In general, transitions are sensitive to solvent interactions: e.g. the $\pi \rightarrow \pi^*$ band of β-ionone shifts bathochromically with increasing solvent polarity from 296 nm in methanol to 304 nm in water. A further bathochromic shift occurs[36] in sulphuric acid solution (see Figure 1). At the beginning the bathochromic shift is not very large, but it is

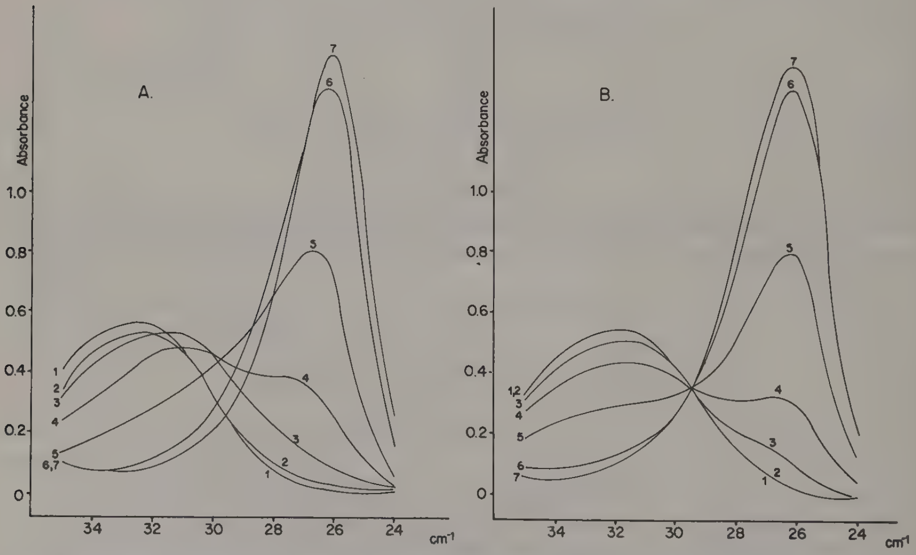


FIGURE 1. Experimental (A) and re-calculated (B) family of UV spectra of α-ionone in sulphuric acid: (1) 19.19%, (2) 29.08%, (3) 38.73%, (4) 45.13%, (5) 53.00%, (6) 64.58%, (7) 75.94%.

very difficult to decide precisely the location of the maximum of absorption of free base, B. This shift can be explained in terms of changing the solvation of the carbonyl group by solvent[62].

The right-hand maxima represent the absorption of the protonated base, BH^+. Again there is a small bathochromic shift with increasing acid concentration as a result of changing the state of cation hydration by solvent. The middle part of the figure represents the broad, irregular maxima, resulting from the overlapping absorptions of mixtures of the two species. The solvent shifts in λ_{max} are such that there is no single isosbestic point.

The $n \rightarrow \pi^*$ band, however, shifts hypsochromically with increasing solvent polarity or concentration of acid, and is overlapped by the $\pi \rightarrow \pi^*$ band. It thus has no practical use.

If the base and ion obey the absorption laws ideally, the family of absorption curves should intersect through an isosbestic point. Then the ionization ratio can be calculated as

$$I = C_{BH^+}/C_B = \frac{A - A_B}{A_{BH^+} - A} \qquad (19)$$

assuming A_B and A_{BH^+} are constant throughout the acidity range.

It is, however, probable that A_B and/or A_{BH^+} will vary across the range of acidities where both species contribute to the absorbance. Various methods have been proposed to take account of this variation[63–66], most of them based on extrapolation of A_B and A_{BH^+} from acidity regions outside the protonation region. The extrapolation requires that absorbance by the substrate outside the titration range be subject only to medium effects (no protolytic, hydrolytic or other reactions).

To overcome these difficulties Zalewski and Dunn[36,42] have used a least-squares computer program for titration curve analysis (TCA). A further attempt was made by Edward and Wong[67], who applied factor analysis (FA) to extract spectral changes accompanying protonation from experimental families of absorption curves.[68] This method was also adopted in an improved TCA method.[69] Computer-aided analysis of experimental absorption data has been developed successfully during the last decade. The first objective of factor analysis is to obtain an 'abstract' solution wherein each data point is expressed as a linear sum of product terms. The number of terms is the number of factors. The standard FA procedure applied to the digitalized set of spectra shown by Figure 1 (absorbance was read at 5-nm intervals to form the initial data matrix) indicates that two factors explain more than 96% of total data variability. Thus any absorbance $A_{n,p}$ could be expressed by equation 20, in which C represents the factor for wavelength p, L represents its loading for the n-th spectrum and ε is the unexplained residue. Now we can reconstitute a new family of absorption spectra.

$$A_{n,p} = C_{1,p}L_{n,1} + C_{2,p}L_{n,2} + \varepsilon \qquad (20)$$

Abstract factor analysis has been supported by target transformation[70] or key-set and spectral resolution[71] procedures, and the reliability of the final result has been increased.

Factor analysis offers a good possibility not only to improve experimental absorption curves which lack an isosbestic point, but also to calculate the spectra of unmeasurable species. This problem frequently appears with simple aliphatic ketones which are only half-protonated in approximately 80% sulphuric acid and the estimated pK_{BH^+} values of which vary with the authors[96,72–75], or with α,β-unsaturated ketones with strong electron-withdrawing substituents[37]. In these cases absorption spectra are very incomplete even in concentrated sulphuric acid, and experimental estimation of A_{BH^+} is not possible.

Transformation of an abstract solution into a real solution and finding real spectra of protonated base BH^+ and free base has been proposed[76–78] and applied to 3-cyano-5,5-dimethylcyclohex-2-en-1-one.[37]

Other experimental difficulties that can spoil UV-VIS measurements are: (i) precipitation of the investigated base in a colloidal form when dissolving the stock solution in sulphuric acid, (ii) failure of absorption laws, (iii) impurity of the tested base, (iv) decomposition of B and BH^+ or both with time.

The researcher must be aware of these possibilities. Decomposition, for example, can be detected by repeating measurements after a suitable time. Such a test must be performed occasionally, especially when the concentration of sulphuric acid is greater than 70%. If the results change, absorbance must be extrapolated back to mixing time in 'kinetic-like' experiments. Stability of a given base in acid may be checked by extraction of organic material after dilution with water.

Of the many acids which may be used for base strength determination, sulphuric acid is most frequently used. Perchloric acid is very convenient for compounds which tend to undergo dehydration or condensation[79]. Other mineral or organic strong acids are occasionally used in such experiments.

B. Nuclear Magnetic Resonance

1. *Data acquisition in protonation studies*

The NMR technique may be of value for studying some kinds of weak bases, but for others it is unable to distinguish the difference between hydrogen bonding and protonation. For example, ^1H NMR was used with success to obtain fairly good p*K* values for acids and amides[80], but fails when applied to alcohols or ethers[81].

The applicability of the NMR method relies on the sensitivity of substituent chemical shifts to changes in the polarity of the C—O bond during protonation. Sensitivity of protons towards this polarity decreases with distance. Thus α-protons are deshielded by 0.4–1.0 ppm relative to protons in the unprotonated ketone. According to the physical background of NMR, the observed chemical shift for a given proton resonance is time- and species-averaged. Thus, at the acidity of the medium corresponding to equilibrium, the observed proton shift lies midway between the shifts for the protonated and unprotonated ketone. The plot of substituent chemical shift vs. medium acidity resembles that of a titration curve. Agreement between experimental and theoretical titration curves is limited by the standardization of chemical shift, by the type of base and substituents and by medium effects.

Internal standardization is necessary to give a precise measure of the chemical shift changes of the ketone as a result of protonation rather than as a result of changes in the magnetic environment. Cyclohexane or, better, tetramethylammonium chloride are recommended[82]. The chemical structure of the base is generally the limiting factor controlling the precision of measurement. α-Methyl protons are preferred to other signals and other substituents. Sometimes the presence of other functional groups capable of protonating or strong hydrogen bonding can obscure protonation of C=O. Weak hydrogen bonds normally do not affect basicity determination. Chemical shifts of protonated ketones remain constant as the acidity increases and the upper part of the titration curve remains flat.

Limitations of ^1H NMR measurement of ketone basicity are the following: relatively low sensitivity (± 0.2 p*K* units or more) and the possibility of ketones undergoing side-reactions in acidic media which is increased at high concentrations of the ketone. This difficulty could be overcome by application of a Fourier transformation technique.

Rapid determination, possibility of low-temperature measurements for relatively unstable systems, and the fact that not all side-reactions interfere with substituent chemical shifts used in p*K* determinations are the advantages of ^1H NMR.

Carbon nuclear magnetic resonance has been also applied to determine basicity of carbonyl compounds. The advantage of ^{13}C NMR is that the nucleus closest to the site of protonation can be probed and large chemical shift changes on protonation should be obtained. In consequence, better precision may be achieved than in ^1H NMR. Additionally, ^{13}C NMR spectra produced with proton decoupling are rather simple even for complex molecules. One serious disadvantage of this method is the long measurement time required to produce good spectra using the natural abundance of isotopes. The greater chemical shift and the fact that for each carbon there is only one sharp peak lower the probability of spectral interference by decomposition products when the measurement time is long.

In ^{13}C NMR spectra there is no problem in assigning the carbonyl carbon and α-carbons. The time required to record satisfactory Fourier transform spectra is strongly dependent on the acidity of the medium. In dilute acids this time is as long as a few hours but in concentrated acids it is around 20 minutes. This fact decreases the danger of the occurrence of side-reactions.

Substantial downfield chemical shifts connected with the protonation of the carbonyl group plotted against medium acidity produce titration curves typical of weak bases. $\delta(H_2SO_4) - \delta(H_2O)$ for C=O in an isolated carbonyl group is in the range of 30 ppm[75] and decreases in the case of unsaturated ketones to 10 ppm[83]. The chemical shift variations on protonation are smaller for other carbon atoms and may be downfield or upfield. In various enones the chemical shift of C-α on protonation is practically constant. ^{13}C NMR spectra, however, indicate localization of positive charge on C-β[84].

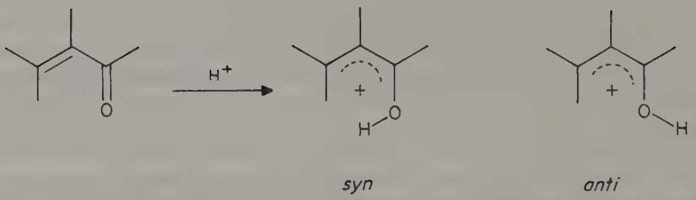
The titration curves resulting from ^1H or ^{13}C NMR may be used to estimate rough values of acidity functions at half-protonation (at the inflection point). Accurate pK_{BH^+} calculations require computation of the ionization ratio I from the standard equation:

$$I = C_{BH^+}/C_B = (\Delta\nu - \Delta\nu_B)/(\Delta\nu_{BH^+} - \Delta\nu) \tag{21}$$

in which $\Delta\nu$ is a difference in chemical shifts between two of the nuclei (e.g. carbonyl carbon and one other carbon) for a mixture of B and BH^+, and $\Delta\nu_B$ and $\Delta\nu_{BH^+}$ relate to the free base and the protonated one, respectively. This procedure avoids bulk susceptibility corrections for external standard and minimizes medium effects, as well as allowing the comparison of I for various C—C or H—H pairs in the molecule. Using chemical shifts of individual nuclei is not recommended.

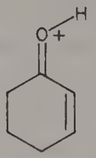
2. *Elucidation of ionic structure*

The other important application of NMR in the field studied is the possibility of structure elucidation and particularly the identification of the site of protonation. It was shown by measurements in superacids (oleum or SbF_5—FSO_3H—SO_2) at low temperatures that protonation of aliphatic saturated ketones leads to an equilibrium mixture of stereoisomers caused by the double-bond character of the protonated carbonyl group[85]. Proton magnetic resonance study indicates the oxonium ion, and not the hydroxy carbonium ion, as the main form. This means that the nature of bonds in the carbonyl group is only slightly modified by protonation and the positive charge is mainly located on the oxygen. ^1H and ^{13}C NMR studies[5] of aliphatic unsaturated ketones again indicate that the site of protonation is the carbonyl oxygen but the ions are of a hydroxyalkyl cation nature. The positive charge is distributed between the carbonyl oxygen atom and the carbon skeleton. Thereby centres of high and low positive charge alternate along the chain (high at the *ipso*- and β-carbons[6]. In some cases both *syn* and *anti* isomers are observed; in others only one isomer is detectable, depending on the stability differences caused by steric effects. For example, two isomers are detectable in protonated methyl vinyl ketone and 3-penten-2-one[5]. A recent paper[6] describes four isomers, s-*cis*/*syn* being much less favourable.



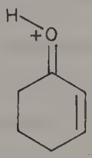
^{13}C NMR spectra for the protonated α,β-unsaturated ketones show that both the carbonyl carbon and the β-carbon are deshielded as compared with the parent compound, but the chemical shift of the α-carbon remains about the same. This deshielding can be related to the positive charge density on carbon[86].

Similar results have been found for alicyclic saturated and unsaturated ketones[87]. The proton on oxygen is deshielded (− 14.9 to − 13.8 ppm) when going from cyclobutanone to cycloheptanone but the α-hydrogens are shifted downfield to different degrees. The protons on oxygen in protonated 2-cyclohexen-1-one are less deshielded than in protonated cyclohexanone and give two singlets as a proof of two isomers:



syn

−12.3 ppm



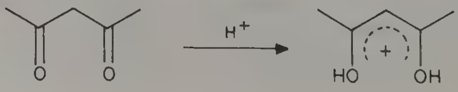
anti

−12.4 ppm

Similar isomers were detected in protonated 2-cyclopentenone[5] and 3-methylene-2-norbornanone[87]. In the last compound, the *anti* isomer is more favoured. When the conjugation between the enone moiety and the additional double bond(s) is inhibited, the charge remains in the enone part 6.

The NMR technique is also a good indicator of isomerization processes which can occur in strongly acidic media. The isomerization of 3-cyclopenten-1-one to the protonated 2-cyclopenten-1-one is an example of interconversion between β,γ- and α,β-unsaturated ketones. Unsaturated ketones in which the carbonyl group is more distant from the olefinic bond undergo diprotonation, as shown by their NMR spectra.

An additional application of NMR is the investigation of the protonation of diketones. Among these, the most interesting are the 1,3-diones which, in certain conditions, are equivalent to the 3-hydroxy-2-en-1-one moiety. 2,4-Pentanedione in the case of monoprotonation has a dihydroxyallylic structure[88a], related to the protonated enolic form of the diketone, as shown by ^{1}H NMR. 1,3-Cyclohexanedione and its 2-methyl derivative are only monoprotonated in a strong acid system. ^{13}C NMR spectra of monoanions of β-diketones were also reported[88b].



C. Raman Spectroscopy

Raman spectroscopy has been used occasionally to determine basicity of weak organic bases in sulphuric acid[89,90] by utilizing the area of absorption bands of C—H (3000–2900 cm^{-1}) and C=O (1750–1600 cm^{-1}) as a function of the acid concentration. On protonation, the intensity of the C=O vibration decreases and finally disappears, and pK_{BH^+} may be calculated. Unfortunately, no data have been reported on protonation of enones by this method and data are available only for simple ketones[89] and carboxylic acids[90]. The high concentration of base (up to 20% by weight) required in the Raman method severely limits its application and precision.

Raman spectroscopy has been used to study the structures of species present in sulphuric acid in support of explanation of acid–weak base interaction[23,24].

D. Indirect Methods

In addition to various methods leading to direct calculation of equilibrium constants for protonation or deprotonation reactions, there are many methods for indirect characterization of acid-base equilibria.

For example, Arnett and coworkers[74,91] have developed a thermochemical method for comparing a wide variety of bases in strong acids through their heats of protonation, ΔH_{BH^+}. An analogous approach to the deprotonation of carbon acids in strong bases has been described[92]. The thermochemical approach involves the measurement of partial molar heats of solution ΔH_S of the acid at dilution 10^{-3}–10^{-2} M in DMSO and then in 0.1 M alkali DMSYL$^-$ solution in DMSO, when the heat of deprotonation $\Delta H_D = \Delta H_S^{DMSYL^-} - \Delta H_S^{DMSO}$. DMSYL$^-$ is the potassium or cesium salt of the lyate anion as a very strong base; ΔH_D for various systems is linearly correlated to the pK_a data in DMSO[93]. Thus ΔH_D and ΔH_{BH^+} may serve as acid-base characteristics in the range of 50 pK_a units from superacid media ($H_0 \sim -14$) to superbasic media ($H_- \sim 34$).

Successful calorimetric treatment has been described for calculation of equilibrium constant and reaction enthalpy for the complexation of carbonyl compounds with boron trifluoride in methylene chloride[94,95]. The enthalpy of complexation $\Delta H°$ for various classes of carbonyl compounds (N-ammoniobenzamidates[96], unsaturated ketones[97,98]) depends linearly on pK_{BH^+} and follows an extrathermodynamic relationship. The $\Delta H°$ value for strong bases is lower than for weak bases.

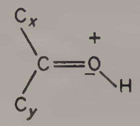
The relative gas-phase acidities may be measured with a pulsed ion cyclotron resonance spectrometer. Equilibrium constants for the general reaction of anions[99]:

$$A^- + BH \rightleftharpoons B^- + AH$$

are used to establish the relative acidities of the two acids AH and BH in the absence of solvation[99,100a,b]. A similar approach is possible for cations and leads to relative basicity data.[101a,b].

A measure of relative acidity of AH and BH in the gas phase is the standard Gibbs free energy $\delta\Delta G°_{acid} = -RT \ln K$ from which, by incorporating some standard reactions in the relative scale of acidity, one can establish an absolute basicity scale. Larger values of $\delta\Delta G°_{acid}$ are characteristic for weaker acids.

Organic compounds with carbonyl groups are weak acids, deprotonating on the carbon α to the electron-withdrawing substituent. However, the site of reprotonation of the resulting anion is not unequivocal and depends on various structural and environmental factors[41]. The number of enones studied is not very large and most existing data refer to very simple compounds. The method is suitable for the study of substituent effects and structural effects[99] by application of familiar LFER, as well as for the study of solvation effects on the acidity of carbon acids. The gas-phase basicity of cyclic ketones reflects the size of the alicyclic ring in a slightly different way from the number of carbon atoms in linear ketones[102]. This is a consequence of the increased repulsion between carbons X and Y of protonated ketones as compared to unprotonated ones.



V. RESULTS AND DISCUSSION

A. Alicyclic Enones

Alicyclic enones are relatively strong bases in mineral acids as indicated in Table 1. Their basicity does not depend very much on the size of the alicyclic ring. Cyclopentenone (**7**) and cyclohexenone (**12**) are bases of about equal strength, their pK_{BH^+} being reported as -3.6^{36} and -3.15^{20b}. The difference comes from application of uncorrected[11b] or corrected[67] acidity functions H_A, respectively, and data treatment with different strategies. The protonation constant of 1-androsten-(5α)-3,11,17-trione (**56**) (for structures of typical enones see Chart 1), in which the enone moiety is equivalent to 2-cyclohexenone (**12**), is -3.60^{109}. The pK_{BH^+} of (**12**) reported by Butler[83] has been calculated from ^{13}C NMR shifts of $^{13}C{=}O$ and $^{13}C_\beta$ and is in satisfactory agreement with other data.

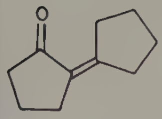
Data on basicity of unsubstituted cyclic enones of other ring sizes are not available in the literature. The accessible data on mono- and disubstituted alkyl or phenyl cyclopropenones[103–106] were derived from NMR data and the H_0 acidity function and have the status of 'half-protonation' values. Assuming that those compounds follow the H_A acidity function in their protonation, pK_{BH^+} would be in the range -1.7 to -2.6. This suggests a base strengthening effect of the small ring with steric strain. The estimation of pK_{BH^+} for unsubstituted cyclopropenone is not possible because only data for alkyl substituted derivatives are available.

There are two main sources of experimental data on pK_{BH^+} of alicyclic enones. The one is in papers by Azzaro, Gal, Geribaldi and coworkers[97,98] and the other is a set of papers by Zalewski and Dunn[36,109] and Zalewski and coworkers[79,107,108]. Both groups use the UV-VIS indicator method, but use different sets of H_A and different methods of data processing. Consequently, the difference in the values of pK_{BH^+} is constant for similar compounds. pK_{BH^+} values calculated by Cox and Yates[20b] were supported by experimental data ($\log I$ vs. $\%H_2SO_4$) submitted by Zalewski[36,107–109] and thus are mutually correlated.

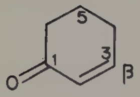
Keeping in mind standards of correlation analysis in organic chemistry[110,111] one should compare sets of data from one source rather than data for individual compounds from different sources. Literature pK_{BH^+} data within particular sets and also between sets follow the requirements of linear free-energy relationships and can be used to consider the effect of structure on the basicity of enones.

The structure–basicity relationship must take into consideration the choice of reference enone, the long-range structural effects on pK_{BH^+}, the description of α- and β-substituent effects, and the construction of similarity models.

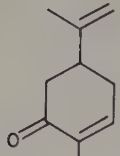
The influence of structure on basicity will be discussed assuming the additivity rule at least within the examined series of compounds in the case of the simultaneous action of two or more structural elements. The effect of such elements will be expressed in terms of differences ΔpK_{BH^+} between substituted and unsubstituted (reference) molecules. The



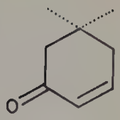
(11)



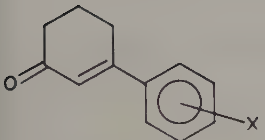
(12)



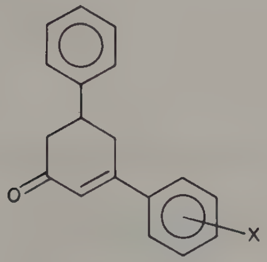
(17)



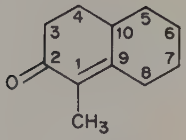
(18)



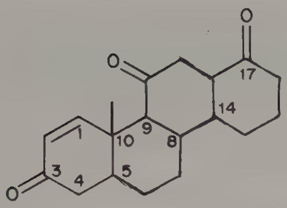
(35–42)



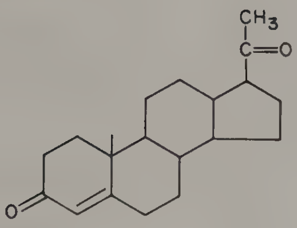
(43–51)



(52)



(56)



(60)

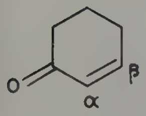
CHART 1

basicity of an enone may then be calculated by the equation:

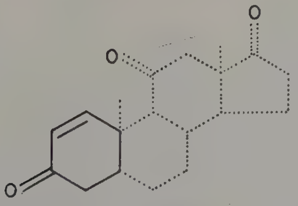
$$pK_{BH^+} = pK^0_{BH^+} + \sum \Delta pK_{BH^+} \qquad (22)$$

within a maximum error of 0.1 pK_{BH^+} unit.

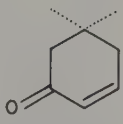
a. The choice of reference enone. Most pK_{BH^+} data for alicyclic enones presented in Table 1 refer to compounds with a six-membered ring. Thus 2-cyclohexenone (**12**) will serve as reference base with $pK_{BH^+} = -3.60$. The same basicity is characteristic for one steroid molecule of equivalent structure (**56**). The basicity of 5,5-dimethyl-2-cyclohexenone (**18**) is equal[97] to that of 2-cyclohexenone (**12**) within experimental error.



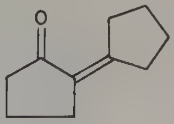
(12)



(56)



(18)



(11)

TABLE 1. A. Basicity data for monocyclic enones in sulphuric acid

No.	Compound	pK_{BH^+}	Slope[a]	Ref.	pK_{BH^+}	Slope[b]	Ref.	$-\Delta H°(kJ\,mol^{-1})$	$\Delta\nu$[c]	Ref.
1	2-Me-cyclopropenone	-3.5	—	103						
2	2,3-Me_2-cyclopropenone	-2.3	—	103						
3	2,3-Pr_2-cyclopropenone	-1.9	—	104						
4	2,3-Bu_2-cyclopropenone	—	—	—					381	105
5	2,3-Bu^t_2-cyclopropenone	—	—	—					398	105
6	2,3-Ph_2-cyclopropenone	-2.5	—	106					376	105
7	2-Cyclopentenone	-3.55 ± 0.03	1.01	36	-3.17 ± 0.03	0.50 ± 0.01	20b			
8	3-Me-cyclopentenone	-2.82 ± 0.3	1.00	36	-2.40 ± 0.04	0.50 ± 0.01	20b			
9	2,3-Me_2-cyclopentenone	-2.55 ± 0.02^d	0.97	36	-2.82 ± 0.04	0.56 ± 0.01	20b			
10	3-Me-2-OH-cyclopentenone	-3.27 ± 0.04	1.03	36	-2.85 ± 0.06	0.49 ± 0.02	20b			
11	Cyclopentylidenecyclopentanone	-2.56 ± 0.03	0.97	36						
12	2-Cyclohexenone	-3.60 ± 0.04^e	1.01	36	-3.15 ± 0.09	0.44 ± 0.02	20b			
13	3-Me-cyclohexenone	-2.83 ± 0.03^d	1.03	36	-2.39 ± 0.06	0.47 ± 0.02	20b			
14	3,5-Me_2-cyclohexenone	-2.86 ± 0.04^d	1.01	36	-2.38 ± 0.05	0.46 ± 0.01	20b			
15	3-OH-cyclohexenone	-0.84 ± 0.02^d	1.00	36	-0.59 ± 0.02	0.54 ± 0.03	20b			
16	3-OEt-cyclohexenone	-0.77 ± 0.04	0.94	36	-0.47 ± 0.03	0.47 ± 0.06	20b			
17	d-Carvone	-2.92 ± 0.07	1.01	36						
18	5,5-Me_2-2-cyclohexenone				-3.22 ± 0.05		97	83.58 ± 0.34		97
19	3-CN-cyclohexenone				-5.27 ± 0.05		37	64.46 ± 0.53		97
20	3-CH_3COO-cyclohexenone				-4.15 ± 0.05		97	72.55 ± 0.57		97
21	3-Br-cyclohexenone				-3.63 ± 0.05		97	77.28 ± 0.18		97
22	3-Cl-cyclohexenone				-3.36 ± 0.05		97	77.87 ± 0.33		97
23	3-$NCCH_2$-cyclohexenone				-3.53 ± 0.05		97	79.71 ± 0.26		97
24	3-EtO_2CCH_2-cyclohexenone				-3.17 ± 0.05		97	83.50 ± 0.49		97
25	3-$EtCOCH_2$-cyclohexenone				-3.10 ± 0.05		97	85.44 ± 0.69		97
26	3-MeCOO-cyclohexenone						97	85.11 ± 0.35		97

27	3-EtCOO-cyclohexenone							83.67 ± 0.24	97
28	3-Ph-cyclohexenone				− 2.71 ± 0.05		97	86.48 ± 0.29	97
29	3-Me-cyclohexenone				− 2.50 ± 0.05		97	90.56 ± 0.41	97
30	3-EtS-cyclohexenone				− 1.43 ± 0.05		97	96.64 ± 0.80	97
31	3-MeO-cyclohexenone				− 0.73 ± 0.05		97	99.89 ± 0.20	97
32	3-EtO-cyclohexenone				− 0.69 ± 0.05		97	101.25 ± 0.35	97
33	3-OH-cyclohexenone				− 0.45 ± 0.05		97		
34	3-NH_3^+-cyclohexenone				− 3.25 ± 0.05		97		
35	3-(*p*-$O_2NC_6H_4$)-cyclohexenone				− 3.20 ± 0.03	1.01	98	80.28	98
36	3-(*p*-NCC_6H_4)-cyclohexenone				− 3.09 ± 0.03	0.96	98	82.20	98
37	3-(*p*-BrC_6H_4)-cyclohexenone				− 2.83 ± 0.03	0.91	98	84.87	98
38	3-(*p*-ClC_6H_4)-cyclohexenone				− 2.80 ± 0.03	0.92	98	85.41	98
39	3-(*p*-FC_6H_4)-cyclohexenone				− 2.67 ± 0.03	0.97	98	86.06	98
40	3-(*p*-PhC_6H_4)-cyclohexenone				− 2.60 ± 0.03	1.05	98	87.16	98
41	3-(*p*-Tol)-cyclohexenone				− 2.53 ± 0.03	0.93	98	88.79	98
42	3-(*p*-An)-cyclohexenone				− 2.05 ± 0.03	1.14	98	90.44	98
43	3, 5-Ph_2-cyclohexenone	− 3.16 ± 0.07	1.01	108	− 2.80 ± 0.09	0.51 ± 0.03	20b		
44	3-(*p*-Tol)-5-Ph-cyclohexenone	− 3.06 ± 0.03	0.99	108	− 2.67 ± 0.08	0.49 ± 0.02	20b		
45	3-(*p*-An)-5-Ph-cyclohexenone	− 2.70 ± 0.06	0.99	108	− 2.09 ± 0.12	0.60 ± 0.05	20b		
46	3-(*p*-$\overset{+}{N}H_3C_6H_4$)-5-Ph-cyclohexenone	− 3.47 ± 0.06	1.01	108	− 3.18 ± 0.12	0.51 ± 0.03	20b		
47	3-(*p*-$\overset{+}{N}Me_2HC_6H_4$)-5-Ph-cyclohexenone	− 3.56 ± 0.03	1.00	108	− 3.14 ± 0.04	0.49 ± 0.01	20b		
48	3-(*p*-ClC_6H_4)-5-Ph-cyclohexenone	− 3.31 ± 0.05	1.01	108	− 2.95 ± 0.05	0.51 ± 0.01	20b		
49	3-(*p*-BrC_6H_4)-5-Ph-cyclohexenone	− 3.28 ± 0.05	1.01	108	− 2.89 ± 0.08	0.51 ± 0.02	20b		
50	3-(*p*-$O_2NC_6H_4$)-5-Ph-cyclohexenone	− 3.59 ± 0.07	1.02	108	− 3.26 ± 0.08	0.52 ± 0.02	20b		
51	3, 3-di(*p*-An)-cyclohexenone	− 2.64 ± 0.05	1.00	108	− 2.00 ± 0.15	0.50 ± 0.06	20b		

---

[a] The slope of log [BH^+]/[B] vs. H_A acidity function[11b].
[b] The slope of log [BH^+]/[B] vs. H_A acidity function[67].
[c] $\Delta\nu$ of infrared vibration of OH···O=C hydrogen bond and OH.
[d] pK_{BH^+} data in perchloric acid were also reported[107] to be similar.
[e] pK_{BH^+} from ^{13}C NMR was reported as − 2.9[83].

TABLE 1. B. Basicity data for polycyclic enones in sulphuric acid and in perchloric acid

No.	Compound	H_2SO_4			$HClO_4$ (Ref. 107)	
		pK_{BH^+}	Slope[a]	Ref.	pK_{BH^+}	Slope[a]
52	1-Me-$\Delta^{1,9}$-decalone-2	-2.47 ± 0.03	0.99	36	-2.57 ± 0.03	1.01
53	3-Me-$\Delta^{1,9}$-decalone-2	-2.82 ± 0.03	0.98	36	-2.87 ± 0.03	0.99
54	10-Me-$\Delta^{1,9}$-decalinedione-2, 5	-3.54 ± 0.04	0.97	36	-3.40 ± 0.02	1.02
55	1, 10-Me_2-$\Delta^{1,9}$-decalinedione-2, 5	-3.32 ± 0.03	0.98	36	-3.30 ± 0.05	1.00
56	1-Androsten-(5α)-3, 11, 17-trione	-3.60 ± 0.03	0.99	109	-3.60 ± 0.04	1.02
57	4-Androsten-3, 17-dione	-2.85 ± 0.02	1.00	109	-2.88 ± 0.03	1.02
58	17β-Hydroxy-4-androsten-3-one (testosterone)	-2.85 ± 0.02	1.00	109	-2.76 ± 0.04	0.97
59	17α-Me-testosterone	-2.84 ± 0.04	0.99	109		
60	4-Pregnen-3, 20-dione (progesterone)	-2.87 ± 0.03	0.98	109	-2.83 ± 0.02	0.99
61	4-Pregnen-17α, 21-diol-3, 11, 20-trione (Cortisone acetate-17α)	-2.98 ± 0.03	0.98	109		
62	4, 17α-Me_2-testosterone	-2.59 ± 0.03	0.99	109		
63	4, 17α-Me_2-11β-hydroxytestosterone	-2.81 ± 0.03	1.03	109		
64	4-Fluorotestosterone	-4.59 ± 0.03	1.02	109		
65	4-Chlorotestosterone	-4.65 ± 0.06		116		
66	4-Bromo-4-cholesten-3-one	-4.80 ± 0.05		116		
67	4-Bromo-17α-Me-testosterone	-4.70 ± 0.05		116		
68	6α-Fluoro-17α-Me-testosterone	-3.56 ± 0.04	1.02	109		
69	6α-Fluoro-progesterone	-3.44 ± 0.05	0.98	109		
70	4, 6-Androstadien-3, 17-dione	-2.46 ± 0.02	1.01	109	-2.43 ± 0.04	0.98
71	4, 6-Andrestadien-3-one 17β-propionate	-2.31 ± 0.02	0.98	109		
72	6-Dehydro-6-Me-cortisone acetate	-2.49 ± 0.02	0.98	109	-2.45 ± 0.02	0.98
73	2α-Me-testosterone	-2.80 ± 0.03	1.01	109		
74	2α-Me-progesterone	-2.92 ± 0.04	0.97	109	-2.85 ± 0.04	1.02
75	2α, 17α-Me_2-11β-hydroxytestosterone	-3.11 ± 0.02	1.00	109		
76	2α-Me-11β-hydroxyprogesterone	-3.20 ± 0.04	0.98	109	-3.25 ± 0.04	1.02
77	2α-Fluorotestosterone	-4.66 ± 0.05	0.99	109		
78	2α-Fluorotestosterone propionate	-4.71 ± 0.03	1.00	109		
79	17β-Hydroxy-17α-Me-4, 9(11)-androstadien-3-one	-2.91 ± 0.04		112		
80	17β-Hydroxy-4, 9(11)-androstadien-3-one	-2.82 ± 0.03		112		
81	9α-Fluorohydrocortisone	-3.05 ± 0.04		112		
82	9α-Fluorohydrocortisone acetate	-3.12 ± 0.05		112		

[a] The slope of $\log[BH^+]/[B]$ vs. H_A acidity function.

This means that the structural elements indicated by dotted lines do not affect the protonation constant, pK_{BH^+}. Finally, equation 22 may be rewritten in the form:

$$pK_{BH^+} = -3.60 + \sum \Delta pK_{BH^+} \tag{23}$$

characterizing the s-*trans* enone moiety.

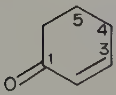
b. Long-range structural effects. This term will comprise, within this work, all structural elements and substituents more or less remote from the enone moiety. By this definition only α and β carbons are excluded from such a description. In other words, long-range effects do not need a through-the-bonds influence on the π-electron distribution in the enone as base or ion. The collection of enones in Table 1 having such elements is large. Comparing various pairs of similar compounds one can calculate ΔpK_{BH^+} values for most common long-range structural elements. These increments are presented in Table 2.

Representation of s-*cis* enones is only by one compound, cyclopentylidenecyclopentanone (**11**), having one α and two β methylene groups as substituents and $pK_{BH^+} = -2.56$. The s-*cis* conformation (**11**) may be equivalent to or very similar to 2,3-dimethylcyclopentenone (**9**). In fact their pK_{BH^+} values are equal within experimental error and this allows us to suppose that the basicity of the carbonyl group in cyclic enones does not depend on s-*cis* or s-*trans* conformation.

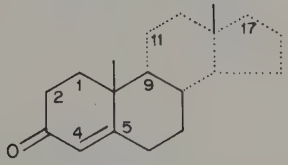
It is obvious from data in Table 2 that remote alkyl groups and aromatic rings do not affect the basicity of the carbonyl group; nor do substituents in a steroid molecule beyond C_{11}. Presence of a C=O group or a fluorine atom decreases basicity of the enone in some way which is dependent on distance. This leads to the conclusion that the inductive effect through σ-bonds or a field effect is responsible for this base-weakening effect[112]. It is well

TABLE 2. Increments ΔpK_{BH^+} for long-range effects

Structural elements or substituents	Structure	ΔpK_{BH^+}
5-Me, 5,5-Me$_2$	**A**	0.00
5-Ph	**A**	0.00
4,4-Me$_2$	**A**	0.00
6α-Me	**B**	0.00
2α-Me	**B**	0.00
17-Me, OH, C_{17}=O, 17-COMe	**B**	0.00
11-OH	**B**	−0.30
9-C=O	**B**	−0.75
11-C=O	**B**	−0.15
2α-F	**B**	−1.35
6α-F	**B**	−0.70
9α-F	**B**	−0.10



(A)



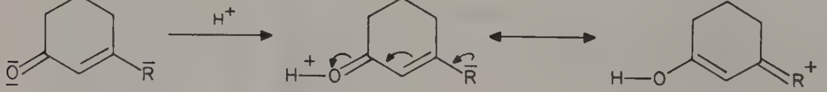
(B)

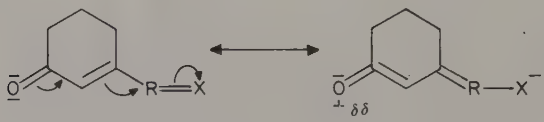
known that inductive interaction is strongly distance-dependent and greatly diminishes after 2 or 3 σ-bonds[113–115].

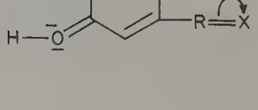
c. α-Substituent effects. α-Methyl substitution (**9**,**52**,**55**,**62**,**63**) makes the bases stronger than the corresponding unsubstituted (**8**,**54**,**54**,**59**,**59**) compounds by approximately 0.3 $\mathrm{p}K_{\mathrm{BH}^+}$ unit. The other α-substituents studied, namely OH (**10**), F (**64**), Cl (**65**) and Br (**66**,**67**), are base-weakening. This is in the direction expected from the sign of the inductive effect exerted by these groups. Excluding alkyl groups which are known as + I, all others are − I, i.e. they attract electrons from the system of π electrons. In the case of enones, such substituents attract electrons from the oxygen atom and thus decrease the electron density and the basicity. The strong inductive effect of α-substituents is not weakened by their mesomeric effect + M, because mesomeric interaction from the α position is forbidden[116]. In this respect an α-substituent resembles a *meta* substituent in aromatic compounds.

d. β-Substituent effects. The number of various β-substituents in the enones studied is relatively large. Enones substituted by methyl groups in the β-position (e.g. **8**,**13**,**14**,**29**) are stronger than the unsubstituted ones by 0.75 $\mathrm{p}K_{\mathrm{BH}^+}$ unit. A β-methylene group (or chain) has the same base-strengthening effects, which is seen in numerous bicyclic compounds and steroids (e.g. **53**,**57**,**58**,**59**,**60**), the $\mathrm{p}K_{\mathrm{BH}^+}$ for all these compounds being ~ −2.85. These effects are explainable in terms of the + I inductive effect[36] of the alkyl group, which stabilizes the conjugate acid (BH^+) more than the enone. Hyperconjugation will have a similar influence.

Stabilization of positive charge in protonated enone by resonance may produce much larger changes in basicity, as is illustrated by compounds (**15**,**33**) with β-OH groups. They are about 2.6 $\mathrm{p}K_{\mathrm{BH}^+}$ units more basic than the unsubstituted enone. Very similar is the effect of β-alkoxy groups (**16**,**31**,**32**) and SR groups (**30**). Electron-donating substituents stabilize the protonated base by resonance with various efficiencies, depending on the electrical properties of the substituents. On the other hand, electron-attracting substituents are base-weakening, since they tend to increase the electron density on themselves and decrease the electron density on the carbonyl group, and thus the lone pairs of electrons on the oxygen are less available to react with the proton. For the same reason, the protonated base is destabilized due to two electron deficient sites in the molecule: the substituent and the oxonium ion. This effect may be very strong, as exemplified by 3-CN- (**19**) and 3-acetoxy-2-cyclohexenenones (**20**) which are weaker bases by 2 and 1 $\mathrm{p}K_{\mathrm{BH}^+}$ unit respectively than the parent compound.

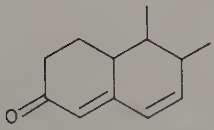




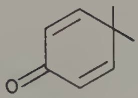


Halogens (**21, 22**) are moderate base-weakening substituents. Separation of a strong base-weakening substituent from the β-carbon by a methylene group (**23**-CH_2CN, **24**-$CH_2COOC_2H_5$) reduces its influence dramatically.

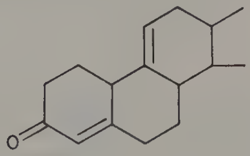
A second conjugated olefinic bond in the molecule will yield a dienone structure. pK_{BH^+} values were reported[109] for three different dienone moieties:



$pK=-2.40$



$pK=-2.80$

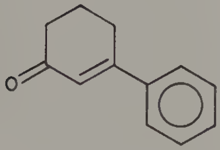


$pK=-2.82$

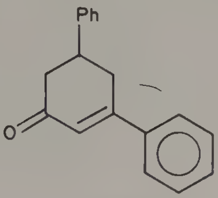
(80)

The linear dienone (**70, 71**) is a stronger base than the parent enone (**12**) by approximately 1.20 pK_{BH^+} unit. This quantity is a summation of two effects: that of the methylene chain, which is base-strengthening, and that of the olefinic bond. A conjugated olefinic bond increases the possibility and efficiency of mesomeric interaction between carbonyl group and substituent. This interaction is weaker in the cross-conjugated dienone (**101**) ($\Delta pK_{BH^+} = 0.8$) and diminishes when conjugation of the olefinic bonds is no longer possible (**80**).

The extension of the unsaturated system through substitution of a phenyl group in the β-position produces a stronger base by 0.5 pK_{BH^+} unit (**28, 35–42** and **43–51**). Phenyl ring substituents R influence basicity in agreement with the Hammett equation. An additional phenyl group at C-5 does not affect the basicity of the carbonyl group at all (**43**).



(28)



(43)

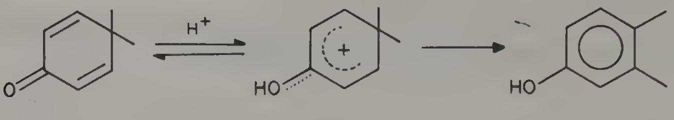
B. Cross-conjugated Enones

Derivatives of cyclohexa-2, 5-dienone including two and more fused rings (e.g. steroids) form a very interesting class of compounds which undergo dienone-phenol rearrangement in acidic media[117]. This reaction has great practical importance in the synthesis of phenolic steroids and other natural products.

Cross-conjugated ketones were shown to have different properties from normal enones. For instance, $\nu_{C=O}$ is shifted to higher values and accompanied by two less intensive and poorly resolved bands. In addition, the carbonyl group of cross-conjugated ketones does not give the reactions characteristic of a C=O group[118]. The distinct difference is, however, the dienone-phenol rearrangement.

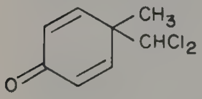
Waring and coworkers[119,120] examined the kinetics of this rearrangement for a number of alicyclic ketones (one or two rings) in sulphuric and perchloric acid. They made use of the protonation equilibrium constant pK_{BH^+} to rationalize the reaction mechanism. Similar work has been done on cross-conjugated steroids[121] and santonines[122].

The cross-conjugated dienone (**104**) protonates to its monocation having the carbonyl oxygen protonated structure (**a**) (hydroxyarenium ion[123]) and then rearranges into the phenol (**b**)[119].

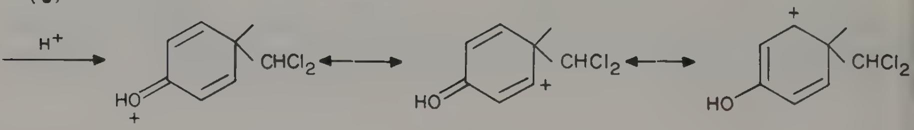


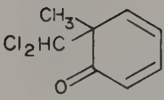
(104) (a) (b)

Some cross-conjugated dienones behave abnormally[124]. 4-Methyl-4-dichloromethylcyclohexa-2, 5-dienone (**c**) and its linear isomer 6-methyl-6-dichloromethylcyclohexa-2, 4-dienone (**d**) could be dissolved in concentrated sulphuric acid and then recovered by dilution with water. These and similar compounds do not undergo the dienone-phenol rearrangement as normal dienones[125]. The UV spectra of these dienones showed considerable changes which can be interpreted as resulting from the formation of delocalized ions.

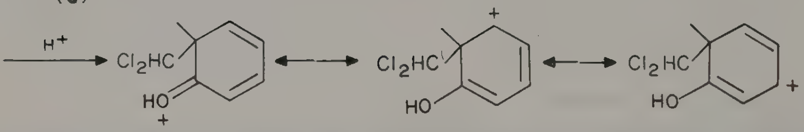


(c)





(d)



Ketones of structure (**c**) showed λ_{max} in neutral solvents in the region of 230 nm, and in concentrated sulphuric acid two bands were present around 270 nm ($\log \varepsilon > 4.0$) and 300 nm ($\log \varepsilon \sim 3.5$). Ketones of structure (**d**) showed λ_{max} in ethanol around 310 nm. However, after protonation in concentrated sulphuric acid two bands were present, one around 250 nm and another around 390 nm. ^{1}H NMR spectra in carbon tetrachloride and concentrated sulphuric acid are consistent with the structures of the dienones and oxygen-protonated species. Unfortunately pK_{BH^+} data were not reported.

The protonation equilibrium of various cross-conjugated enones has been investigated in both sulphuric and perchloric acids by the UV-VIS indicator method[112,120,126]. Three well-separated maxima were found, one characteristic of free base, around 245 nm, and two characteristic of the ion (around 260 and 305 nm). The shorter-wavelength peak of that cation was usually free from solvent effects, but two other peaks were more sensitive towards solvent in more acidic medium.

Most of monocyclic dienones (**103–107, 109, 110**) follow the amide acidity function H_A having an m value close to, but not equal to, unity. Some monocyclic (**108–110**) and bicyclic (**113**) dienones and steroids (**116**) have m values much higher than unity and pK_{BH^+} values much more negative than H_A values at half-protonation. Table 3 shows the available pK_{BH^+} and $H_{A(1/2)}$ data for more than twenty cross-conjugated ketones, the structures of which are shown in Chart 2. In general, cross-conjugated ketones are stronger bases than the appropriate enones by approximately 0.75 ± 0.10 unit[112,126]. (One can compare pairs **104–12, 105–13, 114–53** or **116–57**, for example.)

An α-methyl group (see Table 4) is base-strengthening by about 0.25–0.35 units (compare pairs **110/104** or **114/112**) and a β-methyl group by about 0.45 units (compare **104** with **105, 107** or **117**) due to the σ-inductive effect of alkyl[109]. The experimental fact that an ethyl group is only slightly more active than methyl, by 0.05 units (see **106** and **107**), is in line with an earlier conclusion that stabilization of arenium ions by various alkyls is comparable[128]. This can be supported by σ_F constants[113] of various alkyl groups.

Methyl groups more remote from the enone moiety do not influence pK_{BH^+}, as shown by **104** and **112**. The chain of methylene groups forming a fused ring (**112, 113, 116**) increases the ability of the carbonyl group to be half-protonated in acids of one H_A unit lower acidity. This effect is more pronounced than in enones (0.75 H_A unit). Branches on this methylene chain, as in compounds **112–113** or **116–125**, affect pK_{BH^+} very little.

The remote hydroxyl group in steroid molecules at C-11 (**117, 119, 120, 121**) and the carbonyl group (**125**) decrease basicity by approximately 0.2 pK_{BH^+} unit. Of course more distant hydroxyl groups or keto groups do not affect basicity. In contrast, the close lactone oxygen in santonine (**126**) weakens basicity by 1.3 pK_{BH^+} unit as compared to **112**.

Strongly electronegative substituents, such as fluorine or bromine, affect basicity to a higher degree. 9α-Fluorine in steroids (**122, 123, 124**) decreases basicity as compared to **117** by 0.4 pK_{BH^+} unit, and bromine in **102** weakens basicity of **101** by 2.7 units. Those facts were explained[112] as a consequence of the σ-inductive or field effect which weakens rapidly with distance[113–115] and disappears after 2–3 intervening bonds. Bromine in **102** is located at the α-carbon atom, close to the carbonyl group, and attracts electrons from the conjugated bonds system. Two C—C bonds separate the β-carbon atom and C-9 in steroids; thus such a distance weakens the effect of fluorine.

The effect of the substituent and structure elements on basicity has been rationalized[112] by finding an empirical equation:

$$pK_{BH^+} = -2.80 + \sum \Delta pK_{BH^+} \qquad (24)$$

and increments ΔpK_{BH^+} values. This equation allows us to calculate basicity constants pK_{BH^+} with an accuracy of ± 0.1 unit from a knowledge of the structure itself. No experimental pK_{BH^+} value for the parent dienone, 2,5-cyclohexadienone, has been reported in the literature. The basicity of 4,4-Me$_2$-2,5-cyclohexadienone (**104**) was reported as -2.37[126] and -2.86[127] in later work. The last value agrees with $pK^\circ_{BH^+} = -2.80$ from equation 24. The increments ΔpK_{BH^+} for substituents and structural elements are given in Table 4.

The fact that cross-conjugated ketones may be treated either as derivatives of 2,5-cyclohexadienone or of cyclohexenone (**12**) confirms the uniform nature of substituent and structural effects on the basicity of various cyclic enones.

In addition, pK_{BH^+} values of twelve dienones reported by Waring[116,120,129] follow the Hammett equation

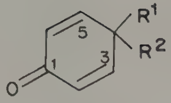
$$pK_{BH^+} = -2.66 \pm 0.12 - 2.32 \sum \sigma^+_{m,p} \qquad (25)$$

Statistically calculated $pK^\circ_{BH^+}$ values in equations 24 and 25 are in close agreement, within experimental error.

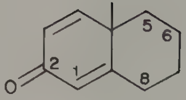
TABLE 3. Basicity data of cross-conjugated dienones

No.	Compound	pK_{BH^+}[a]	Slope[b]	$H_{A(1/2)}$[c]	Ref.
101	4-Me-4-Pr-cyclohexa-2,5-dienone	-2.43 ± 0.12	1.09 ± 0.10		126
		-2.86			127
103	4-Me-4-Et-cyclohexa-2,5-dienone	-2.26 ± 0.10	1.05 ± 0.10		126
104	4,4-Me$_2$-cyclohexa-2,5-dienone	-2.37 ± 0.03	1.03 ± 0.01	-2.37 ± 0.03	126
		-2.85			127, 117
105	3-Me-cyclohexa-2,5-dienone	-2.01 ± 0.03	1.13 ± 0.03	-2.01 ± 0.03	117
106	3-Et-cyclohexa-2,5-dienone	-1.97 ± 0.06	1.12 ± 0.03	-1.97 ± 0.06	117
107	3,5-Me$_2$-cyclohexa-2,5-dienone	-1.38 ± 0.02	1.05 ± 0.03	-1.38 ± 0.02	117
108	2,5-Me$_2$-cyclohexa-2,5-dienone	-1.86 ± 0.04	1.28 ± 0.08	-1.86 ± 0.04	117
109	2,6-Me$_2$-cyclohexa-2,5-dienone	-4.2 ± 0.1	1.86 ± 0.14	-2.93 ± 0.05	120
110	2-Me-cyclohexa-2,5-dienone	-2.7 ± 0.2	1.30 ± 0.08	-2.45 ± 0.07	120
		-2.52 ± 0.1			127
111	4-CHCl$_2$-3,4,5-Me$_3$-cyclohexa-2,5-dienone	-2.31 ± 0.10	1.07 ± 0.02	-2.31 ± 0.10	120
112	10-Me-1(9),3-decalinedien-2-one	-1.93 ± 0.10	1.14 ± 0.07	-1.82 ± 0.07	120
113	8α,10-Me$_2$-1(9),3-decalinedien-2-one	-1.95 ± 0.12	1.50 ± 0.20	-1.68 ± 0.08	120
116	1,4-Androstadien-3,17-dione	-2.10 ± 0.20	1.30 ± 0.05	-1.92 ± 0.08	120
117	11β-Hydroxy-1,4-androstadien-3,17-dione	-2.08 ± 0.05			112
118	17α-Me-17β-OH-1,4-androstadien-3-one	-1.78 ± 0.08			112
119	17α-Me-11β,17β-(OH)$_2$-1,4-androstadien-3-one	-1.96 ± 0.05			112
120	17α-Me-11α,17β-(OH)$_2$-1,4-androstadien-3-one	-1.66 ± 0.05			112
121	11β,17α,21-(OH)$_3$-1,4-pregnandien-3,20-dione	-1.95 ± 0.06			112
122	9α-F-11β,17α,21-(OH)$_3$-1,4-pregnandien-3,20-dione	-2.34 ± 0.06			112
123	9α-F-11β,16,17α,21-(OH)$_4$-1,4-pregnandien-3,20-dione	-2.45 ± 0.06			112
124	9α-F-11β,17α-(OH)$_2$-6α-Me-1,4-pregnandien-3,20-dione	-2.47 ± 0.06			112
125	6α-Me-1,4-androstadien-3,11,17-trione	-2.26 ± 0.06			112
102	2-Br-4-Me-4-Pr-cyclohexa-2,5-dienone	-5.15			127
114	3,10-Me$_2$-1(9),3-decalinedien-2-one	-2.18			122
115	8-Me-1(9),3-decalinedien-2-one	-1.95			122
126	Santonine	-3.10			122

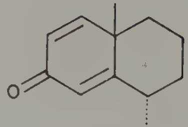
[a] pK_{BH^+} calculated in terms of H_A acidity function.
[b] Slope of $\log[BH^+]/[B]$ vs. H_A.
[c] H_A value at half-protonation.



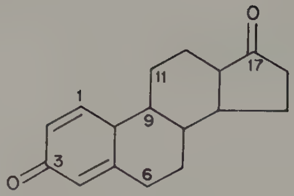
(101—109)



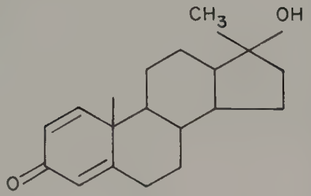
(112)



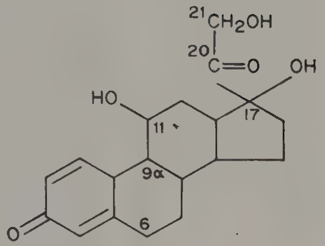
(113)



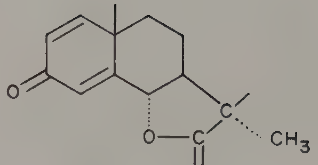
(116)



(118)



(121)

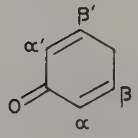


(126)

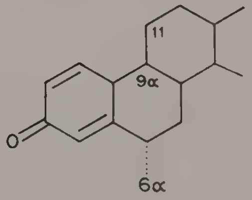
CHART 2

TABLE 4. Values of increments ΔpK for various substituents and structures in cross-conjugated dienones

Substituent or structural element	ΔpK_{BH^+}	Valid for structure
β-Me	~0.30	**A**, **B**
α-Me	~0.50	**A**, **B**
β′-Me	~0.60	**A**, **B**
β-CH_2CH_2—	1.00	**B**
11β-OH	−0.20	**B**
9α-F	−0.40	**B**
α-Br	−2.70	**A**, **B**
11-C=O	−0.30	**B**
6α-Me	−0.10	**B**



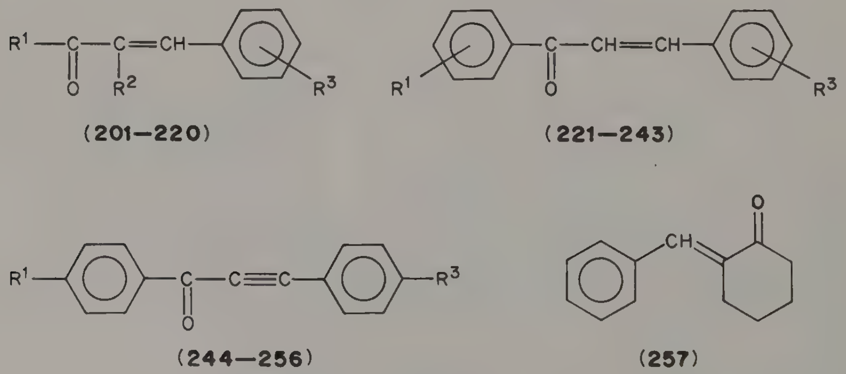
(A)



(B)

C. Alkyl-styryl Ketones

Unsaturated aliphatic ketones substituted by a β-phenyl ring are known as alkyl-styryl ketones (e.g. **201**, Chart 3). The possible variation of substituents R^1, R^2 and R^3 gives compounds with various properties and widely distributed in nature. The general preparative route to this class of compounds is the Claisen–Schmidt condensation of benzaldehyde with ketones[130–132]. The basicity of alkyl styryl ketones[133,134] reported in Table 5 is comparable with the basicity of alkyl-substituted cyclohexenones or aliphatic enones. The magnitude of H_A at half-protonation must be discussed, however. The effect of alkyl substituent R^1 is quite pronounced; larger alkyl groups decrease the basicity by



(201–220) **(221–243)**

(244–256) **(257)**

CHART 3

0.9 pK_{BH^+} unit from Me to Bu^t. A styryl group like R^1 is base-strengthening by more than 1.5 pK_{BH^+} unit (**206**) as a result of increased stabilization by resonance of the resulting ion. Alkyl substituents such as R^2 (**207, 208**) are base-weakening by approximately 0.4 pK_{BH^+} unit.

Basicities of methyl styryl ketones with various substituents R^3 were not reported, but are known for four derivatives (**217–220**) of Bu^t-styryl ketone (**205**). *p*-Substituents affect the basicity in agreement with their electronic properties as described by the Hammett equation. Thus *p*-OMe (**218**) is the strongest, and *p*-NO_2 (**220**) the weakest base in this series. The effects of substituents in the aromatic ring on the relative basicity (measured as $\Delta\nu_{OH}$ of the complex between phenol and the ketone) reflect the properties of the substituent[134,135]. The $\Delta\nu_{OH}$ shift is larger for substituents increasing basicity, and less for substituents of the opposite type. According to Zuckermann and coworkers[135] *s-trans* isomers are more basic than *s-cis*, as reflected by IR spectroscopy. The Hammett equation is satisfied with a correlation coefficient $r > 0.96$.

Also, two-parameter equations (with Swain–Lupton $\mathscr{F}$, $\mathscr{R}$ or Taft σ_I, σ_R) work very well[135].

The effect of substituents in the aromatic ring (R^3) on pK_{BH^+} and on $\Delta\nu_{OH}$ is linear, and follows the equation[134]

$$pK_{BH^+} = 0.062\Delta\nu_{OH} - 17.81 \qquad (r = 0.995,\ n = 10) \tag{26}$$

which is valid also for substituted chalcones (**239–243**). Variation of substituents in phenyl rings yields bases of various strength. The strongest bases have OMe (**240**) or $(OMe)_2$ (**242**) substituents, in agreement with theory.

Chalcone (**221**) is the parent compound of many naturally-occurring compounds. With $pK_{BH^+} = -4.92$[136] it is a base of medium strength comparable with alkyl styryl ketones (**201, 202**). Chalcone and its 2′-hydroxy derivatives (**222–229**) and various 2′-benzyloxy derivatives (**230–238**) were found to follow the Hammett H_0 acidity function[138]. This result solves the ambiguity connected with the dispute whether chalcones are or are not Hammett bases[139]. The $pK_{BH^+} = -4.92$ obtained for chalcone (**221**) is in good agreement with the earlier result[140].

The basicities of *o*-hydroxy- (**222**) and *o*-benzyloxy-chalcone (**230**) are less than that of chalcone by approximately 0.3 pK_{BH^+} unit due to steric hindrance to solvation, and formation of an intermolecular hydrogen bond in (**222**). pK_{BH^+} values of derivatives with various R^3 substituents clearly reflect the electron-accepting or electron-donating property, as described by the Hammett σ constants. The following Hammett equations hold:

$$pK_{BH^+} = -5.07 - 1.10\sigma \qquad (r = 0.93) \tag{27}$$

(for compounds **222–229**)

and

$$pK_{BH^+} = -5.10 - 2.19\sigma \qquad (r = 0.95) \tag{28}$$

(for compounds **230–238**)

Statistically calculated $pK^{\circ}_{BH^+}$ for unsubstituted compounds, -5.07 (**222**) and -5.10 (**230**), are higher by 0.15 pK_{BH^+} unit than the observed values. In both series, compounds (**226, 233**) were excluded from the Hammett plot: the group NMe_2 is much more basic than the carbonyl group and protonates easily. Thus σ_p for this group does not reflect the electron-attracting power of this substituent. Some deviation of both nitro compounds (**229, 238**) may be caused by partial ring closure in sulphuric acid of medium concentration.

The magnitude of ρ clearly shows that the benzyloxy compounds are about twice as sensitive towards substituents as the hydroxy compounds. Intermolecular hydrogen

TABLE 5. Basicity pK_{BH^+} and acidity pK_a of various alkyl and phenyl styryl ketones

Substituents				Basicity				Relative basicity		Acidity	
No.	R^1	R^2	R^3	$-pK_{BH^+}$	Slope	$-H_{A(1/2)}$	Ref.	$\Delta\nu_{OH}$	Ref.	pK_a	Ref.
Alkyl styryl ketones											
201	Me	H	H	4.83 ± 0.08	1.00 ± 0.05	3.33	133	—		21.09 21.65	135 136
202	Et	H	H	4.99 ± 0.07	0.99 ± 0.01	3.40	133	—		—	
203	Pr	H	H	4.80 ± 0.05	1.02 ± 0.01	3.30	133	—		—	
204	Pr^i	H	H	5.29 ± 0.07	1.07 ± 0.06	3.54	133	—		—	
205	Bu^t	H	H	5.72	—		134	197	134	—	
206	CH=CHPh	H	H	3.47	1.00 ± 0.01	2.60	133	258/154	135	—	
207	Me	Me	H	5.28 ± 0.11	1.00 ± 0.01	3.54	133	—	—	—	
208	Me	Et	H	5.22 ± 0.10	1.04 ± 0.07	3.50	133	—	—	—	
209	Me	H	*p*-OMe	—				268/163	135	22.09	135
210	Me	H	*p*-Br	—						21.60	135
211	Me	H	*p*-Cl	—				249/144	135	21.42	135
212	Me	H	*m*-Cl	—						21.37	135
213	Me	H	*m*-Br	—						21.23	135
214	Me	H	*p*-CN	—						20.65	135
215	Me	H	*p*-Me	—				258/156	135	—	
216	Me	H	*p*-NO_2					220/130	135	—	
217	Bu^t	H	*p*-Me	5.39	—		134	200	134	—[f]	
218	Bu^t	H	*p*-OMe	4.75	—		134	208	134	—	
219	Bu^t	H	*p*-Cl	5.90	—		134	194	134	—	
220	Bu^t	H	*p*-NO_2	6.74	—		134	180	134	—	
	Chalcones and other compounds										
221	H		H	4.92			138				
222	*o*-OH		H	5.22 ± 0.03			138				
223	*o*-OH		*p*-OH	4.66 ± 0.04			138				
224	*o*-OH		*p*-OMe	4.58 ± 0.07			138				
225	*o*-OH		*p*-Me	4.85 ± 0.02			138				

226	*o*-OH	*p*-N(Me)$_2$	5.64 ± 0.05			138		
227	*o*-OH	*p*-Cl	5.40 ± 0.03			138		
228	*o*-OH	*p*-Br	5.40 ± 0.03			138		
229	*o*-OH	*p*-NO$_2$	5.80 ± 0.03			138		
230	*o*-OCH$_2$Ph	H	5.28 ± 0.02			138		
231	*o*-OCH$_2$Ph	*p*-OH	4.25 ± 0.02			138		
232	*o*-OCH$_2$Ph	*p*-OMe	4.46 ± 0.02			138		
233	*o*-OCH$_2$Ph	*p*-NMe$_2$	5.55 ± 0.02			138		
234	*o*-OCH$_2$Ph	*p*-F	5.51 ± 0.02			138		
235	*o*-OCH$_2$Ph	*p*-Cl	5.45 ± 0.02			138		
236	*o*-OCH$_2$Ph	*p*-Br	5.30 ± 0.02			138		
237	*o*-OCH$_2$Ph	*p*-COOH	5.75 ± 0.03			138		
238	*o*-OCH$_2$Ph	*p*-NO$_2$	6.85 ± 0.05			138		
239	*p*-Tol	*p*-Me	4.06			135	223	135
240	*p*-An	*p*-Me	3.20			135	236	135
241	*p*-ClC$_6$H$_4$	*p*-Me	5.02			135	207	135
242	*p*-An	*p*-OMe	2.82			135	248	135
243	*p*-An	*p*-Cl	3.97			135	223	135
244	H	H	6.51			141		
245	H	*p*-OMe	6.02			141		
246	H	*p*-Me	6.18			141		
247	H	*p*-Cl	6.82			141		
248	H	*p*-Br	6.90			141		
249	H	*m*-Br	7.14			141		
250	*p*-OMe	H	5.86			141		
251	*p*-Me	H	6.00			141		
252	*m*-Me	H	6.34			141		
253	*p*-Cl	H	6.98			141		
254	*p*-Br	H	6.98			141		
255	*m*-Br	H	7.46			141		
256	*p*-NO$_2$	H	7.77			141		
257	Benzylidene-cyclohexanone		4.55 + 0.08	0.97 ± 0.02	3.14	133		
258	Dibenzylidene-cyclohexanone		4.06 ± 0.07	1.04 ± 0.01	2.90	133		

bonding between a carbonyl group and an *o*-hydroxy group will be the driving force for this phenomenon.

Finally, a collection of $\mathrm{p}K_{\mathrm{BH}^+}$ data for unsaturated ketones with a triple bond was reported[141]. The parent compound (**244**) is a much weaker base than chalcone, by 1.5 $\mathrm{p}K_{\mathrm{BH}^+}$ unit, and its basicity is comparable to acetophenone ($\mathrm{p}K_{\mathrm{BH}^+} = -6.15$[9a] or -6.26[142] in terms of the H_0 acidity function). The experimental $\mathrm{p}K^{\circ}_{\mathrm{BH}^+}$ value (-6.51) is in very good agreement with that calculated from Hammett equations:

$$\mathrm{p}K_{\mathrm{BH}^+} = -6.47 - 2.40\sigma \qquad (r = 0.993) \qquad \text{for various } \mathrm{R}^1 \tag{29}$$

$$\mathrm{p}K_{\mathrm{BH}^+} = -6.48 - 1.69\sigma \qquad (r = 0.995) \qquad \text{for various } \mathrm{R}^3 \tag{30}$$

or

$$\mathrm{p}K_{\mathrm{BH}^+} = 6.473 \pm 0.013 - (2.39 \pm 0.07)\sigma_{\mathrm{R}^1} - (1.69 \pm 0.07)\sigma_{\mathrm{R}^3} \quad (r = 0.997) \tag{31}$$

The effect of substituents on $\mathrm{p}K_{\mathrm{BH}^+}$ is additive, as shown by the two-parameter equation 31, where the terms agree with those of equations 29 and 30.

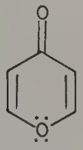
The transmission of the electronic effect of the R^1 substituent is approximately 1.4 times more effective than that of R^3 ($\rho_1/\rho_3 = 2.40/1.69 = 1.42$), and more than reported by Stewart and Yates ($\rho = -2.12$)[9a]. This might be explained by a more effective orbital overlapping between the carbonyl group and the aromatic ring bearing the R^1 substituent. The larger distance between the carbonyl group and the R^3 substituent, as well as the triple bond overlapping with the carbonyl group, must be the key to the weaker interaction. Each of them or both could result in reduced stabilization of the protonated molecule.

Benzylidene cyclohexanone (**257**) and dibenzylidene cyclohexanone (**258**) are bases of medium strength and are stronger than alkyl styryl ketones (**201**–**205**). Their strength is comparable with the basicity of α-alkyl-substituted cyclohexenones. An additional conjugated unsaturated bond is base-strengthening, as expected.

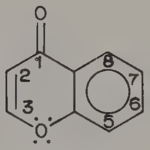
In contrast to the relatively wide interest in the basic properties of alkyl styryl ketones and chalcones, studies of their acidity are very rare[136,137]. Only very few data are available on the acidities of methyl styryl ketones. They are weak acids, as expected. Aromatic ring substituents affect acidity according to their electron accepting or donating ability; however, the relationship between $\mathrm{p}K_{\mathrm{a}}$ and σ is not very good. The experimental data are most probably not very precise and accurate.

D. Pyrone Derivatives

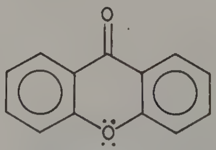
a. γ-Pyrone is a simple compound having a cross-conjugated dienone structure with heterocyclic oxygen (**301**). The heteroatom can be replaced by other atoms such as sulphur or selenium, and the ring may be fused with an aromatic ring to produce chromone (**302**) or



(**301**)

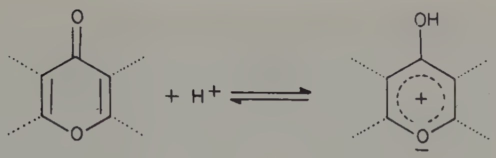


(**302**)



(**332**)

xanthone (**332**). Such structures are frequently found in various natural products. Derivatives of γ-pyrone protonate in acidic solutions producing pyrylium ion.



The UV-absorption spectra are very complicated with 4–6 absorption bands of high intensity. These spectra change with sulphuric acid concentration and allow us to estimate pK_{BH^+}[143] using the H_0 acidity function. Basicity data for a collection of substituted derivatives of γ-pyrone are presented in Table 6.

TABLE 6. Basicity data on γ-pyrone derivatives

No.	R^2	R^3	R^6	R^7	R^8	pK_{BH^+}[a]	Ref.
302 (Chromones)	H	H	H	H	H	−2.05 −2.02 ± 0.02	143 144,53
303 (Chromones)	H	Ph	H	H	H	−1.46 ± 0.01 −1.53	144 146
304 (Chromones)	Ph	H	H	H	H	−2.74 ± 0.02	144
305 (Chromones)	Ph	H	OH	H	H	−2.19 ± 0.09	144
306 (Chromones)	Ph	Me	OH	H	H	−1.94 ± 0.01	144
307 (Chromones)	Ph	Et	OH	H	H	−1.83 ± 0.03	144
308 (Chromones)	Ph	Pr^i	OH	H	H	−1.82 ± 0.03	144
309 (Chromones)	OPh	H	H	H	H	−3.09 ± 0.04	144,145
310 (Chromones)	CHO	H	H	H	H	−3.65 ± 0.04	144
311 (Chromones)	CN	H	H	H	H	−5.64 ± 0.04	144
312 (Chromones)	Me	H	H	H	H	−2.44	144
313 (Thiochromones)	H	H	H	H	H	−1.20	143
314 (Thiochromones)	H	H	Me	H	H	−1.00	143
315 (Thiochromones)	H	H	H	Me	H	−0.98	143
316 (Thiochromones)	H	H	OMe	H	H	−0.82	143
317 (Thiochromones)	H	H	H	OMe	H	−0.80	143
318 (Thiochromones)	H	H	Cl	H	H	−1.62	143
319 (Thiochromones)	H	H	H	Cl	H	−1.58	143
320 (Thiochromones)	H	H	NO_2	H	H	−2.70	143
321 (Thiochromones)	H	H	H	NO_2	H	−2.60	143
322 Salenochromone						−1.46	143
323 (Flavones)	OH	Ph	H	H	H	−2.70	146
324 (Flavones)	H	Ph	H	H	OH	−3.07	146
325 (Flavones)	OMe	Ph	H	H	H	−2.67	146
326 (Flavones)	H	Ph	H	H	OMe	−1.22	146
327 (Flavones)	OH	p-C_6H_4OH	H	H	H	−2.15	146
328 (Flavones)	H	p-C_6H_4OH	H	H	OH	−2.10	146
329 (Flavones)	H	Ph	OH	H	OH	−2.00	146
330 (Flavones)	OH	Ph	H	H	OH	−3.36	146
331 (Flavones)	H	p-C_6H_4OMe	H	H	H	−0.80	146
332 Xanthone						−4.12 −3.24[b]	143 43
333 Thioxanthone						−3.95	143
334 Selenoxanthone						−4.36	143
335 Tetralone						−5.40	114

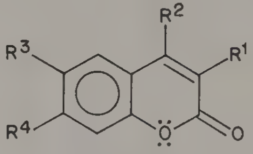
[a] pK_{BH^+} in H_0 units.
[b] pK_{BH^+} in X_0 units (excess acidity).

Chromone (**302**) is a relatively strong base with $pK_{BH^+} = -2.05$ (or -1.75 in terms of the H_A acidity function). Its high basicity results from stabilization of the pyrylium ion structure by the aromatic ring and heterocyclic oxygen. Selenium and sulphur heteroatoms increase the basicity by 0.6 and 0.85 units respectively as a result of lone-pair interaction; however, this is not in relation to their electronegativity[147]. On the other hand, tetralone in which the heteroatom is replaced by a methylene group is a much weaker base with $pK_{BH^+} = -5.40$[116].

Substituents in the aromatic ring (position 6 or 7) change the basicity of the carbonyl group in accord with their electrical properties, as described by the Hammett substituent constants. The position of the substituent in the aromatic ring does not affect pK_{BH^+}.

The second fused aromatic ring in the xanthone series decreases the basicity of the carbonyl group in various degrees. The base-weakening effect in xanthones is not in the same order as in chromones, perhaps due to steric effects caused by the heteroatom in the more rigid xanthone structure.

b. Coumarin (**351**) is an isomer of chromone (**302**) and contains an α-pyrone fragment. Various coumarins are widely distributed natural products and are also used as luminophores in laser production[148]. The basicity of coumarin rings was investigated previously[149,150] in a semi-quantitative manner, and the structure of the protonated species was studied by means of IR[151], ^{13}C NMR[152] and other methods[153].



(**351**)

TABLE 7. Basicity data on substituted coumarins[154]

No.	R^1	R^2	R^3	R^4	$-pK_{BH^+}$	m^a	ν_{OH}	$-pK^b$
351	H	H	H	H	6.82 ± 0.12	1.05 ± 0.09	189	5.77
352	H	CH_3	H	H	5.95 ± 0.10	1.12 ± 0.11	203	5.32
353	H	H	H	CH_3	6.06 ± 0.04	0.97 ± 0.06	200	2.07
354	H	OH	H	H	4.42 ± 0.12	1.25 ± 0.11	—	6.52
355	H	H	H	OH	5.64 ± 0.10	1.10 ± 0.09	—	0.83
356	H	H	H	Br	6.96 ± 0.07	1.07 ± 0.08	180	2.34
357	H	CH_3	H	CH_3	5.44 ± 0.08	1.18 ± 0.12	213	2.71
358	H	CH_3	H	OH	4.42 ± 0.07	1.14 ± 0.07	—	−0.20
359	H	CH_3	H	OCH_3	5.34 ± 0.11	1.23 ± 0.06	216	−0.54
360	H	CH_3	H	Br	6.22 ± 0.15	1.02 ± 0.18	190	2.86
361	CH_3	CH_3	H	OH	4.18 ± 0.14	0.99 ± 0.15	—	−0.86
362	*i*-Pr	CH_3	H	OH	4.45 ± 0.15	0.95 ± 0.18	—	−0.59
363	H	CH_3	H	NH_3^+	7.38 ± 0.03	1.05 ± 0.02	—	9.06
364	H	CH_3	H	$\overset{+}{N}HEt_2$	7.40 ± 0.07	1.13 ± 0.06	—	9.08
365	H	CH_3	OCH_3	H	5.69 ± 0.04	1.01 ± 0.03	215	3.17

[a] The slope of $[BH^+]/[B]$ against H_0.
[b] Basicity in excited state.

Basicity data, pK_{BH^+} in sulphuric acid, are presented for a set of 15 coumarins in Table 7[154]. Unsubstituted coumarin (**351**) is a much weaker base than chromone (**302**), by more than 4 units. Such a strong base-weakening effect may be attributed to the presence of a heterocyclic oxygen next to the carbonyl group and the mesomeric interaction of the aromatic ring through the olefinic bond with the carbonyl group.

β-Substituents (R^2) (**352** and **354**) increase the basicity of the carbonyl group, similarly to simple alicyclic ketones. The base-strengthening effect of a β-methyl group may be seen from comparison of **352** and **357**. An α-methyl group **361** increases the basicity by only 0.22 pK_{BH^+} unit, compared to **358**, in fairly good agreement with alicyclic unsaturated ketones.

Various substituents R^4 in the aromatic ring change the basicity of the carbonyl group in agreement with their electron donor or acceptor properties and the equation:

$$pK_{BH^+} = -5.87 - 1.86\sigma_p \qquad (32)$$

The hydroxy group shows a strong deviation, being more basic than that derived from the Hammett plot. The total effect of R^2 and R^4 substituents may be described by the following equation[154]:

$$pK_{BH^+} = -6.77 - 2.809\sigma^+_{R^4} - 1.575\sigma^+_{R^2} \qquad (r = 0.969,\ n = 10) \qquad (33)$$

in which *para* substituent constants for electrophilic reactions have been used. Agreement between the experimental basicity constants and those derived from regression analysis is very good. Values of m (the slope of $\log[BH^+]/[B]$ against H_0) relatively close to unity mean that the Hammett acidity function H_0 is fairly good for following the protonation of the carbonyl group.

E. Aliphatic Enones

Protonation of aliphatic enones has not been investigated in a systematic way, and only few data were reported. Despite the scarce amount of data, the reported values were evaluated by different researchers by means of various treatments. In a paper by Jensen

TABLE 8. Basicity of aliphatic enones[a]

Compound	pK_{BH^+}	
	in H_2SO_4	in $HClO_4$
3-Buten-2-one	-4.8^b	
3-Methyl-3-buten-2-one	-4.6^b	
3-Penten-2-one	-3.8^b	-3.4^b
3-Methyl-3-penten-2-one	-3.7^b	-3.5^c
4-Methyl-3-penten-2-one	-3.5^e	$-2.9^{b,c}$
(mesityl oxide)	-2.4^f	-2.6^d
4-Phenyl-3-buten-2-one	-3.33^g	
(methyl styryl ketone)		

[a] From Reference 155, unless otherwise indicated.
[b] From the plot of $E_{\lambda_{max}}$ vs. H_A.
[c] From the plot of $\log Q$ vs. H_A.
[d] From the Bunnett–Olsen treatment.
[e] From Reference 42.
[f] From Reference 91.
[g] From Reference 133.

and Thibeault[155] three methods were used to calculate pK_{BH^+}, but not for one compound simultaneously.

The effect of α-methyl groups is base-strengthening by approximately 0.2 pK_{BH^+} unit, in agreement with cyclic enones. A methyl group at the β-carbon increases basicity by 1.0 pK_{BH^+} unit, more than reported for cyclic unsaturated ketones. Two methyl groups increase basicity of the carbonyl group by more than 2 units. Substitution of the β-carbon in the enone moiety with a phenyl group increases the basicity of the enone by 1.5 pK_{BH^+} unit—much more than in cyclic compounds (see Table 8).

This short discussion shows that, as a first approximation, the effect of substituents on basicity is similar to that in cyclic ketones.

F. Acidity of Enones

The C—H acidities of unsaturated ketones were investigated sporadically in alkaline aqueous media, in DMSO or in the gas phase by ion cyclotron resonance[41] or by the flowing afterglow technique[156].

The acidity of a saturated ketone (acetone) has been reported[99] as $\Delta H^\circ_{acid} = 368.8$. Unsaturation as in butenone increases acidity and $\Delta H^\circ_{acid} = 365.2$. The acidity of the α′-deprotonation site in cyclohexenone is similar, but the γ-site is more acidic, as shown by the data of Table 9.

Acidity of the keto tautomers of phenol is higher by approximately 20 kcal mol^{-1}

TABLE 9. Acidity of enones in the gas phase

Compound	ΔH^0_{acid} (kcal mol^{-1})	Ref.
Acetone	368.8	41, 99
Butenone	365.2	41
Cyclohexenone		
α′-site	365.0 ± 5	41
γ-site	360.3	41
4,4-Me_2-cyclohexenone	366.8	41
Acetophenone	363.2	41, 99
2,4-Cyclohexadienone	344 ± 3	156
2,5-Cyclohexadienone	340 ± 2	156

TABLE 10. Acidity of ketones and enones in aqueous media

Compound	pK_a	Ref.
Acetone	19.20	26
Acetylacetone	9.0	26
Cyclopentanone	16.7	26
Acetophenone	19.5	26
Benzylideneacetone	21.65	136
$RCOCH_2CO$-Me	20.17[a]	157
$RCOCH_2COR'$	20.79[a]	157
$RCOCH_2CO$-R′	23.81[a]	157
$ArCOCH_2CO$-Me	22.27[a]	157

[a] As pK^0_a from the Hammett plot.

compared to cyclohexenone as reference, however two different experimental procedures were applied. The cross-conjugated tautomer of phenol is a stronger acid than the linear isomer.

Not enough data exist in order to discuss the influence of structure and substituents on acidity. The following sequence, $CH_3 < CH{=}CH_2 < Ph$, seems to be true, and follows the inductive order of these groups. Also, very few data exist on the acidity of enones in aqueous media (Table 10). Some data on the acidity of alkyl styryl ketones were cited in Table 5, pK_a being in the range of 20.5–22. Recently[157] acidities of various 1,3-diketones were analyzed using the Hammett equation.

The pK_a values indicate a weak acidic character of ketones and enones. However, it is not possible to draw any valuable conclusions because of the very limited data available.

VI. REFERENCES

1. J. N. Brønsted and K. Pedersen, *Z. Phys. Chem.*, **108**, 185 (1924); J. N. Brønsted, *Chem. Rev.*, **5**, 322 (1928).
2. R. G. Pearson and R. L. Dillon, *J. Am. Chem. Soc.*, **75**, 2439 (1953).
3. G. A. Olah, G. K. Surye and M. Saunders, *Acc. Chem. Res.*, **16**, 440 (1983).
4. P. Ahlberg, G. Jönsell and C. Engdahl, *Adv. Phys. Org. Chem.*, **19**, 223 (1983).
5. G. A. Olah, Y. Halpern, Y. K. Mo and G. Liang, *J. Am. Chem. Soc.*, **94**, 3554 (1972).
6. K. Müllen, E. Kotzman, H. Schnieckler and B. Frei, *Tetrahedron Lett.*, **25**, 5623 (1984).
7. (a) K. Yates and R. Stewart, *Can. J. Chem.*, **37**, 664 (1959).
   (b) K. Yates and H. Wai, *Can. J. Chem.*, **43**, 2132 (1965).
   (c) M. R. Sharif and R. I. Zalewski, *Bull. Polon. Acad. Sci., Ser. Sci. Chem.*, **29**, 385 (1981).
8. (a) R. Stewart and M. R. Granger, *Can. J. Chem.*, **39**, 2508 (1961); R. Stewart and K. Yates, *J. Am. Chem. Soc.*, **82**, 4059 (1960).
   (b) R. I. Zalewski, *Bull. Polon. Acad. Sci., Ser. Sci. Chem.*, **20**, 853 (1972).
   (c) E. Dawidziak, J. Niedbała and R. I. Zalewski, *Bull. Polon. Acad. Sci., Ser. Sci. Chem.*, **26**, 75 (1975).
   (d) Z. Geltz, H. Kokochińska, R. I. Zalewski and T. M. Krygowski, *J. Chem. Soc., Perkin Trans. 2*, 1069 (1983).
9. (a) R. Stewart and K. Yates, *J. Am. Chem. Soc.*, **80**, 6355 (1958).
   (b) A. Levi, G. Modena and G. Scorrano, *J. Am. Chem. Soc.*, **96**, 6585 (1974).
   (c) M. Azzaro, J. F. Gal and S. Geribaldi, *J. Org. Chem.*, **47**, 4981 (1982).
10. P. Bonvicini, A. Levi, V. Lucchini, G. Modena and G. Scorrano, *J. Am. Chem. Soc.*, **95**, 5960 (1973); G. Perdoncin and G. Scorrano, *J. Am. Chem. Soc.*, **99**, 6983 (1977).
11. (a) R. A. Cox, L. M. Druet, A. E. Klausner, T. A. Modro, P. Wan and K. Yates, *Can. J. Chem.*, **59**, 1568 (1981).
    (b) K. Yates and J. B. Stevens, *Can. J. Chem.*, **43**, 529 (1965).
12. (a) N. C. Marziano, G. M. Cimino and R. C. Passerini, *J. Chem. Soc., Perkin Trans. 2*, 1975 (1973).
    (b) R. A. Cox and K. Yates, *Can. J. Chem.*, **62**, 2155 (1984).
13. L. P. Hammett, *Chem. Rev.*, **16**, 67 (1935).
14. E. M. Arnett and G. W. Mach, *J. Am. Chem. Soc.*, **88**, 1177 (1966); R. H. Boyd, *J. Am. Chem. Soc.*, **85**, 1555 (1963).
15. R. A. Cox and K. Yates, *Can. J. Chem.*, **61**, 2225 (1983).
16. R. P. Bell, Preface to, *The Proton in Chemistry*, 2nd edn., Methuen, London, 1973.
17. R. I. Zalewski, A. Y. Sarkice and Z. Geltz, *J. Chem. Soc., Perkin Trans. 2*, 1059 (1983).
18. C. C. Perrin, *J. Am. Chem. Soc.*, **86**, 256 (1964).
19. N. C. Marziano, P. G. Traverso, A. Tomasin and R. C. Passerini, *J. Chem. Soc., Perkin Trans. 2*, 309 (1977).
20. (a) R. A. Cox and K. Yates, *Can. J. Chem.*, **59**, 2116 (1981).
    (b) R. A. Cox and K. Yates, *J. Am. Chem. Soc.*, **100**, 3861 (1978).
21. J. F. Bunnett and F. P. Olsen, *Can. J. Chem.*, **44**, 1899, 1917 (1966).
22. A. Bagno, G. Scorrano and R. A. More O'Ferrall, *Rev. Chem. Intermed.*, **7**, 313 (1987).
23. E. R. Malinowski, R. A. Cox and U. Haldna, *Anal. Chem.*, **56**, 778 (1984).

24. R. A. Cox, U. Haldna, K. L. Idler and K. Yates, *Can. J. Chem.*, **59**, 2591 (1981).
25. R. A. Cox, *J. Am. Chem. Soc.*, **96**, 1059 (1974).
26. For review see: J. R. Jones, *Prog. Phys. Org. Chem.*, **9**, 241 (1971); and *The Ionization of Carbon Acids*, Chap. 4, Academic Press, London, 1973.
27. G. Schwarzenbach and R. Sulzberger, *Helv. Chim. Acta*, **27**, 348 (1944); J. Verdu and F. Pereda, *An. Quim.*, **76**, 261 (1980); G. Yagil, *J. Phys. Chem.*, **71**, 1034 (1967).
28. D. Dolman and R. Stewart, *Can. J. Chem.*, **45**, 911 (1967).
29. G. Yagil and M. Anbar, *J. Am. Chem. Soc.*, **85**, 2376 (1963).
30. M. Eigen and L. de Mayer, *Proc. R. Soc. London, Ser. A*, **247**, 505 (1958).
31. R. Stewart, *Quart. Rep. Sulphur Chem.*, **3**, 99 (1968).
32. B. G. Cox and P. T. McTigue, *Aust. J. Chem.*, **20**, 1815 (1967); J. Keuttemma and J. J. Lindberg, *Suomen Kemistilehti*, **B 33**, 98 (1960).
33. F. G. Bordwell and M. J. Bausch, *J. Am. Chem. Soc.*, **108**, 1979 (1986); A. N. Talvik, *Org. React.*, **9**, 233 (1972).
34. J. T. Edward, M. Sjöström and S. Wold, *Can. J. Chem.*, **59**, 2350 (1981).
35. N. Heinrich, W. Koch, G. Frenking and H. Schwarz, *J. Am. Chem. Soc.*, **108**, 593 (1986).
36. R. I. Zalewski and G. E. Dunn, *Can. J. Chem.*, **47**, 2263 (1969).
37. R. I. Zalewski and S. Geribaldi, *J. Chem. Soc., Perkin Trans. 2*, 113 (1987).
38. M. Tanabe and D. F. Crowe, *J. Chem. Soc., Chem. Commun.*, 564 (1973).
39. A. G. Schultz and D. S. Kashdan, *J. Org. Chem.*, **38**, 3814 (1973).
40. J. M. Gruber and G. M. Rubottom, *J. Org. Chem.*, **42**, 1051 (1977).
41. J. E. Bartmess and J. P. Kiplinger, *J. Org. Chem.*, **51**, 2173 (1986).
42. R. I. Zalewski and G. E. Dunn, *Can. J. Chem.*, **46**, 2469 (1968).
43. R. A. Cox and K. Yates, *Can. J. Chem.*, **62**, 2155 (1984).
44. V. Luccini, G. Modena, G. Scorrano, R. A. Cox and K. Yates, *J. Am. Chem. Soc.*, **104**, 1958 (1982).
45. C. D. Johnson and B. Stratton, *J. Org. Chem.*, **51**, 4100 (1986).
46. A. Ebber, U. L. Haldna and A. Murshak, *Org. React.*, **23**, 40 (1986).
47. R. A. Cox and R. Stewart, *J. Am. Chem. Soc.*, **98**, 488 (1976).
48. R. A. Cox, R. Stewart, M. J. Cook, A. R. Katritzky and R. D. Tack, *Can. J. Chem.*, **54**, 900 (1976).
49. T. J. Hannigan and W. J. Spillane, *J. Chem. Soc., Perkin Trans. 2*, 851 (1982).
50. J. Toullec, *Adv. Phys. Org. Chem.*, **18**, 1 (1982).
51. H. Hart, *Chem. Rev.*, **79**, 515 (1979).
52. R. P. Bell and P. W. Smith, *J. Chem. Soc.* (*B*), 1518 (1966).
53. M. Novak and G. M. London, *J. Org. Chem.*, **42**, 2494 (1977).
54. J. P. Guthrie and P. A. Cullimore, *Can. J. Chem.*, **57**, 240 (1979).
55. P. Haspra, A. Sutter and J. Wirz, *Angew. Chem., Int. Ed. Engl.*, **18**, 617 (1979).
56. C. F. Bernasconi and P. Paschalis, *J. Am. Chem. Soc.*, **108**, 2969 (1986).
57. Y. Chiang, A. J. Kresge and Y. S. Tang, *J. Am. Chem. Soc.*, **106**, 460 (1984).
58. Y. Chiang, A. J. Kresge and J. Wirz, *J. Am. Chem. Soc.*, **106**, 6392 (1984).
59. F. G. Bordwell, J. E. Bartmess and J. A. Hantala, *J. Org. Chem.*, **43**, 3095 (1978).
60. E. M. Arnett and G. Scorrano, *Adv. Phys. Org. Chem.*, **3**, 83 (1976).
61. E. M. Arnett, *Prog. Phys. Org. Chem.*, **1**, 223 (1963).
62. R. A. Cox and K. Yates, *Can. J. Chem.*, **59**, 1560 (1981).
63. L. A. Flexer, L. P. Hammett and A. Dingwall, *J. Am. Chem. Soc.*, **57**, 2103 (1935).
64. A. R. Katritzky, A. J. Waring and K. Yates, *Tetrahedron*, **19**, 465 (1963).
65. C. T. Davies and T. A. Geissman, *J. Am. Chem. Soc.*, **76**, 3507 (1954).
66. R. Stewart and K. Yates, *J. Am. Chem. Soc.*, **82**, 4059 (1960).
67. J. T. Edward, M. Sjöstörm and S. Wold, *Can. J. Chem.*, **59**, 2350 (1981); J. T. Edward and S. C. Wong, *J. Am. Chem. Soc.*, **99**, 4229 (1977).
68. R. L. Reeves, *J. Am. Chem. Soc.*, **88**, 2240 (1966).
69. R. I. Zalewski, *J. Chem. Soc., Perkin Trans. 2*, 1639 (1979).
70. E. R. Malinowski and D. G. Hoovery, *Factor Analysis in Chemistry*, Wiley–Interscience, New York, 1980.
71. E. R. Malinowski, *Anal. Chim. Acta*, **134**, 129 (1982); F. J. Knorr and J. H. Futrell, *Anal. Chem.*, **51**, 1236 (1979).

72. U. L. Haldna and K. E. Laaneste, *Org. React.*, **3**, 61 (1966).
73. H. J. Campbell and J. T. Edward, *Can. J. Chem.*, **38**, 2109 (1960).
74. E. M. Arnett, R. P. Quirk and J. J. Burke, *J. Am. Chem. Soc.*, **92**, 1260 (1970).
75. R. A. McClelland and W. F. Reynolds, *Can. J. Chem.*, **54**, 718 (1976).
76. (a) W. H. Lawtone and E. A. Sylwestre, *Technometrics*, **13**, 617 (1971).
    (b) T. Blasffert, *Anal. Chim. Acta*, **161**, 135 (1984).
    (c) A. Gustavasson and J. E. Sundquist, *Anal. Chim. Acta*, **167**, 1 (1985).
77. (a) A. Meister, *Anal. Chim. Acta*, **161**, 149 (1984); *J. Theor. Biol.*, **94**, 541 (1982).
    (b) D. J. Legett, *Anal. Chem.*, **49**, 276 (1977).
78. R. I. Zalewski and D. Nitschke, *in preparation.*
79. R. I. Zalewski, *unpublished work.*
80. J. T. Edward, J. B. Leane and I. C. Wang, *Can. J. Chem.*, **40**, 1521 (1962).
81. E. Grunwald, A. Loewenstein and S. Meiboom, *J. Chem. Phys.*, **27**, 641 (1957).
82. G. C. Levy, J. D. Cargoli and W. Racella, *J. Am. Chem. Soc.*, **92**, 6238 (1970).
83. A. R. Butler, *J. Chem. Soc., Perkin Trans. 2*, 959 (1976).
84. A. R. Butler and H. A. Jones, *J. Chem. Soc., Perkin Trans. 2*, 963 (1976).
85. G. A. Olah, M. Calin and D. H. O'Brien, *J. Am. Chem. Soc.*, **89**, 3586 (1967).
86. L. D. McKeever, R. Waack, M. A. Doran and E. B. Baker, *J. Am. Chem. Soc.*, **91**, 1057 (1969).
87. G. A. Olah and M. Calin, *J. Am. Chem. Soc.*, **90**, 938 (1968).
88. (a) G. H. Olah and M. Calin, *J. Am. Chem. Soc.*, **90**, 4672 (1968).
    (b) J. B. Lambert and S. M. Wharry, *J. Chem. Soc., Chem. Commun.*, 172 (1978).
89. N. C. Deno and M. J. Wisotsky, *J. Am. Chem. Soc.*, **85**, 1715 (1963).
90. S. Hoshino, H. Hosoya and S. Nagakura, *Can. J. Chem.*, **44**, 1961 (1966).
91. E. M. Arnett, R. P. Quirk and J. W. Larsen, *J. Am. Chem. Soc.*, **92**, 3977 (1970).
92. E. M. Arnett, T. C. Moriarty, L. E. Small, J. P. Rudolph and R. P. Quirk, *J. Am. Chem. Soc.*, **95**, 1492 (1973).
93. C. D. Ritchie and R. E. Uschold, *J. Am. Chem. Soc.*, **90**, 2821 (1968); **89**, 1721 (1967).
94. J. F. Gal, L. Elegant and M. Azzaro, *Bull. Soc. Chim. Fr.*, 427 (1976).
95. J. F. Gal, C. Calleri, L. Elegant and M. Azzaro, *Bull. Soc. Chim. Fr.*, 311 (1979).
96. J. F. Gal and D. G. Morris, *J. Chem. Soc., Perkin Trans. 2*, 431 (1978).
97. M. Azzaro, J. F. Gal, S. Geribaldi, *J. Org. Chem.*, **47**, 4981 (1982).
98. M. Azzaro, J. F. Gal, S. Geribaldi, A. Gree-Luciano and C. Calleri, *J. Chem. Res. (S)*, 134 (1979).
99. J. F. Bartmess, J. A. Scott and R. T. McIver jr., *J. Am. Chem. Soc.*, **101**, 6046, 6056 (1979).
100. (a) J. F. Bartmess and R. T. McIver, jr., *J. Am. Chem. Soc.*, **99**, 4163 (1977).
    (b) M. J. Pellerile and J. I. Braumann, in *Comprehensive Carbanion Chemistry*, Part A (Eds. E. Buncell and T. Dust), Chap. 2, Elsevier, Amsterdam, 1980.
101. (a) J. F. Wolf, R. W. Shaley, I. Koppel, M. Taagepera, R. T. McIver jr., J. L. Beauchamp and R. W. Taft, *J. Am. Chem. Soc.*, **99**, 5417 (1977).
    (b) T. V. Craige, G. Klass, J. H. Bowie and A. I. Blair, *J. Chem. Res. Synop.*, 386 (1980).
102. G. Bondroux and R. Harriet, *Tetrahedron Lett.*, **25**, 5755 (1984).
103. R. Breslow and J. Altman, *J. Am. Chem. Soc.*, **88**, 504 (1966).
104. R. Breslow, J. Altman, A. Krebs, E. Mahooni, I. Murata, R. A. Peterson and J. Posner, *J. Am. Chem. Soc.*, **87**, 1326 (1965).
105. D. Bostwick, H. F. Henneike and H. P. Hopkins, jr., *J. Am. Chem. Soc.*, **97**, 1505 (1975).
106. R. Breslow, T. Eicher, A. Krebs, R. A. Peterson and J. Posner, *J. Am. Chem. Soc.*, **87**, 1320 (1965).
107. R. I. Zalewski, *Bull. Polon. Acad. Sci., Ser. Sci. Chem.*, **18**, 353 (1970).
108. V. D. Orlov, R. I. Zalewski and V. H. Trojan, *Ukr. Khim. Zh.*, **45**, 1093 (1979).
109. R. I. Zalewski and G. E. Dunn, *Can. J. Chem.*, **48**, 2338 (1970).
110. J. Shorter, *Correlation Analysis of Organic Reactivity*, Research Studies Press, Plenum Press, London 1982.
111. T. M. Krygowski and R. I. Zalewski, MATCH Communications in Mathematical Chemistry (*submitted*).
112. H. Kokocińska and R. I. Zalewski, *Bull. Polon. Acad. Sci., Ser. Sci. Chem.*, **25**, 915 (1977).
113. W. F. Reynolds, *Prog. Phys. Org. Chem.*, **14**, 165 (1983).
114. R. D. Topsom, *Acc. Chem. Res.*, **16**, 292 (1983).
115. A. M. Aissani, J. C. Baum, R. F. Langler and J. L. Ginsburg, *Can. J. Chem.*, **64**, 532 (1986).
116. R. I. Zalewski, *Zesz. Nauk. Akad. Ekon.* N^0 51 *Poznaniu*, 3 (1973).

117. K. L. Cook and A. J. Waring, *J. Chem. Soc., Perkin Trans. 2*, 84 (1973).
118. A. Smoczkiewicz, R. I. Zalewski and H. Podkowińska, *Wiad. Chem.*, **21**, 311 (1965); A. A. Forist, *Anal. Chem.*, **31**, 913 (1959).
119. K. L. Cook and A. J. Waring, *J. Chem. Soc., Perkin Trans. 2*, 88 (1973).
120. M. J. Hughes and A. J. Waring, *J. Chem. Soc., Perkin Trans. 2*, 1043 (1974).
121. H. Kokocińska and R. I. Zalewski, *Bull. Polon. Acad. Sci., Ser. Sci. Chem.*, **27**, 575 (1979).
122. A. J. Waring, *J. Chem. Soc., Perkin Trans. 2*, 373 (1984).
123. K. L. Cook, M. J. Hughes and A. J. Waring, *J. Chem. Soc., Perkin Trans. 2*, 1506 (1972).
124. H. Budzikiewicz, *Tetrahedron Lett.*, 12 (1960).
125. E. C. Friedrich, *J. Org. Chem.*, **33**, 413 (1968).
126. J. W. Pilkington and A. J. Waring, *J. Chem. Soc., Perkin Trans. 2*, 1349 (1976).
127. A. J. Waring, *J. Chem. Soc., Perkin Trans. 2*, 1029 (1979).
128. D. M. Brouver and J. A. van Dorn, *Recl. Trav. Chim. Pays-Bas*, **89**, 88 (1970).
129. J. W. Pilkington and A. J. Waring, *Tetrahedron Lett.*, 4345 (1973).
130. O. S. Tee and N. R. Iyengar, *J. Am. Chem. Soc.*, **107**, 455 (1985).
131. W. S. Emerson, G. H. Birum and R. I. Louley, *J. Am. Chem. Soc.*, **75**, 1312 (1953).
132. J. B. Bentley, K. B. Everard, R. Marsden and L. E. Sutton, *J. Chem. Soc.*, 2959 (1949).
133. R. I. Zalewski and Z. Geltz, *Zesz. Nauk. Akad. Ekon. Poznaniu*, 62 (1978).
134. D. Beanpera, J. P. Seguin and J. P. Doucet, *C.R. Acad. Sci. Paris, Ser. C*, **276**, 1123 (1973).
135. L. A. Kutulja, L. P. Pivovarevitsh, Ju. H. Surov, L. M. Samonovskij and S. V. Zuckerman, *Zh. Org. Khim.*, **11**, 2094 (1975).
136. S. T. Hamdi, J. R. Jones and T. G. Rumney, *J. Chem. Soc., Perkin Trans. 2*, 846 (1976).
137. A. Kaukaanpera, P. Salomaa, L. Oinonen and M. Mattsen, *Finn. Chem. Lett.*, 25 (1978).
138. E. R. David, G. B. Szabo, M. Rakosi and Gy. Litkei, *Acta Chim. (Budapest)*, **94**, 57 (1977).
139. L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill, New York, 1970; E. Hogfeldt and J. Bigeleisen, *J. Am. Chem. Soc.*, **82**, 15 (1960); R. G. Dowing and D. E. Pearson, *J. Am. Chem. Soc.*, **83**, 1718 (1961).
140. S. V. Zuckerman, L. A. Kutulja, V. M. Nikitschenko and V. F. Lavroushin, *Zh. Obshch. Khim.*, **33**, 3181 (1963).
141. Ja. P. Striabin, V. C. Pisareva and S. P. Kopschunov, *Zh. Org. Khim.*, **13**, 788 (1977).
142. C. C. Greig and C. D. Johnson, *J. Am. Chem. Soc.*, **90**, 6453 (1968).
143. I. Degani, R. Fochi and G. Spunta, *Bollettino Scientifico della Facolta di Chimica Industriale, Bologna*, **26**, 3 (1968).
144. M. Zsuga, T. Nagy and V. Szabo, *Magy. Kem. Foly.*, **86**, 108 (1980).
145. M. Zsuga, V. Szabo, F. Korodi and A. Kios, *Acta Chim. Acad. Sci. Hung.*, **101**, 73 (1979).
146. Ju. L. Frolov, Ju. M. Sapozhnikov, K. B. Petrushenko and F. C. Lure, *Izv. Acad. Sci. SSR, Ser. Khim.*, 1888 (1977).
147. A. L. Alhwed and E. G. Rochov, *J. Inorg. Nucl. Chem.*, **5**, 264 (1958).
148. C. V. Shank and A. Dienes, *Appl. Phys. Lett.*, **17**, 189 (1970).
149. G. J. Jekatan, R. J. Junean and S. G. Schulman, *Anal. Chem.*, **44**, 1044 (1972).
150. O. Welfbeis, *Z. Phys. Chem.*, **125**, 15 (1980).
151. M. E. Perlson, V. P. Zwoliński and Ju. N. Scheinker, *Zh. Prikl. Spektrosk.*, **16**, 544 (1972).
152. S. A. Sojka, *J. Org. Chem.*, **40**, 1175 (1975); G. A. Olah and A. T. Ku, *J. Org. Chem.*, **35**, 3916 (1970).
153. I. V. Sokolova and L. I. Loboda, *Zh. Strukt. Khim.*, **23**(6), 35 (1982).
154. O. A. Ponomariev, E. R. Vasina, S. N. Jarmolenko and V. G. Mischina, *Zh. Obshch. Khim.*, **55**, 179 (1985).
155. J. L. Jensen and A. T. Thibeault, *J. Org. Chem.*, **42**, 2168 (1977).
156. C. S. Shiner, P. E. Vorduam and S. R. Kass, *J. Am. Chem. Soc.*, **108**, 5699 (1986).
157. M. N. Kabatschnik and T. A. Mastrinkova, *Zh. Obshch. Khim.*, **55**, 713 (1985).

The Chemistry of Enones
Edited by S. Patai and Z. Rappoport

CHAPTER 10

Nucleophilic attacks on enones

DANIÈLE DUVAL* and SERGE GÉRIBALDI*
Laboratoire de Chimie Physique Organique, Université de Nice, Parc Valrose, 06034 Nice Cedex, France

---

*We dedicate this chapter to our fathers

I. INTRODUCTION

A knowledge of the parameters that govern chemical reactions and their control is of paramount importance to the chemist striving to devise synthetic strategies, and aiming at the synthesis of the desired product, with the best possible yield and with the correct stereochemistry.

This chapter treats the vast field of nucleophilic attacks on enones. Our purpose is not to give an exhaustive account of the numerous reactions between nucleophilic agents and enonic systems, nor to discuss the advantages of the alternative models of the reaction mechanisms. Rather we review the most recent works on the subject, with the aim of defining the parameters that govern both the regio- and stereochemistry of nucleophilic attacks, in the widest sense, on typical ambident electrophiles: enones and enals.

II. FORMATION OF A CARBON–CARBON BOND FROM NUCLEOPHILIC ADDITIONS OF ORGANOMETALLIC COMPOUNDS

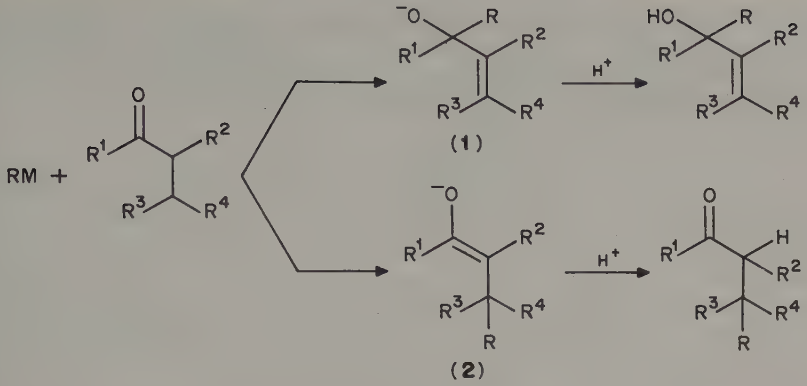
The most frequently met nucleophilic attack, and the synthetically most useful, on α,β-unsaturated aldehydes (enals) and ketones (enones) or quinones, is the addition of organometallic compounds in the widest sense, in which a new carbon–carbon bond is formed.

Considering the multiplicity of substrates and reagents, we will discuss the preparative aspects only to a minor extent and shall emphasize the mechanistic aspects, particularly the regioselectivity of these reactions, that has been developed in the last few years. Enals and enones behave as ambident electrophiles, as a consequence of the delocalization of the electron density in the C=C—C=O system. The additions of organometallic reagents (RM) can therefore proceed via two pathways: addition to the carbon atom of the carbonyl group $C_{(1)}$ [$C_{(1)}$ attack] or to the carbon involved in the double bond $C_{(3)}$ [$C_{(3)}$ attack]. This results in the formation of either oxy-anions of alcoholate type **1** or of enolate type **2**, which then generally leads to the addition of a proton (equation 1) and/or to an elimination (Knoevenagel, Darzens and Wittig type reactions, cyclopropanation or 2,3-dihydrofuran formation[1]).

The stabilization of oxy-anions of type **1** results in the formation of the products of the 1,2-addition to enals or enones (to the carbonyl group), while stabilization of oxy-anions of type **2** results in the formation of 1,4-addition (to the ethylenic bond) (Michael-type addition).

Regioselectivity of nucleophilic additions to enones and enals has been extensively studied[2], and theoretical interpretations have been proposed in terms of the Klopman theory[3]. Simply stated, reactions at $C_{(1)}$ are under charge control (hard site), while reactions at $C_{(3)}$ are under frontier control (soft site)[4–7]. Indeed, examination of the wide field of experimental results obtained with nucleophilic reagents RM under kinetic control reveals general trends[8]. Organometallic reagents can be divided into two classes:

(i) Those in which the metal is directly bound to the nucleophilic centre: (a) organoalkali



(1)

metal derivatives (particularly organolithium reagents) in which M^+ is a hard cation prefer 1,2- over 1,4-additions[9,10]; (b) organocadmium, cuprates and palladium compounds lead to the attack of $C_{(3)}$; (c) organomagnesium and organoaluminium compounds show an intermediate behaviour and undergo both 1,2- and 1,4-additions.

(ii) Those in which the metal is not bound to the nucleophilic centre but in which the nucleophile reacts with enals or enones through its carbon atom (e.g. alkaline enolates): (a) loose enolate–M^+ ion pairs, in which the cation is free to be eventually complexed by the α-enone, imply a major attack on the carbon of carbonyl group; (b) tight enolate–M^+ ion pairs give an intermediate behaviour.

In fact, a delicate balance exists between the different interactions which favour 1,2- versus 1,4-addition. The nature of the products formed and the ratio of the $C_{(1)}$ and $C_{(3)}$ adducts depend on: (a) the nature and geometry of the organic part of the organometallic compound (number, nature and bulkiness of the substituents on the carbanionic centre), (b) the nature of the cationic counterpart, (c) the nature of the electrophilic partner (enals, enones or quinones) and particularly the relative steric hindrance around the carbonyl carbon and the β-ethylenic carbon, and (d) the experimental conditions used (solvent, temperature, presence of additives).

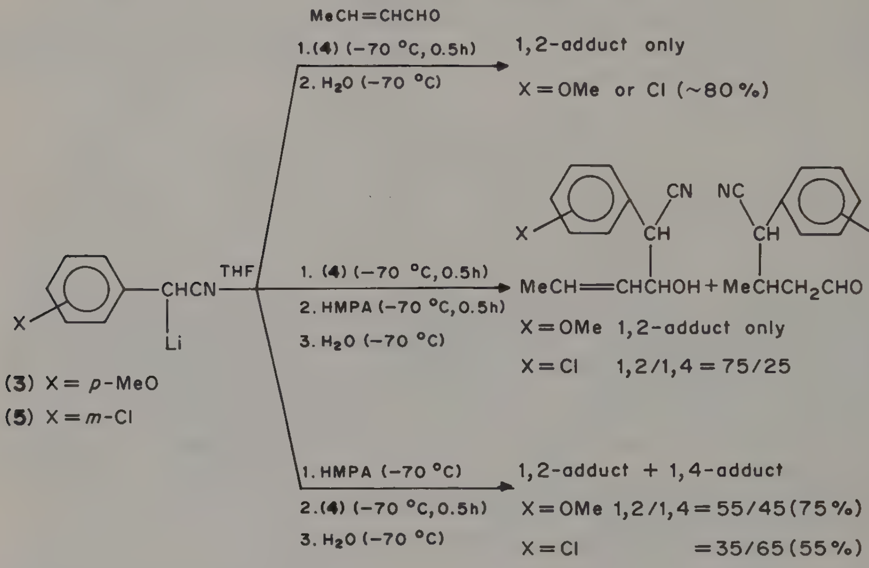
Any interpretation and predictions are all the more difficult, because reversibility of some of the reactions makes it difficult to assess whether the products are formed directly or after equilibration.

For each class of 'organometallic reagents', we collected typical examples from the large variety of experimental and theoretical results described in the literature in the last 10–15 years and discussed them from the standpoint of the influence of the above factors on the mode of addition.

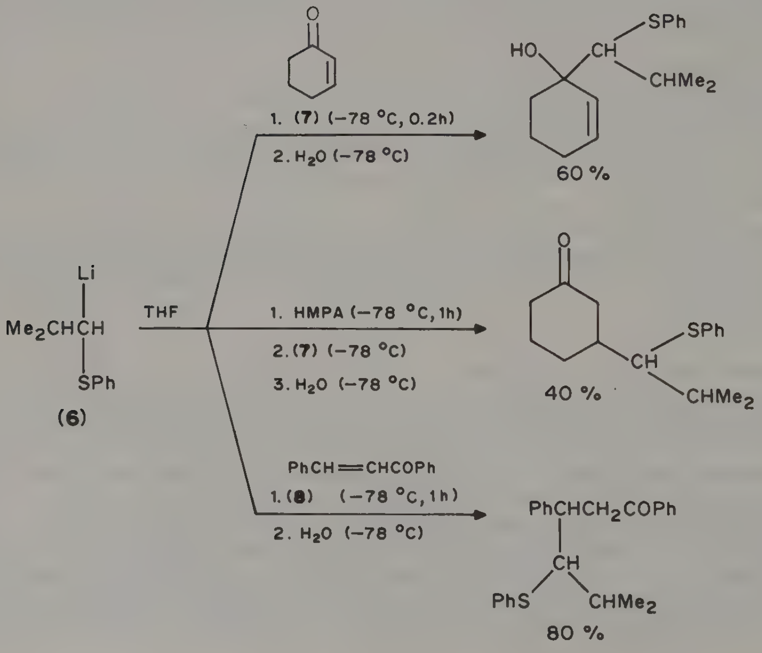
A. Organo Alkali Metal Reagents

A large variety of organo alkali metal reagents, mainly organolithiums, react with enals, enones and quinones and, as expected, all possibilities, including formation of the pure $C_{(1)}$ or $C_{(3)}$ adduct to a mixture of both, have been encountered, depending on the nature of the reactants and the reaction conditions[11–13].

Among organometallics, organo alkali metal reagents are perhaps those for which the regioselectivity of addition is the most dependent upon the above factors. This is exemplified by some results of Seyden-Penne and coworkers[14,15]. Whereas 1,4-addition is observed only under kinetic control between lithiated *p*-methoxyphenylacetonitrile (**3**) and crotonaldehyde (**4**) (equation 2), 1,4-addition is observed under thermodynamic control when the closely related lithiated *m*-chlorophenylacetonitrile (**5**) is substituted for the *p*-methoxy substituted reagent (equation 2). In contrast, 1-lithio-1-phenylthio-2-methylpropane (**6**), which needs HMPA to add 1,4 to cyclohexenone (**7**) at – 78 °C, reacts 1,4 with chalcone (**8**) in THF at the same temperature (equation 3).



(2)



(3)

The theory of generalized perturbation applied to reactivity has been important for the development of the understanding of the regioselectivity of additions of organoalkali reagents to enals and enones.

Assuming that the transition state is reactant-like and that complexation phenomena do not exist, 1, 2-addition should result from charge control (predominant coulombic term), whereas 1, 4-addition results from frontier orbital control (energy gap control or matrix element control interaction). Under charge control, 1, 2-addition is favoured as the total charge on the nucleophilic centre is greater. Under frontier energy gap control, dominant 1, 4-addition is expected when the HOMO energy level of the reagent is high. Under matrix element (overlap control) ($H^2_{\mathrm{LU,HO}}$) a large proportion of 1, 4-adduct is expected if this term has a high value. For a given reagent, an increase of frontier orbital control is expected if the $C_{(1)}$ positive charge on the substrate and/or the LUMO energy level decreases and/or the $C_{(3)}$ coefficient in LUMO increases[16]. These considerations provide an interpretation for the differences between the modes of reaction of charge-localized anions **9**[17–20] and charge-delocalized anions **10**–**12**[16,20–26] with α-enones.

$$\underset{(\mathbf{9})}{R\bar{C}XY} \qquad \underset{(\mathbf{10})}{Ph\bar{C}XY} \qquad \underset{(\mathbf{11})}{X\bar{C}HCO_2R'} \qquad \underset{(\mathbf{12})}{(EtO)_2PO\bar{C}RX}$$

$R = H$ or Me, $X = CN$ or CO_2R', $Y = H$ or Cl

For instance, when a comparison is made between the calculated parameters of chalcone, *p*-methoxychalcone and benzalacetone, and the proportions of 1, 2- and 1, 4-adducts formed after 30 min reaction at 20 °C and *t*-BuOK as base under kinetic control with phosphonoester **13**, phosphononitrile **14** and phosphine oxide **15** (Table 1)[24], it appears that the greater the charge delocalization on the anionic reagent, the greater the frontier control and the more favoured $C_{(13)}$ attack: the ester reagent **13** gave more $C_{(3)}$ attack than nitrile **14**; the phosphine oxide **15** gave more $C_{(3)}$ attack than **14** and, in fact, even more than **13**. Only benzalacetone has a relatively high total charge q_1 on the carbon of the carbonyl group. It is also the only ketone which gave substantial amounts of dienes resulting from a Wittig-type reaction. Chalcone and *p*-methoxy chalcone both have lower carbonyl q_1 and LUMO levels: carbonyl attack is less favoured and $C_{(3)}$ attack is more important.

$$\underset{(\mathbf{13})}{(EtO)_2POCH_2CO_2Et} \qquad \underset{(\mathbf{14})}{(EtO)_2POCH_2CN} \qquad \underset{(\mathbf{15})}{Ph_2POCH_2CN}$$

TABLE 1. Certain characteristics of enones and experimental results obtained with the anions derived from **13**–**15**[24]

Enone	E_{LUMO}[a]	q_1[a]	$C_{(3)}$[a]	Reagent	Yield (%)	
					1, 4-adduct	1, 2-adduct
PhCH=CHCOPh	−0.132	+0.30	0.513	**13**	90	<2
				14	70	<5
(p-MeOC$_6$H$_4$)CH=CHCOPh	−0.183	+0.25	0.503	**13**	90	<2
				14	60	10
PhCH=CHCOMe	−0.226	+0.38	0.563	**13**	35	15
				14	30	55
				15	40	<2

[a] Calculation by the Hückel method.

TABLE 2. Characteristics of anionic reagents α to nitrile and experimental results obtained with 2-cyclohexenone[21,23,28]

Anion	Geometry[a]	q_c^{tot} [a]	E_{HO}(eV)[a]	C_c^{2p} [a]	C_c^{2s} [a]	$C_{(1)}$ attack	$C_{(3)}$ attack
$[CH_2CN]^-$	pyramidal	−0.398	2.50	0.801	0.403	≥95	5
	planar	−0.391	2.94	0.823	—		
$[ClCHCN]^-$	pyramidal	−0.240	0.95	0.753	0.471	≥95	5
	planar	−0.252	1.69	0.814	—		
$[PhCHCN]^-$	planar	−0.251	1.66	0.709	—	≤5	95
$[PhC(Cl)CN]^-$	planar	−0.130	0.90	0.708	—	≤5	95
$[(HO)_2P(O)CHCN]^-$	planar	−0.461	1.20	0.787	—	≤5	95[b]

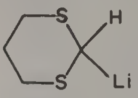
[a] Total charge density (σ + π) and HOMO parameters (energy level E_{HO} and orbital atomic coefficients on anionic carbon C_c) calculated for the more stable geometry of anions, from a STO-3G basis set[28].

[b] Experimental results for $[(EtO)_2P(O)CHCN]^-$ [24–26]

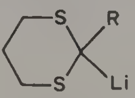
Reactions with phosphorylated anions are also a good example of the limits of the use of Klopman's theory to rationalize the regioselectivity. When the additions of anions derived from **13** and **14** are extended to other 3-aryl and 3-alkyl substituted α-enones such as crotonophenone, 3-buten-2-one, cyclohexenone or 3-methylcyclohexenone, it is not possible to correlate $C_{(3)}$ reactivity with the LUMO characteristics of these α-enones. This has been interpreted in terms of the relative position of the transition states, which should involve rehybridization of the α-enone moiety with π energy loss of the system associated with steric factors for $C_{(3)}$ disubstituted compounds[25,27]. In the same way, all attempts to correlate the characteristics obtained by *ab initio* calculations for anionic reagents α to the nitrile group and experimental results of their attacks on cyclohexenone under kinetic control in conditions where electrophilic participation of the cation or ion pairing with the anion are not important, are at the least hazardous as is shown in Table 2.

The proportions of 1, 2- and 1, 4-additions cannot be interpreted (at least for these reagents) by taking into account only the attractive charge and frontier interactions. The repulsive terms between nucleophile and electrophile occupied orbitals must be considered. If the nucleophile contains many occupied orbitals and if the carbanion centre is sp^2 hybridized, 1, 4-addition will be strongly favoured. If the carbanion centre is pyramidal, 1, 2-addition predominates in spite of the fact that calculations show only a trend towards this process[28].

The importance of the repulsive terms and steric factors is exemplified by results obtained under kinetic control with the lithiated derivatives of 1, 3-dithiane (**16**) and 2-substituted-1, 3-dithiane (**17**) with enals and enones (Table 3). In THF or THF–HMPA, conjugate addition is more favoured for **17** (R = Ph) than for **16** due to repulsive interactions between occupied orbitals of the nucleophiles and electrophiles: these interactions, more important for **17** than **16**, and on $C_{(1)}$ more than on $C_{(3)}$, lead to an increase of $C_{(3)}$ addition for **17**. When the substitution on $C_{(3)}$ increases, the proportion of 1, 4-adduct decreases, and even in THF–HMPA the 1, 4-addition of **17** to 3-methylbutenal is low[29,30]. On the other hand, repulsive interactions on $C_{(1)}$ should be weaker for enals than for α-enones. Hence, the 1, 2-addition is favoured in the former case[9].



(16)



R = Me, $SiMe_3$, Ph

(17)

TABLE 3. Addition of reagents **16** and **17** (R = Ph) to enals[29]

Enal	Solvent	Reagent	$C_{(1)}$ attack	$C_{(3)}$ attack
MeCH=CHCHO	THF	**16**	>95	<5
	THF	**17**	65	35
	80:20 THF–HMPA	**16**	55	45
	80:20 THF–HMPA	**17**	<5	>95
PhCH=CHCHO	THF	**16**	>95	<5
	THF	**17**	85	15
	80:20 THF–HMPA	**16**	75	25
	80:20 THF–HMPA	**17**	35	65
Me_2C=CHCHO	THF	**16**	>95	<5
	THF	**17**	>95	<5
	80:20 THF–HMPA	**16**	>95	<5
	80:20 THF–HMPA	**17**	65	35
CH_2=CMeCHO	THF	**16**	>95	<5
	THF	**17**	65	35
	80:20 THF–HMPA	**16**	45	55
	80:20 THF–HMPA	**17**	<5	>95

These results also show the major influence of media having large dissociating and basic powers upon the regioselectivity of organoalkali additions to enones and enals. Thus, under kinetic control, the presence of a cosolvent such as HMPA or DMPU (1,3-dimethyl-2-oxohexahydropyrimidine) generally promotes conjugate addition to a significant extent, as exemplified by results obtained with lithiated derivatives **16** and **17** and cyclohexenone (Table 4).

The very important influence of solvents on the mode of addition of nucleophiles to enals and enones has been frequently noted and efficiently exploited[11,13,22,34]. It has been explained only recently by considering the effect of the cation counterpart on the regioselectivity of addition[35]. Briefly, the reagent can exist in two forms according to the nature of the ions and the media: solvent-separated ion pairs (loose ion pairs) and close (contact) ion pairs (tight ion pairs). In the first case, the carbanion interacts only weakly with the alkali counterion, so that a complex can be formed between the cation and the

TABLE 4. Addition of 2-lithio-1,3-dithianes to 2-cyclohexenone in various media

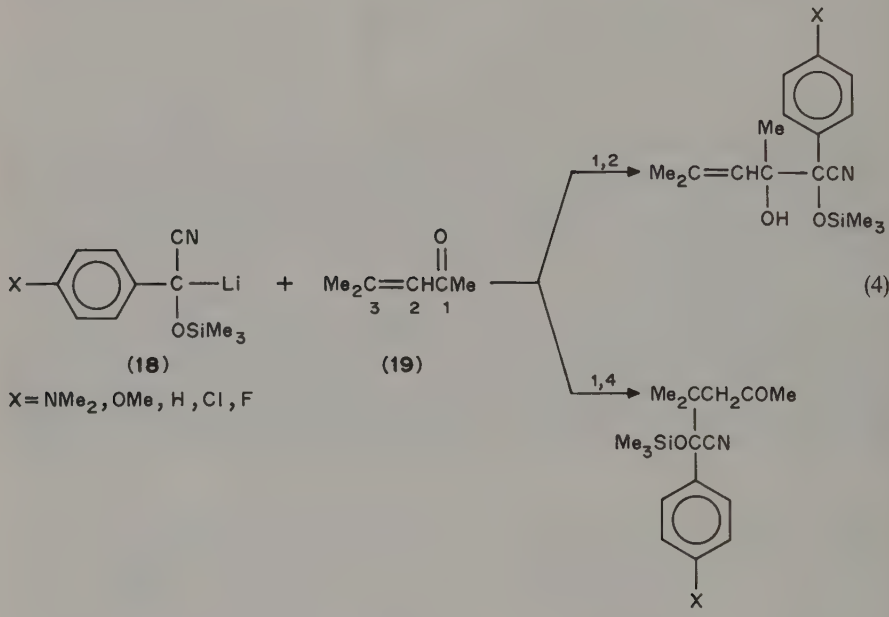
Reagent	Solvent and additive (eq.)[a]	$C_{(1)}$ attack	$C_{(3)}$ attack	Overall yield (%)	Ref.
16	THF	98	2	90	31
16	THF–HMPA (1 eq.)	8	92	76	32
16	THF–HMPA (2eq.)	5	95	—	33
16	THF–DMPU (4 eq.)	8	92	70	31
17 (R = Me)	THF–Hexane (1:1)[b]	>99	0	—	33
17 (R = Me)	THF–HMPA (1 eq.)	8	92	70	32
17 ($R = SiMe_3$)	THF–Hexane (1:1)[b]	>99	0	—	33
17 ($R = SiMe_3$)	THF–HMPA (2 eq.)	3	97	—	33

[a] eq. = equivalent = mmol/mmol of dithiane.

[b] (1:1) = 50% THF, 50% Hexane.

oxygen of the carbonyl group. The stability of the complex increases as the Lewis acid character of the cation increases ($Li^+ > Na^+ > K^+$). Thus, the reactions involving Li^+ seem to be the most interesting ones, because the cation is able to give stable complexes with the carbonyl group as well as to interact more or less strongly with the nucleophile. The complex formation increases the electrophilicity of the carbonyl group by increasing the charge on the $C_{(1)}$ atom and by decreasing the energy level of its LUMO, which favours regioselective attack at $C_{(1)}$ under charge control as much as under frontier orbital control. The complexation control also implies electrophilic assistance by the cation for both attacks at $C_{(1)}$ and $C_{(3)}$ depending on the nature of nucleophile and substrate. In the case of tight ion pairs, the nucleophile interacts strongly with the counterion (lithium) and the latter, which interacts only weakly with the oxygen of the carbonyl group, forms an associated species. Ion-pair association reduces the nucleophilicity of the carbanion by decreasing the charge on the nucleophile and the energy level of its HOMO, and then promotes the attack by nucleophiles on the $C_{(3)}$ atom.

The influence of solvation is strikingly manifested in the reactions between the trimethylsilyl ethers of *para*-substituted benzaldehyde cyanohydrins **18** and mesityl oxide (**19**)[36–38] (equation 4).



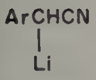
(4)

(**18**) (**19**)

X = NMe$_2$, OMe, H, Cl, F

Regioselectivity depends upon the nature of the *para*-substituent and consequently upon the 'hardness' of nucleophiles in a given solvent; it also depends on the solvent. For instance, with **18** (X = H), under conditions of kinetic control a mixture of products of addition to $C_{(1)}$ and $C_{(3)}$ is formed rapidly and irreversibly in THF, in DME or in a mixture of these solvents whereas, in ether, only the addition to the C=C bond is observed. This was explained by assuming that ether promoted the conversion of the loose ion pairs of the reagent into tight ion pairs[36–39]. The accompanying decrease of the negative charge on the carbanionic centre is responsible for the preferential attack on the $C_{(3)}$ atom, despite the decrease in the energy of the HOMO of the nucleophile[13].

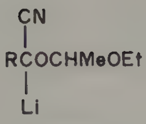
An interesting example of cation counterpart effect associated with the solvent effect is the change of rates of conjugate addition of lithiated arylacetonitriles (**20**) or of cyanohydrin ethers **21** to α-enones[21,23,40–43] and bicyclic α, γ-dienones[44]. For instance, the addition of **20** (Ar = Ph) to 3, 5, 5-trimethyl-2-cyclohexen-1-one (isophorone) for 1 min at −70 °C gives 45% of 1,4-addition in THF and 10% in 4:1 THF–HMPA[21,23]. By contrast, the conjugate 1,6-addition of **20** and **21** to α, γ-dienones **22** or **23** is performed in considerable yield only in the presence of HMPA. In the former case, complexation between Li^+ and the carbonyl group of isophorone in THF induces electrophilic assistance for $C_{(3)}$ attack, because $C_{(1)}$ attack is sterically inhibited due to the interaction between the phenyl ring and the *gem* dimethyl groups. In THF–HMPA, the complexation is unlikely, since Li^+ is strongly solvated in HMPA, therefore the electrophilic assistance is suppressed. In the latter case, the 1,6-addition requires anionic activation and the solvation of Li^+ allows the nucleophilic attack, owing to the decrease of anion–cation interaction[44].



$\underset{\text{Li}}{\text{ArCHCN}}$

(20)

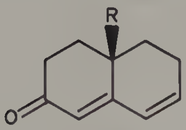
Ar=Ph
or p-MeOC$_6$H$_4$



$\overset{\text{CN}}{\underset{\text{Li}}{\text{RCOCHMeOEt}}}$

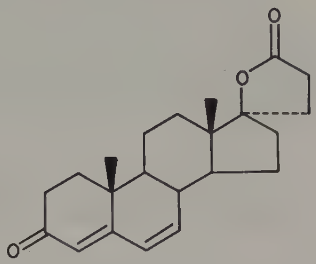
(21)

R=Ph or CH=CHMe



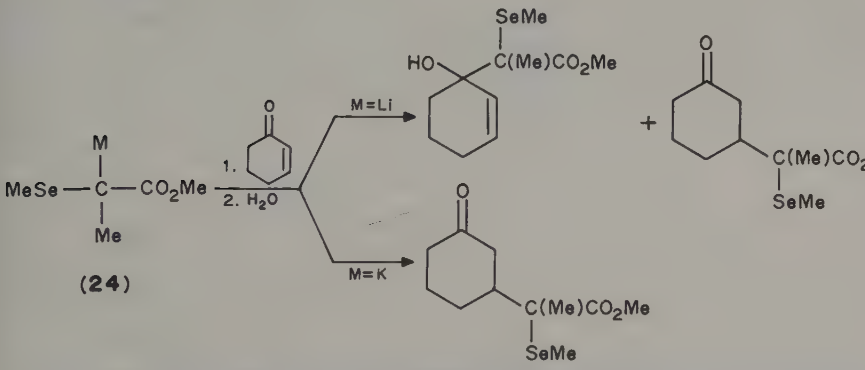
(22)

R=H or Me



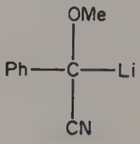
(23)

The complexation of the carbonyl group depends strongly on the Lewis acid character of the metallic cation. The methyl 1-lithio-1-methyl selenopropionate (**24**) (M = Li) reacted with 2-cyclohexenone in THF at −78 or −110 °C for 12 min to give after hydrolysis a mixture of both the $C_{(1)}$ and C(3) adducts in a ratio of 70:30 and in 75% overall yield. Under similar conditions the potassium derivative **24** (M = K) gives exclusively the $C_{(3)}$ adduct in 79% yield[45] (equation 5).



(5)

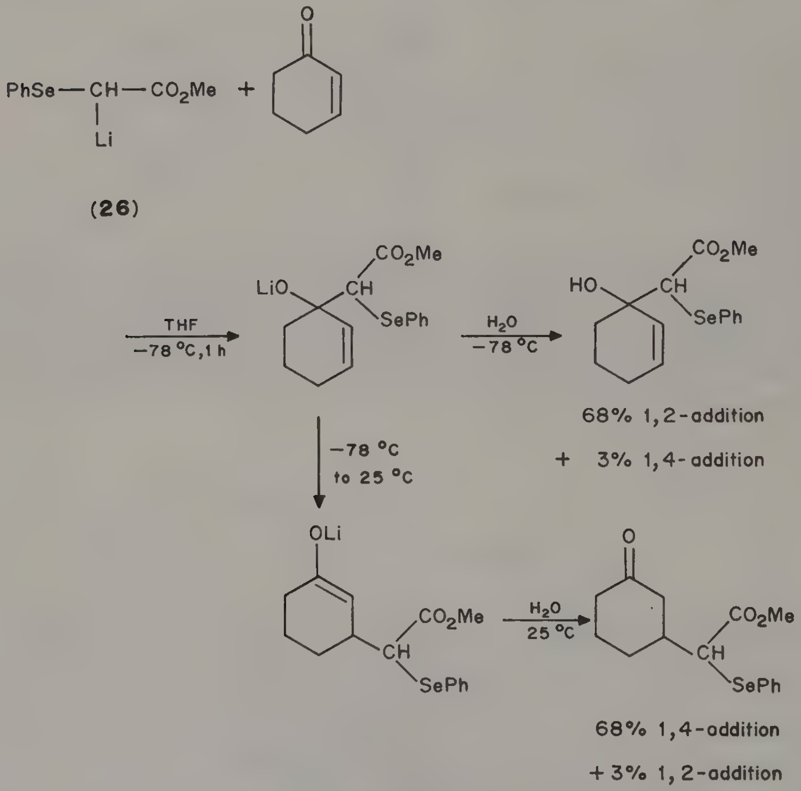
The structure of the reagent can itself affect the complexation effect of cations when a chelation between the cation and a basic group of the reagent is possible. This is the case of the lithiated cyanohydrin ether **21** (R = Ph) in which the two oxygens can chelate the lithium cation, unlike its homologue **25**. So, **25** leads to a mixture of 1, 2- and 1, 4-adducts with isophorone in THF under kinetic control, whereas only 1, 4-addition is observed with **21**. The greater bulk of **21** also favours the conjugate addition[46].



$$\mathrm{Ph{-}\overset{\displaystyle OMe}{\underset{\displaystyle CN}{C}}{-}Li}$$

(25)

In conclusion, except for rare particular cases of reverse effect[9,47], 1, 4-additions to enals and enones are favoured under kinetic control by using highly polar aprotic solvents such as HMPA. Moreover, 1, 4-additions can also be realized with or without HMPA at higher temperature under thermodynamic control[11,21,46,48–51] as exemplified by the reaction of methyl 1-lithio-1-selenophenyl acetate (**26**) with 2-cyclohexenone (equation 6)[51].



(6)

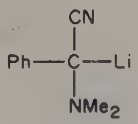
This equilibration, due to the reversibility of the 1, 2-adduct formation, is observed with carbanions quite well stabilized and/or delocalized (high HOMO) and can formally occur

TABLE 5. Influence of temperature on the mode of addition of 1-lithio-1-phenyl-1,3-dithiane **17** to 2-cycloheptenone and 2-butenal

Substrate	Method	$C_{(1)}$ attack	$C_{(3)}$ attack	Overall yield (%)	Ref.
2-Cycloheptenone	THF, −78 °C for 10 min, quench	90	10	100	49
	THF, −78 to 25 °C for 1 h, quench	0	100	86	49
2-Butenal	THF, −70 °C for 30 min, quench	35	65	75	30
	THF–HMPA, −70 °C for 30 min, quench	95	5	80	30
	THF, −70 to 20 °C for 2 h, quench	35	65	70	30

in a cage of solvent or via the existence of two completely independent moieties[11]. Reversibility is highly substrate-dependent. For instance, the 2-lithio-2-phenyl-1,3-dithiane (**17**) (R = Ph) leads exclusively to the 1,4-adduct of cycloheptenone in THF when the temperature is raised from −78 to 25 °C[49], whereas no change of the 1,2/1,4 ratio is observed when the reaction is carried out at high temperature with enals[30] (Table 5). The latter case can be explained by the higher stability of secondary alcoholates versus tertiary ones[52–54]. In the other instances, when the metallated enolate formed by 1,4-addition is sterically hindered, an increase in temperature leads to a decrease in the yield of conjugate addition, due to retro-Michael reactions[46]. Lastly, an increase in the reaction temperature in order to favour the 1,4-adduct can also result in the decomposition of the starting reagent[55].

Because the carbonyl-counterion complexation effect can in principle participate in the mode of addition of organoalkali reagents to enones and enals[35], Lewis acids can be used when the nucleophilic additions are very sensitive to the degree of substitution of electrophiles. The changes in the yields and in the regioselectivity of additions depend upon the nature of the reagent and substrate and upon the experimental conditions[36,56–58]. For instance, both 1,2- and 1,4-additions of the lithiated derivative of α-dimethylaminophenylacetonitrile (**27**) to 3-methyl-2-cyclohexenone, isophorone[59] and mesityl oxide are accelerated in THF using BF_3–Et_2O, Ti(OPr-*i*)$_4$ and $ZnCl_2$ as additives; 1,2-addition and 1,4-addition are observed under kinetic control and thermodynamic control, respectively. The increase in 1,2-addition is easily explained if the carbonyl–Lewis acid complexation decreases the repulsive interactions due to the carbonyl lone pairs[28]. The strongly favoured 1,4-addition results from (i) a stabilization of the enolate species[60], (ii) structural modifications of the nucleophilic reagent and (iii) a decrease in the activation energy of the 1,4-addition[59]. With the same enones, LiBr is quasi-ineffective[59] suggesting the existence of a complexation between the carbonyl group and the lithium cation of the loose ion pair **27** in THF. On the other hand, adding $ZnCl_2$ to the reaction mixture of lithiated arylacetonitriles **20** and mesityl oxide results in a strong increase of 1,2-addition[56].

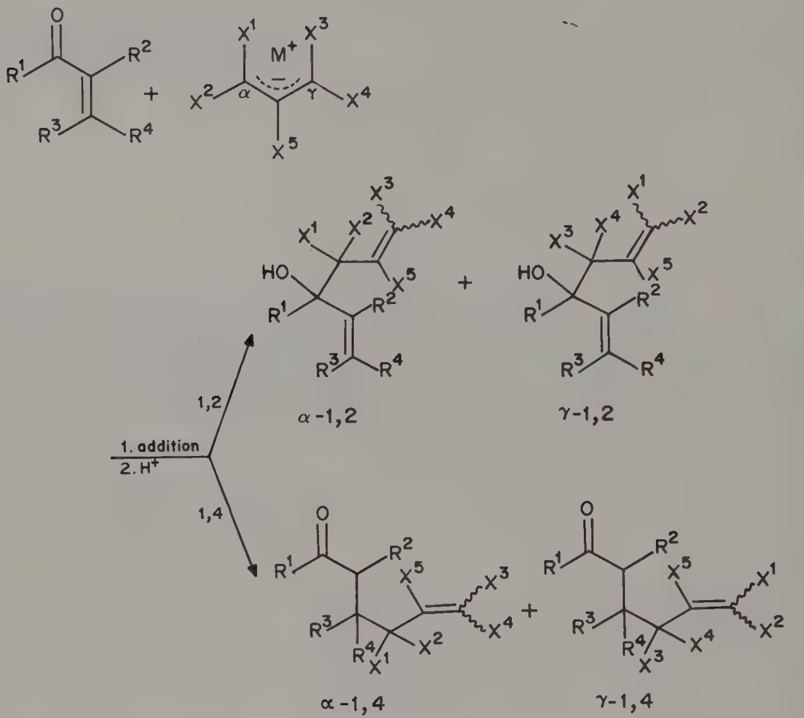


$$\mathrm{Ph{-}\overset{\displaystyle CN}{\underset{\displaystyle NMe_2}{C}}{-}Li}$$

(27)

Predictions based on regioselectivity are more difficult when the organoalkali reagents are ambident nucleophiles. This is because anions not only present the usual concern for

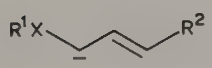
1,2- versus 1,4-reactivity, but also raise the added problem of α versus γ addition (equation 7).



(7)

A third aspect, namely the geometrical isomerism of substituents, comes into play simultaneously when the ambident nucleophile is highly substituted[61–64].

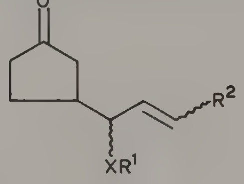
The mode of reaction is influenced by the nature of substituents bound to the allylic moiety. In a series of reagents containing sulphur, the carbanions **28** and **29** derived from allylic sulphides[65,66] and sulphones[67–70] undergo kinetically controlled conjugate addition to 2-cyclopentenone in THF at −78 °C in the presence of HMPA to give the allylic sulphides **31**[65,66] and sulphones **32**[63,69]. The sulphoxide derivative **30** gives the vinylic sulphoxide **33**[71–74], arising from reaction through the γ position of **30**. In addition, **33** was obtained as a single geometric isomer possessing the (*E*) configuration[63,71].



(28) X=S

(29) X=SO$_2$

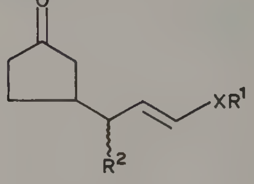
(30) X=SO



α-1,4

(31) X=S

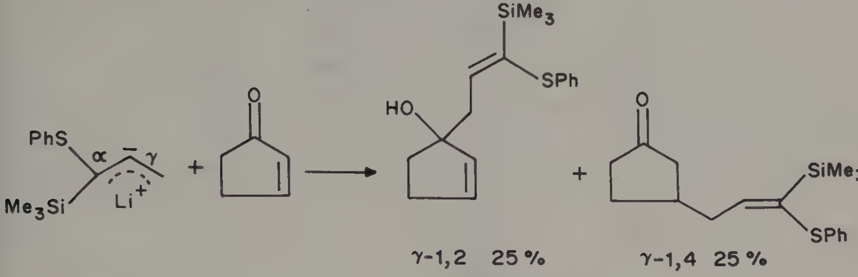
(32) X=SO$_2$



γ-1,4

(33) X=SO

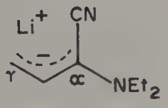
The addition of the 1-phenylthio-1-trimethylsilyl-2-propene lithiated derivative (**34**) to 1-cyclopentenone in THF–HMPA at − 78 °C furnishes a 50:50 mixture of γ-1, 2 and γ-1, 4 adducts, **35** and **36** respectively (equation 8)[75].



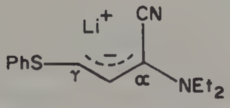
(8)

(34) **(35)** **(36)**

Steric factors on the substrates also play a significant role. For instance, the anion **37** formed from the α-diethylamino-2-butenonitrile and LDA in THF gives products resulting from the attack of the γ-carbon atom of **37** on α-enones. 2-Cyclohexenone, 2-cyclopentenone or methyl vinyl ketone yields only γ-1, 4 addition products, while α, β- or β, β-disubstituted enones such as isophorone or carvone lead to a mixture of γ-1, 2 and γ-1, 4 adducts. However, yields of 1, 4-adducts can be increased by allowing the 1, 2-kinetic products to equilibrate[76]. In the same way, the highly hindered reagent **38** also adds exclusively 1, 4 (α to SPh, γ to CN) across the conjugate systems of cyclopentenone and cyclohexenone in THF when the temperature is raised from − 50° to 0 °C over a period of 2 h[77].



(37)



(38)

An interesting example of a change in regioselectivity of the reaction as the solvent composition is altered or the counterion modified is provided by the reaction of

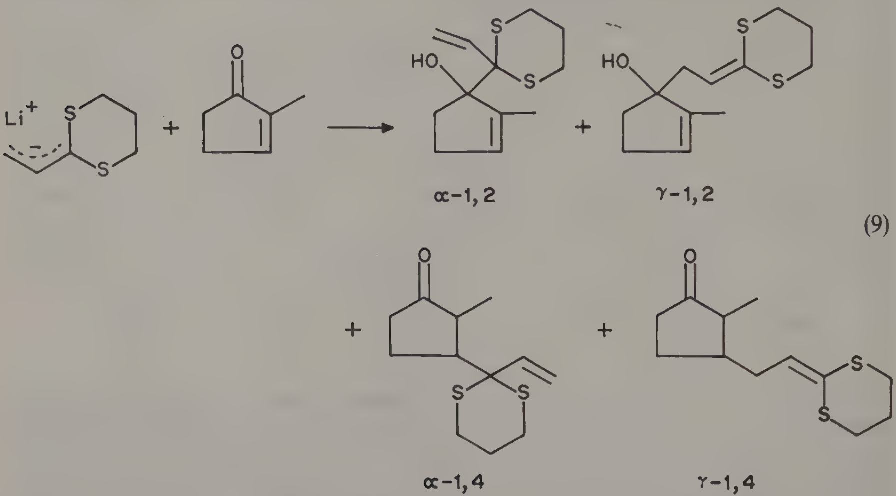
TABLE 6. Addition of 2-ethylidene-1, 3-dithiane anion to 2-methyl-2-cyclopentenone under various conditions[79]

Solvent and additive	Composition of reaction products (%)			Overall yield (%)
	α-1, 2 + γ-1, 2	α-1, 4	γ-1, 4	
THF	24	16	60	82
THF, CuI·(MeO)$_3$P[a]	0	98	2	54
THF, HMPA[b]	0	100	0	66

[a] 1.5 equivalent of CuI·(MeO)$_3$P.

[b] 3 equivalents of HMPA.

2-methylcyclopentenone with the carbanion generated by treating 2-ethylidene-1,3-dithiane with LDA (equation 9)[78,79]. The results are summarized in Table 6.



(9)

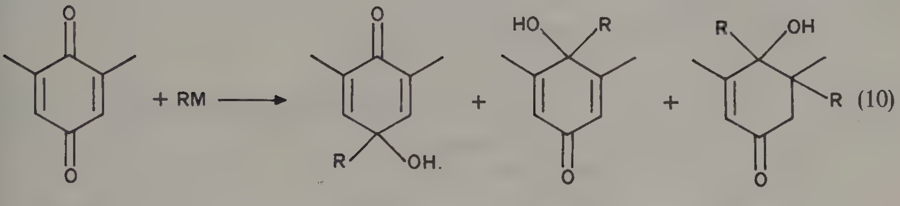
In this example, 1,4-addition predominates over 1,2-addition. Of the 1,4-addition products, γ-addition predominates when the lithium counterion is employed in THF. The increased amount of γ-1,4 adduct formed upon warming (from −78 to 25 °C) arises from an alkoxy-Cope rearrangement[61,80,81]. The preference for γ-1,4 selectivity can be effectively reversed by treating the lithium anion with 3.0 equivalents of HMPA or 1.5 equivalent of $\mathrm{CuI\cdot(MeO)_3P}$ at −78 °C prior to the addition of the enone. Under these conditions, 10/1 to 50/1 α-1,4/γ-1,4 selectivity has been routinely obtained with other cyclenones without the appearance of 1,2-adducts[78,79]. We think that an oxy-Cope rearrangement could also explain the results obtained by Hirama[69], who observed that the reaction of lithiated derivative of allylsulfone on 2-cyclohexenone at −78 °C in THF without HMPA leads to the α-1,2 adduct as the major kinetic product. It is then transformed mainly to the γ-1,4 adduct, slowly at −78 °C or quickly at 0 °C.

With *p*-quinones, 1,2-additions of organoalkali reagents, mainly organolithiums, can be performed at low temperature to produce the corresponding quinols in high yield[82,83]. However, with unsymmetrical quinones these additions exhibit low regioselectivity, except in particular cases[83]. Indeed, the two carbonyl groups can be attacked. The regioselectivity is obtained by blocking one carbonyl group of the quinone with trimethylsilyl cyanide, followed by reaction of the other carbonyl group with the organometallic reagent, the protecting group being then removed with silver fluoride[84]. In fact, selective additions of carbanions to unsymmetrical *p*-quinones can be achieved at either carbonyl carbon by a judicious choice of reaction conditions without the use of a protecting group. The basic principles that are used to achieve these regioselective 1,2-additions have been proposed by Liotta and coworkers[85]. If the carbanion is made sufficiently bulky by varying its counterion, its degree of aggregation and/or its degree of solvation (i.e. steric factors) should dominate the transition state, resulting in regioselective addition to the less hindered carbonyl carbon. By contrast, if the carbanion is relatively small and only weakly solvated, electronic factors should dominate the transition state, resulting in regioselective addition to the more electrophilic carbonyl carbon. The effectiveness of these principles is exemplified by the reaction of 1,6-dimethylbenzoquinone (**39**) with various organometallic reagents (Table 7) (equation 10).

TABLE 7. Addition of organometallic reagents to quinone **39**[85]

Reagent	Solvent	Additive	Temperature (°C)	Reaction products (%)		
				40	**41**	**42**
MeLi	THF	TMEDA[a]	– 107	9	87	—
MeMgBr	THF		– 78	60	—	10
n-BuLi	THF	TMEDA[a]	– 107	12	66	—
n-BuLi	Et_2O		– 78	60	15	—

[a] 6 equivalents.



(39) **(40)** **(41)** **(42)**

In comparison to the relatively large and heavily solvated carbanion of methyl magnesium bromide, which reacts in accordance with the above steric model, the methyl carbanion from methyl lithium in THF–TMEDA is in a non-aggregated, weakly solvated state and reacts in accordance with the electronic model discussed above. With the same organolithiated reagent, changing solvent and cosolvent alters the solvation and aggregation state and reverses the regioselectivity.

Stereoelectronic control has been used to perform regioselective organoalkali additions to enediones[86].

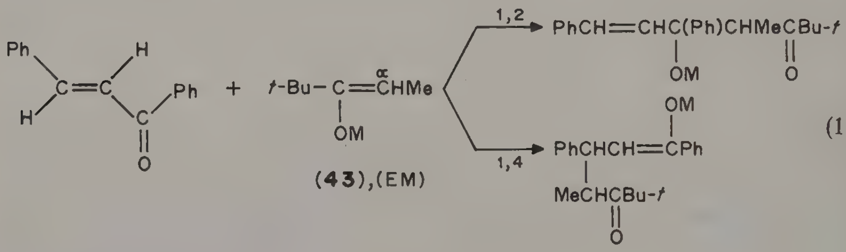
B. Metal Enolates and Related Compounds

Metal enolates are O-metalled species which react with α-enals, α-enones or quinones by their carbon atom. The metal is not bound directly to the nucleophilic centre. Evidently, the mode of reaction (1,2- or 1,4-attack) is highly dependent upon the different factors discussed above for C-metalled organoalkali reagents. However, in our opinion, the most relevant feature of these reagents is the influence of their associative states on the regioselectivity. House and coworkers[87] have shown by spectroscopy the existence of different kinds of ionic association between enolate and cation, depending on the nature of the partners and medium. The ion pairs can be of a loose type (e.g. in polar or strongly solvating solvents, and also, for some structural reason, such as *Z* or *E* configuration) or of a tight type. In the case of a contact ion pair, the reagent can exist in solution as molecular aggregates, especially with non-polar solvents[87–94]. In solvents such as ether or THF, metal enolates react in associated forms and the regioselectivity of additions is very sensitive to changes in nucleophilicity entailed by changes in associative states. This is exemplified by the results obtained by Maroni and coworkers[60] for additions of metal enolates EM **43** of 2,2-dimethyl-3-pentanone to *trans*-chalcone, under kinetic conditions (Table 8) (equation 11).

TABLE 8. Addition of metal enolates of 2, 2-dimethyl-3-pentanone (EM) to *trans*-chalcone in Et_2O at −78 °C[60].

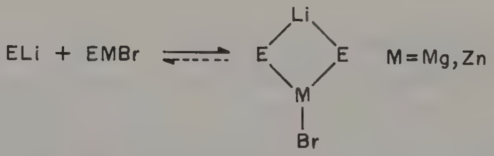
Entry	Enolate formation	Composition of **43**	$\delta^{13}C_{(\alpha)}$[a]	1,2-Adduct	1,4-Adduct	Overall yield (%)
a	*t*-BuCOEt + *i*-Pr_2NLi	ELi	83.1	30	70	55
b	*t*-BuCOEt + *i*-PrMgBr or *t*-BuCOCHBrMe + Mg	EMgBr	95.4	95	5	40
c	*t*-BuCOCHBrMe + Zn	EZnBr	98.7	> 98	< 2	20
d	2 EMgBr + $MgBr_2$	E_2Mg	83.4–95.4	25	75	90
e	ELi + EMgBr	$E_2LiMgBr$	88.2	65	35	40
f	ELi + $ZnBr_2$	$E_2LiZnBr$	90.2	60	40	35
g	E_2Mg + 2ELi	E_4Li_2Mg	88.0	65	35	45
h	$2E_2Mg$ + 2ELi	$E_6Li_2Mg_2$	87.9	70	30	30

[a] Chemical shift (ppm/TMS) of the carbanionic centre of enolates.



(11)

When we compare the regioselectivities of ELi, EMgBr and $E_2LiMgBr$ (entries a, b and e in Table 8) or of ELi, EZnBr and $E_2LiZnBr$ (entries a, c and f), we can see that the 1,2/1,4 ratio from e or f is intermediate between those of a and b or a and c owing to the formation of mixed enolates $E_2LiMgBr$ or $E_2LiZnBr$ (equation 12).



(12)

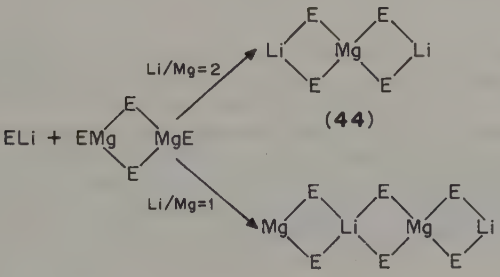
Most surprising are the cases of entries a and d compared to g and h. Metal enolates ELi and E_2Mg lead to a similar 1,2/1,4 ratio (30:70) and should give the same regioselectivity from a mixture of the two metal enolates (entries g and h). In fact, the regioselectivity is reversed (70:30) as the result of participation by associated forms **44** and **45**[91].

Examination of Table 8 also shows that the ratio of 1,2/1,4 attacks increases when the ^{13}C chemical shift of the carbanionic centre of metal enolates increases, i.e. when the charge on this carbon decreases[95]. So, the 1,2-addition is not charge controlled and the 1,2 and 1,4-attacks are probably under orbital control at −78 °C. The less nucleophilic enolates (the most associated or most covalent) lead to the greatest per cent of 1,2-additions (M = MgBr, ZnBr, entries b and c).

Associative states are also influenced by other factors (such as solvent or temperature). This has to be kept in mind for the following discussion.

TABLE 9. Substituent effect of enolates **46**–**49** on the regioselectivity of addition to *trans*-chalcone

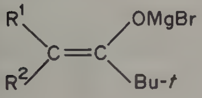
enolate	R^1	R^2	Temperature (°C)	Solvent	Time (min)	1,2-Attack	1,4-Attack	Overall yield (%)	Ref.
46	H	H	20	THF	1	100	0	55	96
46	Me	H	−78	Et_2O	1	>95	<5	40	96
46	Me	Me	−78	Et_2O	1	0	100	<30	96
47	H	H	−78	THF	1–60	80	20	40	96
47	Me	H	−78	Et_2O	1	30	70	55	96
47	Me	Me	−78	Et_2O	1	0	100	80	96
48	H		−50	THF	60	71	29	67	97
48	Me		−50	THF	60	68	32	85	97
48	Et		−50	THF	60	62	38	65	97
48	*i*-Pr		−50	THF	60	50	50	77	97
48	*t*-Bu		−50	THF	60	0	100	88	97
49	H		−45	THF	4	77	23	87	98
49	Me		−45	THF	2	70	30	68	98
49	Et		−45	THF	2	72	28	76	98
49	*i*-Pr		−80	THF	1	<5	>95	40	98
49	Ph		−45	THF	3	<5	>95	60	98



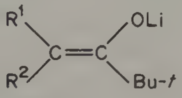
(44)

(45)

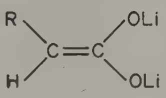
The results obtained from reactions of various metal ‘enolates’ with *trans*-chalcone under kinetic control (Table 9) show that the formation of 1,4-adduct is favoured as the substitution degree of the enolate is increased.



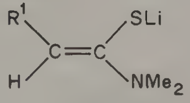
(46)



(47)

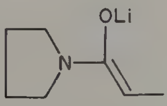


(48)

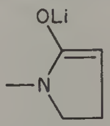


(49)

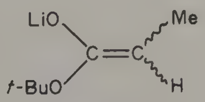
As expected, metal enolates add preferentially to the 1,2-position of α-enals compared to α-enones under kinetic conditions[99–103]. When the steric hindrance around the carbonyl group of the α-enones increases, the 1,4-additions are favoured as exemplified in Table 10 with enolate **48** (R = H), **48** (R = Et), **50** and **51**.



(50)



(51)



(52) *E* or *Z*

TABLE 10. Effect of substituents at the carbonyl group on the regioselectivity of metal enolate additions to $R^2CH{=}CHCOR^1$ in THF

Enone								
R^1	R^2	Reagent	Temperature (°C)	Time (min)	1,2-Attack	1,4-Attack	Overall yield (%)	Ref.
Me	Ph	**48** (R = H)	−50	60	100	0	72	97
Et	Ph		−50	60	100	0	80	97
i-Pr	Ph		−50	60	100	0	73	97
Ph	Ph		−50	60	71	29	67	97
t-Bu	Ph		−50	60	69	31	45	97
Et	Ph	**48** (R = Et)	−50	60	100	0	85	97
Ph	Ph		−50	60	62	38	65	97
t-Bu	Ph		−50	60	0	100	83	97
Et	Me	**50**	−78	20–60	> 97	< 3	78	104
i-Pr	Me		−78	45	29	71	84	104
Ph	Me		−78	60	12	88	92	104
t-Bu	Me		−78	60	< 3	> 97	90	104
Et	Me	**51**	−78	60	> 97	< 3	50	104
i-Pr	Me		−78	60	80	20	64	104
Ph	Me		−78	60	63	37	67	104
t-Bu	Me		−78	60	14	86	67	104

For the four reagents, the isopropyl alkenyl ketones lead to a substantial preference for 1,2-addition in comparison with the corresponding phenyl alkenyl ketones. In both cases, the steric interactions for the 1,2-addition pathway are alike. The difference of behaviour between the two series is explained by the greater repulsive interactions between occupied orbitals of the nucleophiles and electrophiles in the phenyl ketones than in the isopropyl ketones. The resonance effect of the phenyl group which deactivates the carbonyl group towards nucleophilic attack can be also taken into account[97].

The 1,2/1,4 ratio depends also on the steric demand of the group at the β-position of the enones, as shown in Table 11[104,105]. The results show that when the two configurations of

TABLE 11. Effect of substituents at the β-position of enones on the regioselectivity of metal enolate additions to RCH=CHCOBu-*t* in THF at −78 °C[104,105]

Enone R	Reagent	Time (min)	1,2-Attack	1,4-Attack	Overall yield (%)
Me	**50**	60	< 3	> 97	90
Et		15	< 3	> 97	95
Ph		15	< 3	> 97	69
t-Bu		15	54	46	70
Me	**51**	60	14	86	72
Et		15	31	69	58
Ph		15	55	45	55
t-Bu		15	> 97	< 3	60
Me	**52** *Z*	15	< 3	> 97	78
	52 *E*	15	< 3	> 97	85
Et	*Z*	15	< 3	> 97	49
	E	15	< 3	> 97	86
Ph	*Z*	15	14	86	88
	E	15	40	60	95
t-Bu	*Z*	15	—	—	0
	E	15	> 97	< 3	65

TABLE 12. Product distribution as a function of lithiated enolate types for the addition to 2-cyclohexenone in THF

Entry	Reagent	Temperature (°C)	Time (min)	1,2-Attack	1,4-Attack	Overall yield (%)	Ref.
a	t-BuC(OLi)CH$_2$[a]	−47 to −50	10	100	0	93	106
b	t-BuC(OLi)CHMe	−78	1	40	60	—	107
c	t-BuC(SLi)CH$_2$	−78	15	0	100[b]	50	108
d	MeOC(OLi)CMe$_2$	−78	30	95	5	93	109
e	MeOC(OLi)C(OPh)Me	−78	30	92	8	96	109
f	MeOC(OLi)C(OMe)Me	−78	30	86	14	87	109
g	MeOC(OLi)C(SMe)Me	−78	30	90	10	70	109
h	MeOC(OLi)C(SPh)Me	−78	30	0	100	75	109
i	MeOC(SLi)CH$_2$	−78	15	70	30	43	108
j	(CH$_2$)$_4$NC(OLi)CHMe[c]	−78	20	97	3	78	104
k	Me$_2$NC(SLi)CH$_2$	−78	20	100	0	65	108
l	MeSC(OLi)CH$_2$	−78	10	100	0	73	108
m	MeSC(SLi)CH$_2$	−45	15	0	100	86	110
n	MeSC(SLi)CMe$_2$	−55	15	0	100[d]	66	111
o	HC(Me$_2$NNLi)CHMe	0	1	72	28	—	112
p	HC(Me$_2$NNLi)CMe$_2$	−78	1	>90	<10	—	112

[a] Reaction performed in Et$_2$O.
[b] 100% 1,4-S-addition.
[c] The substrate is 4-hexen-3-one.
[d] 1,4-S-addition/1,4-C-addition = 86/14.

enolates exist, *E* enolates exhibit a greater preference for 1,2-addition than *Z* enolates.

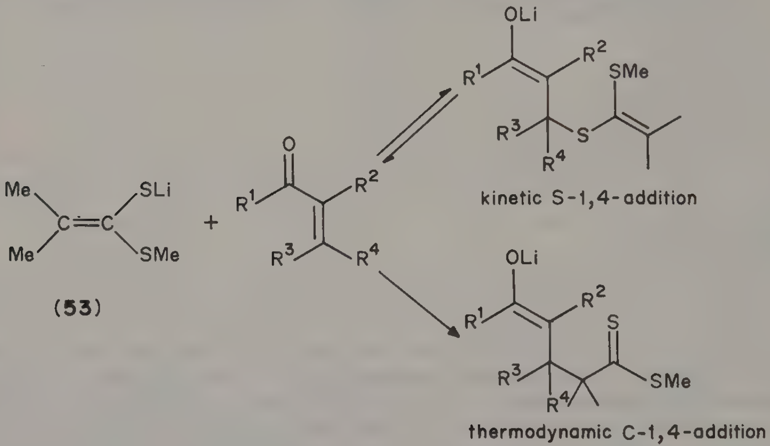
In a homogeneous set of metallated enolates, such as lithiated enolates, it is possible to apply the HSAB concept to predict the preferential orientation of additions according to the nature of the enolates (ketones, thione, amide, thioamide, ester enolates) and of hetero substituent bonded on the carbanionic centre: the most delocalized (soft) enolates should lead to the greatest proportion of 1,4-addition. Some results obtained with 2-cyclohexenone and various lithiated enolates at low temperature are summarized in Table 12.

Except for the surprising cases of 2,2-dimethyl-3-pentanone lithiated enolate (entry b), all O-lithiated derivatives react preferentially on the carbonyl group under kinetic conditions. For the α-thiophenyl derivatives of the methyl propionates series (entry h), it seems that equilibration due to the 1,2-addition reversibility occurs even at −78 °C[109].

TABLE 13. Addition of 53 to α-enones in THF[111]

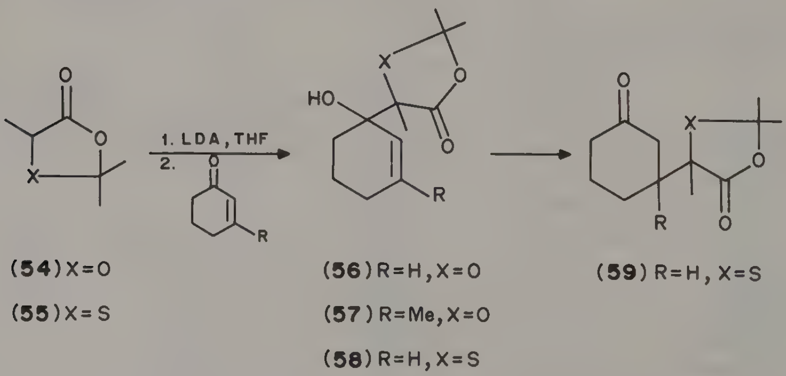
Enone	Temperature (°C)	Time (min)	S-1,4	C-1,4	Overall yield (%)
2-Cyclohexenone	−55	15	86	14	66
2-Cyclohexenone	−55	15			
	and then				
	−20	15	4	96	82
2-Cyclohexenone	−20	10	1	99	72
3-Penten-2-one	−78	20	85	15	39
3-Penten-2-one	−30	20	5	95	70
2-Cyclopentenone	−126	—	0	100	—
2-Cyclopentenone	−78	10	0	100	45
2-Cyclopentenone	−20	10	0	100	70

The lithiated enolates derived from hydrazones (entries o and p) also favour the 1,2-addition. The situation is complex with S-lithiated reagents. Sulphur-lithiated enolates may be considered as softer nucleophiles than the corresponding oxygen-lithiated derivatives. The 1,2-orientation is unfavoured, but the softness is modulated by the nature of the enolates (thioketones, thioesters, dithioesters or thioamides). Thus, the effects of alkoxy or amino groups (entries i and k) counteract the sulphur effect, in contrast to thio and dithioenolates (entries c, m and n). Thioketones give regioselective sulphur 1,4-addition, whereas dithioesters can afford carbon 1,4-additions or sulphur 1,4-additions depending on the substitution of dithioesters, on the nature of enones and on the reaction conditions[111,113,114]. For instance, the reaction of lithium thioenolate of methyl 2-methyldithiopropanoate (**53**) gives kinetic sulphur 1,4-addition and thermodynamic carbon 1,4-addition when temperature and reaction time increase. An exception is that 2-cyclopentenone gives kinetic carbon 1,4-addition (Table 13) (equation 13)[111].



(13)

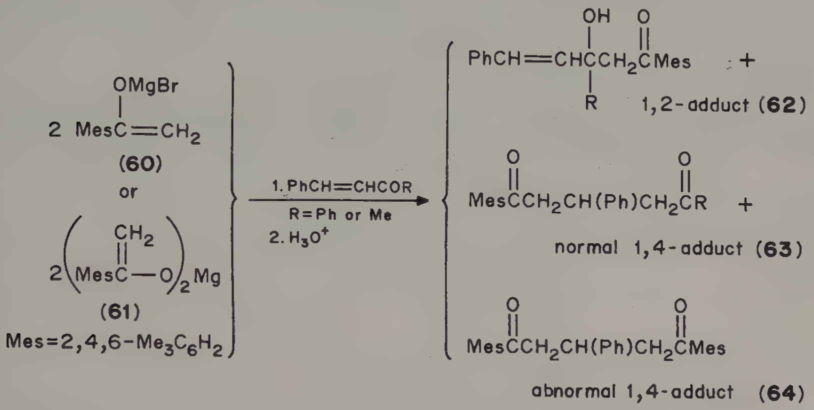
The effects of temperature, time and solvent on the reversibility from 1,2- to 1,4-addition have been largely documented. The reversibility of 1,2-addition is commonly observed for various metal enolates derived from ketones[96,107,115–118], esters[105,111,119], amides[104,120], thioamides[98], imines and hydrazones[112]. It has been exploited extensively to synthesize δ-functionalized ketones. Evidently, the reversibility of 1,2-addition is very sensitive to structural effects of the 1,2-adducts, as exemplified by the reactivity observed with the lithiated derivative of acetonide **54** (equation 14).



(14)

Reaction of **54** with 2-cyclohexenone at either −78 or 25 °C over prolonged reaction times gives only the product of 1,2-addition **56** (82% isolated yield). Substitution of 3-methyl-2-cyclohexenone for 2-cyclohexenone gives only **57**, isolated in 80% yield. When reaction of the ester enolate of **55** with 2-cyclohexenone is followed by addition of one equivalent of 3-methyl-2-cyclohexenone with stirring for 1 hour at 25 °C, only **56** and unreacted 3-methyl-2-cyclohexenone are recovered. Clearly, with the enolate of **54** and 2-cyclohexenone, 1,2-addition is irreversible under these reaction conditions. With thiaacetonide **55**, however, 1,2-addition is reversible and **58** gives the product of conjugate addition **59** at 25 °C[109].

If the 1,2-reversibility is established, reversibility of 1,4-addition is less expected and it leads to problems of redistribution and of stereochemistry. The first problem is illustrated by the reactions of magnesium derivatives **60** and **61** of mesityl methyl ketone with *trans*-chalcone and *trans*-benzalacetone in Et_2O at 20 °C (equation 15) (Table 14).

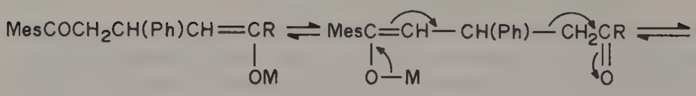


(15)

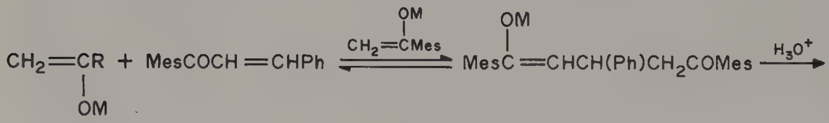
With the reagent **61**, a new 1,4-adduct (**64**) appears that can be explained by the reversibility of the normal 1,4-addition (equation 16) as demonstrated by isolation of acetophenone and 1,3,5-triphenyl-1,5-pentanedione after hydrolysis.

TABLE 14. Product distribution as a function of reaction times for additions of enolates **60** and **61** to chalcone and benzalacetone (20 °C, Et_2O, enolate/enone = 2)[118]

Enone	Reagent	Time (min)	Product distribution (%) 62	63	64	Overall yield (%)
Chalcone	**60**	5	100	0	0	70
		360	87	13	0	100
		1440	70	30	0	100
	61	5	0	100	0	> 90
		1440	0	50	50	> 90
Benzalacetone	**60**	5	100	0	0	100
		1440	> 95	< 5	0	100
	61	5	15	85	0	> 90
		1440	15	59	26	> 90



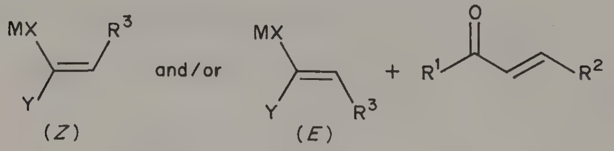
R=Ph or Me, Mes=2,4,6-$Me_3C_6H_2$ M=—MgO— (16)



$$CH_2{=}\underset{\displaystyle OM}{C}R + MesCOCH{=}CHPh \xrightleftharpoons{CH_2=\overset{\displaystyle OM}{C}Mes} Mes\overset{\displaystyle OM}{C}{=}CHCH(Ph)CH_2COMes \xrightarrow{H_3O^+} \quad (64)$$

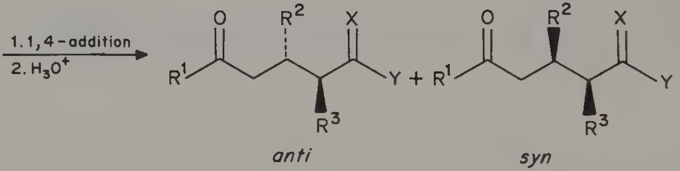
Redistribution reactions arise with **61** and the lithiated derivative of mesityl methyl ketone, but not with **60**. Thus, the phenomenon is joined to the associative states and nucleophilicity of metal enolates[118] and has some importance in the study of the stereochemistry of 1,4-additions.

The geometry of enolates is very important for the stereochemistry of the kinetic Michael-type additions of enolates to enones. Indeed, when the reaction involves a prochiral enolate and a prochiral enone, two diastereomers can be formed (equation 17).



X=O,S

Y=NR_2,OR,SR (17)



In the cases of some lithium enolates of ketones[96,121], esters[105] and dithioesters[122], a correlation has been observed between the enolate *Z* or *E* geometry and the Michael adduct stereostructure, under presumed kinetic conditions. It seems that *E* enolates tend towards *syn* selectivity and *Z* enolates towards *anti* selectivity (Table 15).

With the dithioester enethiolates, Metzner and coworkers[122] explained the stereospecificity of additions with acyclic enones by the intervention of the classical closed transition state[123–127], in which the metal ion is chelated in an eight-membered ring between the oxygen of the enone and the sulphur of enethiolate.

With ester and ketone enolates, Heathcock and Oare[105,121] proposed an open transition state in which the MX and Y groups (equation 17) competitively interact with the substituent R^2 of the enones. Although the chelation between the metal ion and the oxygen of the enone seems difficult, this open transition-state hypothesis explains why stereospecificity is not observed with large Y groups[104].

In our opinion, the attractive suggestion that *Z* enolates tend towards *anti* diastereosel-

TABLE 15. Stereochemistry of the addition of lithium enolates to *E*-s-*cis* enones $R^1COCH{=}CHR^2$ in THF

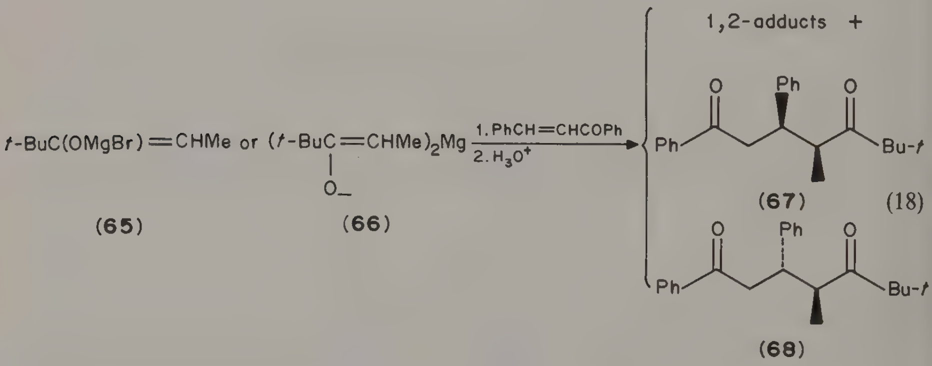
Enones								
R^1	R^2	Enolate	(*E*/*Z* ratio)	Temperature (°C)	Time (min)	*syn* (1,4-adduct)	*anti*	Ref.
t-Bu	Me	*t*-BuOC(OLi)CHMe	(0/100)	−78	15	13	87	105
t-Bu	Ph		(11/89)	−78	15	7	93	105
t-Bu	Ph		(95/5)	−78	15	94	6	105
t-Bu	Ph	PhC(OLi)CHMe	(2/98)	−78	1440[a]	4	96	121
t-Bu	Ph		(87/13)	−20	1440	83	17	121
Me	Me		(2/98)	−78	1440	3	97	121
Me	Me	MeSC(SLi)CHMe	(4/96)	−50	10	8	92	122
Me	Me		(42/58)	−50	10	43	57	122
Ph	Ph		(24/76)	−70	10	28	72	122

[a] Reaction in THF/HMPA.

TABLE 16. Stereochemistry of addition of metal enolates **65** and **66** to *trans*-chalcone in Et_2O[116]

Reagent	Temperature (°C)	Time (min)	1,2-Attack	1,4-Attack	Overall yield (%)	*syn* **67**	*anti* **68**
65	20	1	48	52	85	0	100
66	20	1	0	100	100	15	85
65	20	5	40	60	100	0	100
66	−20	5	0	100	80	0	100
65	20	60	5	95	100	0	100
66	20	60	0	100	100	76	24
66	−20	60	0	100	80	0	100
65	20	1140	0	100	100	0	100
66	20	4320	0	100	100	84	16
66	−20	4320	0	100	80	15	85

ectivity whereas *E* enolates tend towards *syn* selectivity, should be regarded with caution and should not be generalized. First, the stereoselective hypothesis is based on reactions of particular lithiated enolates and enones; second, it is very difficult to confirm that the reactions are under kinetic control when only 1,4-additions are observed. The stereochemistry of 1,4-additions is highly dependent upon the enolate types and their degree of association[96], temperature and reaction times[120], as exemplified by the reactions of metal enolates derived from 2,2-dimethyl-3-pentanone, **65** or **66** and *trans*-chalcone (equation 18)[116] (Table 16).



(18)

In addition to the redistribution phenomenon discussed above, these results clearly show the possibility of reversibility of the 1,4-addition with accompanying changes of stereochemistry[120]. Therefore, even if a diastereoselectivity or diastereospecificity can be interpreted *a posteriori*, in some cases, the prediction of the stereochemistry of a 1,4-addition between metal enolates and enones seems illusive.

In agreement with the results on ambident organoalkali reagents (see Section II.A), ambident metal enolates usually give complex mixtures of α-1,2, γ-1,2, α-1,4 and γ-1,4 adducts. The product distribution is largely dependent upon all the reaction parameters (nature of reagent and substrate, reaction conditions)[128–131] with additional possibility of oxy-Cope rearrangement of the reversibly formed 1,2-adducts[132].

C. Other Organometallic Compounds

1. *Organocopper reagents*

Organocopper reagents are softer nucleophiles than Grignard and organolithium compounds[133]. They are relatively inactive towards saturated ketones and add almost exclusively to enones in a conjugate manner. This is now a well-reviewed part of synthetic methodology[134–143].

In most cases, organocopper reagents are prepared by adding an organomagnesium or an organolithium reagent to a copper(I) species (equations 19–22).

$$\mathrm{RM} + \mathrm{CuX} \longrightarrow \mathrm{RCu} + \mathrm{MX} \tag{19}$$

$$2\mathrm{RM} + \mathrm{CuX} \longrightarrow \mathrm{R_2CuM} + \mathrm{MX} \tag{20}$$

$$\mathrm{RM} + \mathrm{CuR'} \longrightarrow \mathrm{RR'CuM} \tag{21}$$

$$\mathrm{RM} + \mathrm{CuZ} \longrightarrow \mathrm{R(Z)CuM} \tag{22}$$

$$\mathrm{M} = \mathrm{Li, MgX}; \quad \mathrm{Z} = \mathrm{OR', SR', CN}$$

Although lithium diorganocuprates (R_2CuLi) have been the most frequently used, various copper-containing systems have been developed and successfully used with the α-enonic framework (Table 17).

The reactivity profile, which depends on the nature of reagents and substrates, may be altered by several parameters, such as the source of copper(I) species, the CuX/RM ratios[144–146] or reagent/enone ratios[146–150], the gegenion involved (M = Li or MgX)[151–155], the choice of solvent, and the presence of additives (Lewis acids, lithium salts[156–158], solubilizing or stabilizing ligands such as sulphides[154,157,159–161] or phosphines[157,161–167]).

The great number of possible combinations and the different influences of the above parameters on the chemical behaviour of the various organocopper reagents contribute to the complexity of choosing the best suitable reagent and optimum experimental conditions for a given enone. Nevertheless, it is now well established that a regio- and

TABLE 17. Examples of current useful copper-containing systems employed successfully for addition to the α-enonic framework

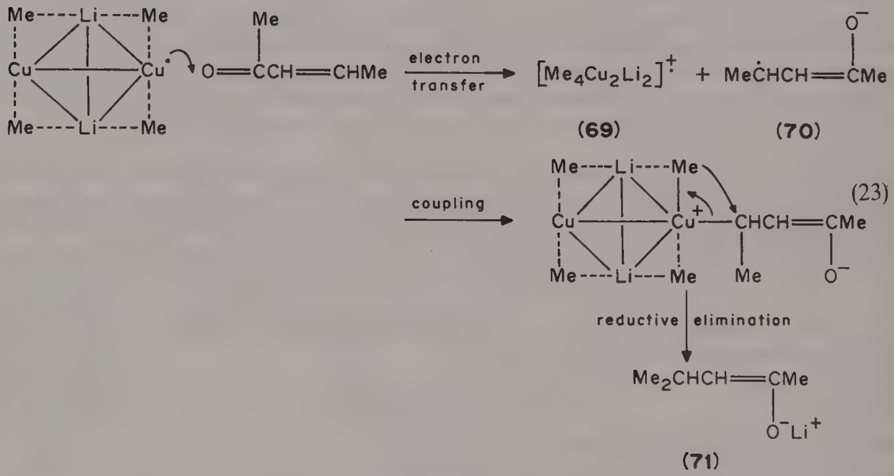
General name	General formula[a]
Copper-catalyzed Grignard reagents	$RMgX/Cu^+$
Organocopper reagent	$RCu \cdot MX$
	$RCu \cdot MX \cdot$Ligand
Organocopper·Lewis acid complex	$RCu \cdot BF_3$
	$RCu \cdot AlCl_3$
	$RCu \cdot Me_3SiCl$
Homocuprates	R_2CuM
	$R_2CuM \cdot$Ligand
Mixed homocuprates	$RR'CuM$ (R' = alkyl, phenyl, alkynyl, 2-thienyl)
Organo (hetero) cuprates	$R(Z)CuM$ ($Z = OR', SR', CN, NR'_2, PR'_2$)
Higher-order cuprates	R_3CuM_2
	$R_2Cu(CN)Li_2$, $RR'Cu(CN)M_2$
Highly aggregated cuprates	R_3Cu_2Li
	$R_5Cu_3Li_2$
	$R_4R'Cu_3(MgX)_2$

[a] M = Li, MgX; X = halide; Ligand = Me_2S, PR_3.

stereoselective conjugate addition is often achieved more effectively by stoichiometric copper than by copper-catalyzed Grignard reagents^{134,135}. Whereas alkyl, vinyl or phenyl groups can be transferred into the β-position of an enone, the alkynyl unit does not, the ethynyl ligand being tightly bound to copper^{164,168}, and allylation being a very versatile process (see Section IV).

Despite the increasing use of these reagents in synthesis, the mechanism by which the copper ion encourages the addition of the anionic moiety to the β-carbon of the unsaturated ketone still remains in question and many controversies exist. Almost all mechanistic studies have used lithium dimethyl cuprate (Me_2CuLi), which is assumed to be a dimeric cluster in $Et_2O^{169-172}$. However, there is widespread agreement that: (i) coordination of the lithium ion to the oxygen of the enone seems a necessary first step^{173,174} (addition of an excess of 12-crown-polyether inhibits the addition^{175}); (ii) the reaction produces an enolate anion; (iii) a six-centre transition state is not a requirement^{176}; and (iv) free alkyl radicals are excluded as intermediates$^{177-179}$.

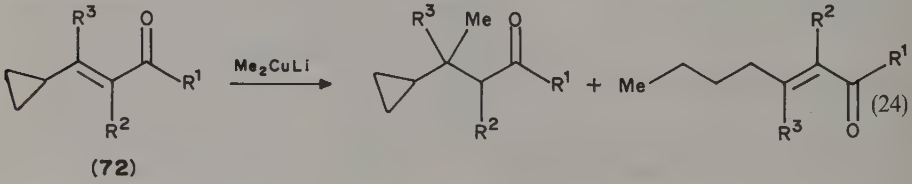
House and coworkers^{162,171,180} suggested that the conjugate addition of lithium dimethyl cuprate proceeds by an initial single-electron transfer from the cuprate to the enone to form an electron-deficient metal cluster **69** and an anion radical **70** (equation 23). Rebonding these two species at the sites of high spin density, followed by intramolecular transfer of a methyl group from the metal cluster to the β-position of the enone, leads to the observed enolate **71**.



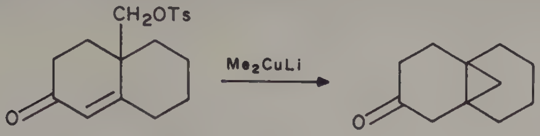
Several reactions which occur concurrently with the conjugate addition of lithium dimethyl cuprate have been cited as evidence for the formation of an intermediate radical anion:

(i) *cis–trans* isomerization^{181},

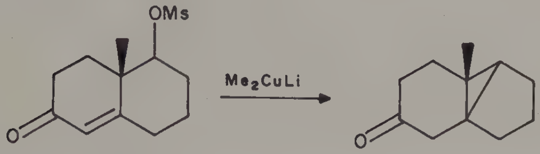
(ii) alkylative ring opening of β-cyclopropyl-α,β-unsaturated ketones **72** (equation 24)^{106,182,183},



(iii) cyclopropane ring formation by internal displacement of a good leaving group in the δ-position of the enone (equations 25 and 26)[184–186],

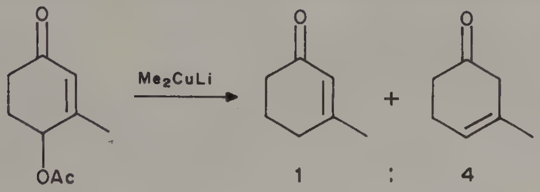


(25)



(26)

(iv) reductive cleavage of γ-O-acetoxy-α, β-unsaturated ketones **73** (equation 27)[186–189].

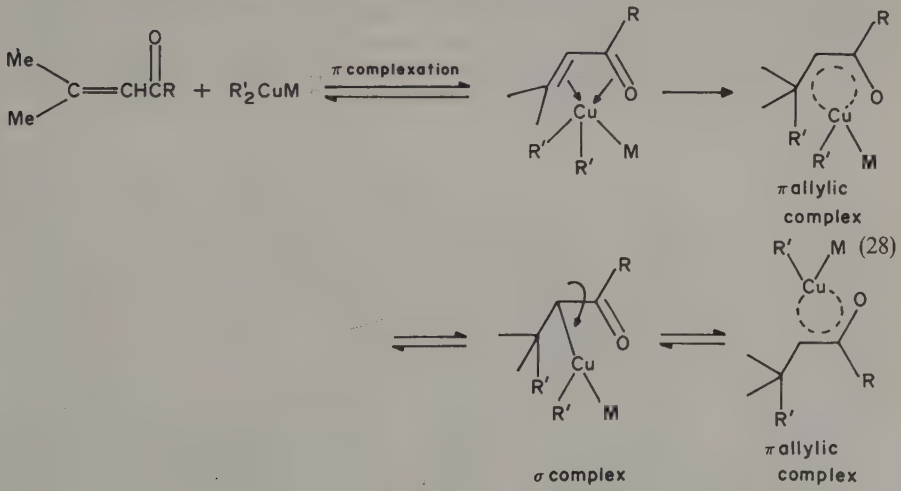


(27)

(73) **(74)** **(75)**

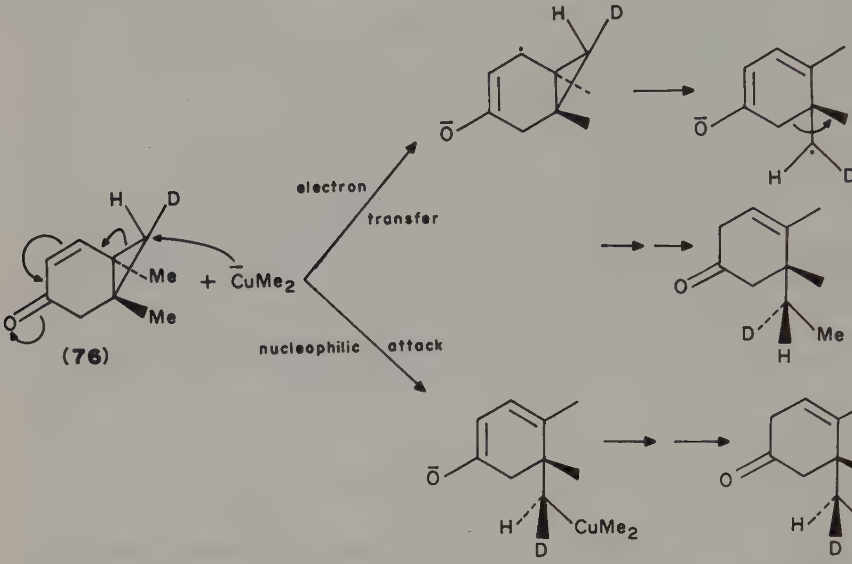
However, no ESR or CINDP signal attributable to an unpaired electron was observed[168,190] and, in the last-named case, when the γ-acetoxy group is replaced by a poorer leaving group, such as alkoxy, the normal addition takes place[191–193].

Other working hypotheses have been formulated which involve either a R^- transfer and formation of an α-cuproketone via π allylic and σ complexes (equation 28)[151,194,195] or via 1, 2-addition of the cuprate to the enone double bond[196,197], or formation of a Cu(III) β-adduct via a dianion formed by a bielectronic transfer[190,198].



(28)

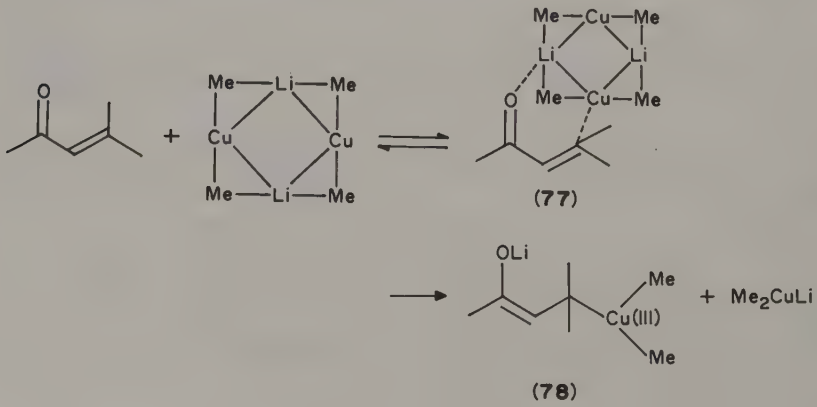
Casey and Cesa showed that the ring opening of the cyclopropyl-α,β-unsaturated ketone **76** is highly stereospecific, providing evidence against an anion radical intermediate and in favour of a direct nucleophilic attack of the cuprate on the cyclopropane ring (equation 29)[199].



(29)

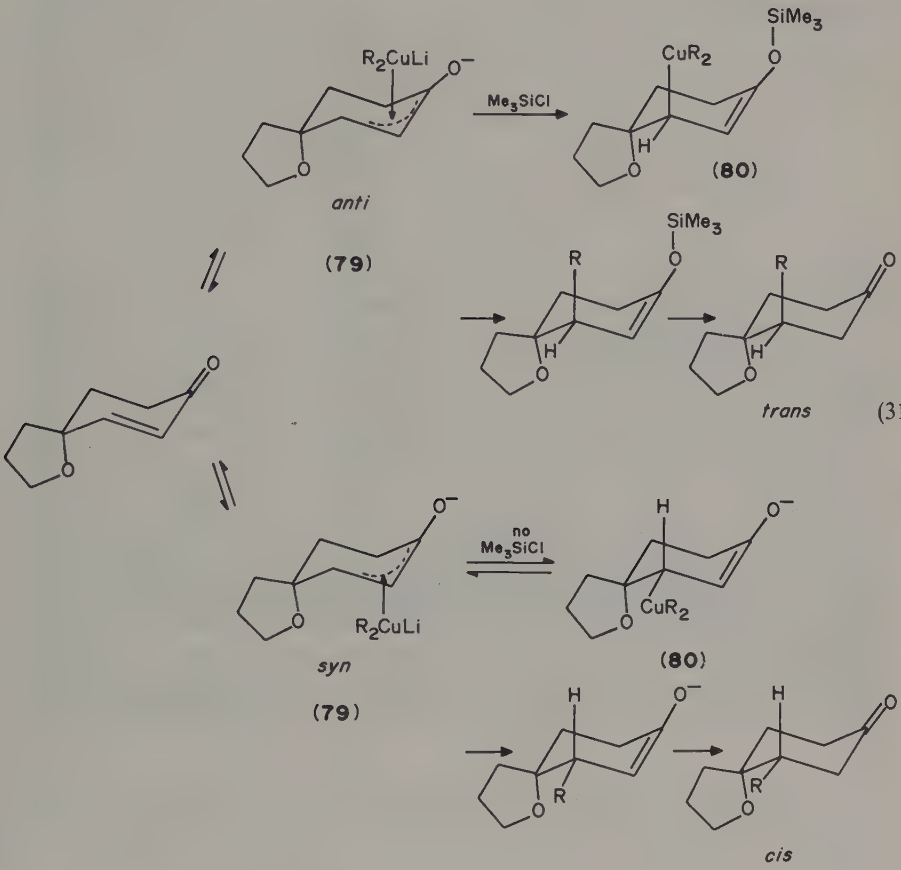
Moreover, on the same type of substrate, Jullien and coworkers[200,201] found no evidence for a correlation between the radical anion half-lives and the formation of ring-opened products. In many cases, the broken bond is different from the bond involved in the reduction by solvated electron in liquid ammonia[202].

In addition Krauss and Smith[156], by kinetic studies using stopped-flow spectroscopy, have implicated an equilibrium of the reactants with the intermediate complex **77**, which may unimolecularly rearrange to form a trialkylcopper(III) species **78** with copper bound to the β-carbon of the lithium enolate (equation 30).



(30)

More recently Corey and Boaz, by trapping intermediates by chlorotrimethylsilane (TMSCl) and studying the stereochemical course of the reaction, provide evidence for a pathway involving a reversible d–π^* cuprate–enone complex **79** and a β-cuprio-adduct **80** (equation 31)[193,203].



(31)

Finally, we think that different mechanisms might be operating depending on the reaction conditions.

For given organocopper reagents or substrates, the success of 1, 4-addition is very much dependent on the solvent. As shown in Table 18, the conjugate addition is usually very fast in solvents such as Et_2O, hexane, toluene or dichloromethane. In more polar and coordinating solvents such as THF, pyridine or DME, the conjugate addition is substantially slower or inhibited. It has been proposed[171] that in such donor solvents the activating effect of Li^+ coordination to the C=O oxygen of the substrate could be hampered by complexation between Li^+ and solvent molecules and therefore could alter the whole reaction. More recent NMR studies[204] indicate that the electronic surroundings of the methyl group in Me_2CuLi are relatively similar in Et_2O and dichloromethane, while in pyridine the ionic character of the C–metal bond and the nucleophilicity of Cu are

TABLE 18. Influence of the solvent on the conjugate addition of organocopper reagents to α-enones

Enone	Reagent	Solvent	Time (min)	Yield (%)	Ref.
Benzalacetone	Me_2CuLi	Et_2O	1	> 98	204
		CH_2Cl_2	1	> 98	204
		PhMe	1	> 98	204
		Hexane	1	> 98	204
		THF	1	85	204
		THF	10	82	204
		Pyridine	1	17	204
		Pyridine	10	28	204
		MeCN	1	28	204
		MeCN	10	50	204
Mesityl oxide	Me_2CuLi	Et_2O	10	82	148
	Me_2CuLi	THF	180	51	148
	$Ph_2Cu(CN)Li_2$	Et_2O	60	98	205
	$Ph_2Cu(CN)Li_2$	DME	60	8	205
	$Ph_2Cu(CN)Li_2$	THF	60	1	205
Isophorone	Me_2CuLi	Et_2O	10	100	148
	Me_2CuLi	THF	300	0	148
	$(CH_2{=}CH)_2Cu(CN)Li_2$	Et_2O	210	98	205
		DME	210	11	205
		THF	210	34	205

changed. Thus, the reduced reactivity of lithium diorganocuprates towards enones in polar solvents is due, at least in part, to structural changes in the cuprate clusters caused by coordination of solvent. Exchange between clusters of different composition could also be anticipated[204].

In reaction of organocopper reagents with α, β-unsaturated aldehydes, a low-polar solvent such as pentane favours conjugate addition versus the 1, 2-addition[155,206,207] (Table 19). However, the solvent effect is less marked using organocuprates stabilized by Me_2S[154].

TABLE 19. Influence of the solvent on the mode of addition of cuprates to enals $R^2R^3C{=}CR^1CHO$

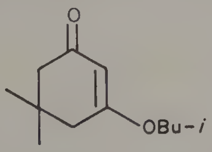
Enal								
R^1	R^2	R^3	Reagent	Solvent	$C_{(1)}$ Attack	$C_{(3)}$ Attack	Overall yield (%)	Ref.
Me	H	Et	Me_2CuLi	Et_2O	18	82	85	206
Me	H	Et	Me_2CuLi	Et_2O/pentane	5	95	75	206
Me	H	Et	Me_2CuLi	Et_2O/THF	60	40	55	206
Me	H	Et	Me_2CuLi, Me_2S	THF	10	90	53	154
Me	H	Et	$Bu_2CuMgCl$	THF	91	9	22	154
Me	H	Et	$Bu_2CuMgCl$	THF/Et_2O	27	73	78	154
Me	H	Et	$Bu_2CuMgCl$, Me_2S	THF	4	96	83	154
Me	H	Et	$Bu_2CuMgCl$, Me_2S	Et_2O/pentane	6.5	93.5	87	154
Me	Et	Et	Me_2CuLi	Et_2O	45	55	75	206
Me	Et	Et	Me_2CuLi	Et_2O/pentane	18	82	86	206
Me	—$(CH_2)_4$—		$Me_5Cu_3Li_2$	Et_2O	22.5	77.5	85.5	155
			$Me_5Cu_3Li_2$	Et_2O/pentane	15	85	88	155

TABLE 20. Influence of substituents in the α and β position of enones on the yields of 1,4-addition in the reaction of R_2CuLi with $R^3R^2C{=}CR^1COMe$[171]

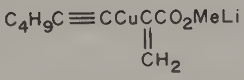
Enone					
R^1	R^2	R^3	E_{red} (V)	Reagent R	1,4-Addition yield (%)
H	H	Me	-2.08	Me[a]	94
H	Me	Me	-2.21	Me[a]	93
Me	Me	Me	-2.35	Me[a]	21
H	H	Me	-2.08	s-Bu[b]	87
H	Me	Me	-2.21	s-Bu[b]	77
Me	Me	Me	-2.35	s-Bu[b]	17–43

[a] In Et_2O at 10–30 °C.
[b] In 1:1:2 Et_2O–Me_2S–cyclohexane, V/V/V, at -50 to -55 °C.

Electronic and steric factors and the degree of substitution of the substrate also play an important role. The nature of the substituent governs the charge distribution of the LUMO orbital. House[208,209] demonstrated a qualitative correlation between the success of copper-mediated conjugate addition reactions and the ease of the enone to insert an electron into the LUMO orbital as quantified by the first electrochemical reduction potential (E_{red}) of the enone. Substrates with reduction potentials more negative than -2.4 V (versus SCE) failed to react with lithium dimethyl cuprate, while those with potentials less negative than -2.4 V react successfully[180]. This is exemplified by the inefficiency of Me_2CuLi to transfer its methyl group to enone **81** ($E_{red} = -2.43$ V) and by decreasing yields observed in reactions of Me_2CuLi and s-Bu_2CuLi with 3-penten-2-one, 4-methyl-3-penten-2-one and 3,4-dimethyl-3-penten-2-one whose reduction potentials are -2.08, -2.21 and -2.35 V, respectively (Table 20). Such a correlation between the reduction potentials and the enone reactivity suffers from the failure to obtain an electrochemical wave of the cuprate reagent[173]. The presence of an electron-withdrawing group in reagent **82** significantly influences its reactivity and leads predominantly to the 1,2-addition products[210].



(81)



$$C_4H_9C{\equiv}CCu\underset{\underset{CH_2}{\|}}{C}CO_2MeLi$$

(82)

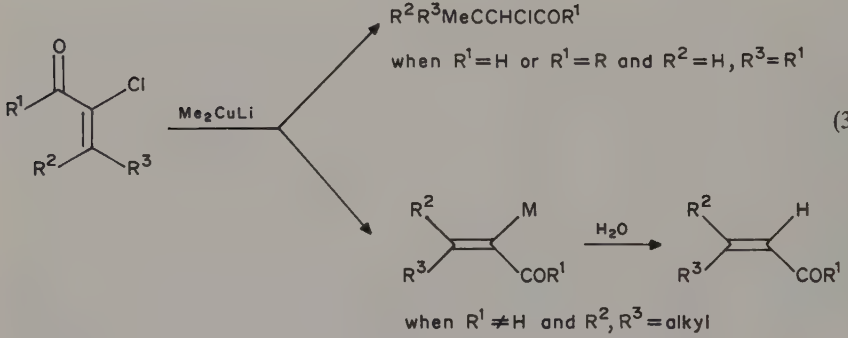
The kind of substituent present on the substrate also affects the course of the reaction. For instance, α-fluoro- and α-chloro-α,β-unsaturated carbonyl compounds whose reduction potentials are greater than -2.4 V react in different ways with lithium dimethyl cuprate[211]. With α-fluoro derivatives, both 1,2- and 1,4-additions are observed, and their ratios depend on the steric hindrance at the β-position (Table 21).

1,4-Addition products are obtained from α-chloroenals and β-monosubstituted-α-chloroenones while β,β-disubstituted-α-chloroenones give only elimination of the halogen via halogen–metal exchange (equation 32).

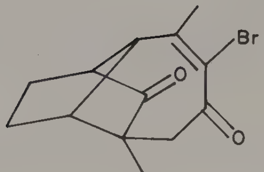
Successful conjugate additions to 2-bromo-2-cyclohexenones and 2-bromo-2-cyclopentenones have been achieved with a variety of organocopper reagents[212]. Reaction of the α-bromo enone **83** with Me_2CuLi affords a mixture of compounds arising from 1,4-addition and halogen exchange[213].

TABLE 21. Reaction of Me_2CuLi with α-fluoro-α, β-unsaturated carbonyl compounds: $R^3R^2C{=}CFCOR^1$ in Et_2O^{211}

Substrate			Temperature (°C)	Time (min)	$C_{(1)}$ attack	$C_{(3)}$ attack	Overall yield (%)
R^1	R^2	R^3					
Bu	H	Pr	−30	90	0	100	80
Me	$—(CH_2)_5—$		−30	60	20	80	64
Et	H	Ph	−45	60	30	70	70
Et	Me	Me	−40	60	23	77	65
Me	Me	*t*-Bu	−10	120	100	0	50
H	H	Pr	−40	30	5	95	33
H	$—(CH_2)_5—$		−40	60	40	60	85



(32)



(83)

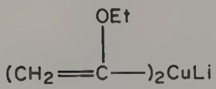
In a general manner, the reactivity of acyclic enones is affected by α, β, β′-substitutions (Tables 20 and 22), while for cyclic enones it is also often affected by substituents which are not directly connected to the reactive site of the molecule (Table 23).

$(CH_2{=}CH)_2CuLi.\,PBu_3$

(84)

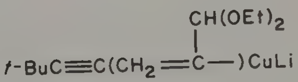
$Bu(NCp_2)CuLi$

(85)



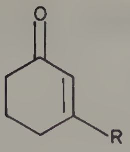
$(CH_2{=}\overset{\displaystyle OEt}{\overset{|}{C}}—)_2CuLi$

(86)

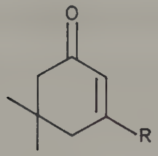


$t\text{-}BuC{\equiv}C(CH_2{=}\overset{\displaystyle CH(OEt)_2}{\overset{|}{C}}—)CuLi$

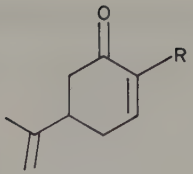
(87)



(88)



(89)



(90)

An increase in the number and/or the bulk of substituents at the β position affords decreasing yields for the same experimental conditions (Table 20, Table 22, entries c, d and f, g and Table 23 entries e, f), or requires change in the experimental conditions, such as time or temperature (Table 22, entries a–e, g, h and Table 23, entries a and b). With α, β-unsaturated aldehydes, steric hindrance at the α, β and β′ positions leads to a relatively important proportion of 1, 2-addition products (Table 24).

In the case of aldehydes, it is noteworthy that the method for workup of reactions is an important factor in determining the yield and the purity of the products. The aldehydes released after conjugate alkylation and protonation are unstable in the reaction medium,

TABLE 22. Influence of substituents in the β position of enones on the yield of 1, 4-addition in the reaction of $R_2CuLi \cdot PBu_3$ with acyclic enones $R^1R^2C{=}CHCOMe$

Entry	Enone		Reagent	Temperature	Time	Addition	Ref.
	R^1	R^2	R	(°C)	(h)	yield (%)	
a	H	H	$CH_2{=}CH$	−78	0.75	70	163
b	Me	Me	$CH_2{=}CH$	−78	2	72	163
c	H	*i*-Pr	Bu	−78 to −40	1.5	94	167
d	Me	Me	Bu	−78 to −40	2	48	167
e	Me	Me	Bu	0	0.1	88	167
f	H	*i*-Pr	*i*-Pr	−78 to −40	1.5	95	167
g	Me	Me	*i*-Pr	−78 to −40	2	68	167
h	Me	Me	*i*-Pr	0	0.2	99	167

TABLE 23. Reactions of organocopper reagents **84–87** with substituted 2-cyclohexenones **88–90**

Entry	Enone	Reagent	Temperature (°C)	Time (h)	1, 4-Addition yield (%)	Ref.
a	**88** (R = H)	**84**	−78	0.5	65	163
b	**88** (R = Me)	**84**	−78	1	72	163
c	**88** (R = H)	**85**	−50 to 25	3	92	214
d	**89** (R = Me)	**85**	−50 to 25	3	29	214
e	**88** (R = H)	**86**	−78 to 0	—	84	215
f	**88** (R = Me)	**86**	−78 to 0	—	0	215
g	**88** (R = H)	**86**			67	216
h	**90** (R = H)	**86**			50	216
i	**90** (R = Me)	**86**	−70	2–3	65	159
j	**88** (R = H)	**87**	−40	2–3	96	159
k	**90** (R = Me)	**87**	−40	2–3	0	159

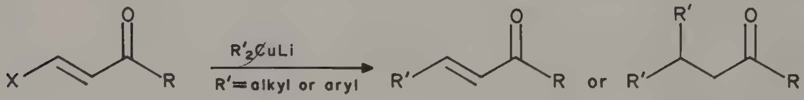
TABLE 24. Influence of substituents on the substrate in the reaction of cuprates with enals $R^3R^2C{=}R^1CHO$

Enal							
R^1	R^2	R^3	Reagent	$C_{(1)}$ attack	$C_{(3)}$ attack	Overall yield (%)	Ref.
H	Pr	H	Me_2CuLi	2	98	84[a]	206
H	Et	Et	Me_2CuLi	18	82	73[a]	206
Me	Et	H	Me_2CuLi	18	82	85[a]	206
Me	Et	Et	Me_2CuLi	55	45	75[a]	206
Me	—$(CH_2)_4$—		Me_2CuLi	64	36	86[a]	206
Me	—$CH_2)_5$—		$Me_5Cu_3Li_2$	0.5	99.5	88	155
Me	—$(CH_2)_4CH(CH_3)$—		$Me_5Cu_3Li_2$	54	46	88	155

[a] Yield of trimethyl silyl enol ether.

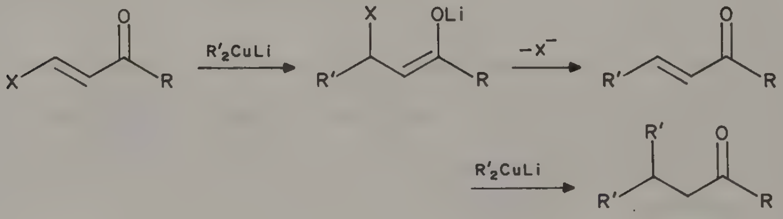
and the yields are improved by quenching the reaction with acetic acid[155] or with trimethylchlorosilane in the presence of triethylamine[153,206].

Depending on the kind of substituent and on the specific reaction conditions, including stoichiometry, the conjugate addition of dialkyl or diaryl organocuprates to enones possessing a heteroatom substituent, such as OAc[217], OEt[218], SBu[217,218] or halide[145,219,220], on the β-carbon, produces enones **91** or **92** (equation 33). Likewise, α-enones which possess a heteroatom substituent on the β' carbon lead to β,β'-dialkylated ketones[221].



X=OAc, OEt, SBu, halide **(91)** **(92)** (33)

The overall reaction sequence might involve an initial 1,4-conjugate addition to generate an enolate which, under the reaction conditions, expels the β heteroatom substituent. Then, the 1,4-conjugate addition of a second equivalent of cuprate affords the dialkylated product **93** (equation 34)[217,218,221].



(34)

(93)

The regioselectivity and the yield of the reaction of organocopper reagents with α,β-unsaturated carbonyl compounds is also affected by the nature and the steric bulk of the organic moiety transferred. While lithium cuprates with primary alkyl, phenyl or vinyl group usually add in conjugate manner to α-enones[171] or unhindered aldehydes[206], the cuprate **94** reacts with crotonaldehyde to afford a mixture of 1, 2- and 1, 4-adducts in 55/45 ratio[153]. The reaction of **94** with 3, 4-dimethyl-3-penten-2-one and of **95** with mesityl oxide are both complicated by the formation of alcohols **96** and **97**[171]. The amount of these by-

TABLE 25. Conversion of 2-cyclohexenone into 3-*t*-butylcyclohexanone using mixed cuprates R(*t*-Bu)CuLi in THF

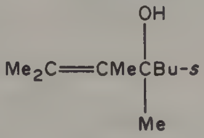
R(*t*-Bu)CuLi R	Temperature (°C)	Time (min)	Overall yield (%)	Ref.
PhS	0	120	86	223
PhO	−30	120	66	223
t-BuO	−50	240	62	223
$PrC{\equiv}C$	−78	15	95	164
$Me_2(MeO)CC{\equiv}C$	−78 to −20	—	95	224

products appears to be related to the amount of thermal decomposition of the cuprate reagent, and therefore the presence of organolithium compounds in the medium[171].

R_2CuLi

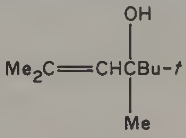
R = *s*-Bu **(94)**

R = *t*-Bu **(95)**



$Me_2C{=}CMe\overset{OH}{\underset{Me}{C}}Bu\text{-}s$

(96)



$Me_2C{=}CH\overset{OH}{\underset{Me}{C}}Bu\text{-}t$

(97)

Ashby and Watkins showed that the higher-order species Me_3CuLi_2 exists to an appreciable degree of equilibrium with Me_2CuLi and free MeLi[170]. This complex, which rapidly reacts with ketones[222], delivers the methyl group in a 1,2 sense upon reaction with the sterically hindered ketone, isophorone, at room temperature[148], whereas only the β-adduct is obtained in good yield at −69 °C[222].

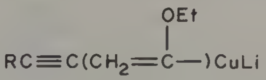
Thus, the efficiency of the conjugate addition of organocopper reagents to α-enones appears to result from a complex balance between the stability and the reactivity of the reagent, the steric hindrance at the substrate and the steric demand of the organic moiety transferred.

As shown in Table 25, in the series of hetero(alkyl)copper reagents Het(R)CuLi, PhS(*t*-Bu)CuLi is the most effective for the conversion of 2-cyclohexenone into 3-*t*-butyl cyclohexanone. This reagent is also the more stable. The stability of the reagents follows the order for Het: PhS > PhO > *t*-BuO > *t*-BuS ~ Et_2N. Moreover, mixed cuprates **98** and **99** using an ethynyl as a residual group afford the β-adduct in the highest yields.

$PrC{\equiv}CCu(Bu\text{-}t)Li$ **(98)**

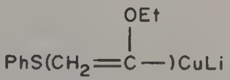
$MeOCMe_2C{\equiv}CCu(Bu\text{-}t)Li$ **(99)**

Mixed cuprates **100** are more effective than the heterocuprate analog **101** (Table 26, entries a–c), but **100** (R = *t*-Bu) is more sensitive to the steric hindrance of the substrate than the corresponding homocuprate **86** (entries b, d–f). The failure of cuprate **100** (R = *t*-Bu) to conjugately add to the more hindered carvone could only qualitatively be attributed to the increased stabilization by the alkyne ligand[159].



$RC{\equiv}C(CH_2{=}\overset{OEt}{C}{-})CuLi$ R = Pr, *t*-Bu

(100)



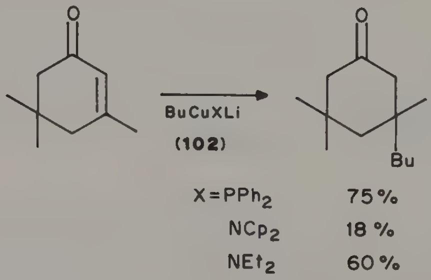
$PhS(CH_2{=}\overset{OEt}{C}{-})CuLi$

(101)

TABLE 26. Reaction of cuprates **86**, **100** and **101** with 2-cyclohexenone and carvone

Entry	Enone	Reagent	Yield (%)	Ref.
a	Cyclohexenone	**100** (R = Pr)	65	225
b	Cyclohexenone	**100** (R = *t*-Bu)	92–95	159,225
c	Cyclohexenone	**101**	50	225
d	Cyclohexenone	**86**	80	159
e	Carvone	**100** (R = *t*-Bu)	0	159
f	Carvone	**86**	65	159

As exemplified by the reaction of the heterocuprates **102** with isophorone (equation 35), steric inhibition in the reagent makes cuprate **102** ($X = NCp_2$) less effective than the less stable but smaller heterocuprate **102** ($X = NEt_2$)[215].



(35)

Lipshutz and coworkers[141,142,205,226–228] have recently introduced higher-order cyanocuprates **103** as reagents with improved stability.

$RR'Cu(CN)Li_2$

(103)

Comparative results summarized in Table 27 show the higher efficiency of these reagents in delivering a vinyl group in conjugate manner to isophorone, except for **103** R = vinyl, R′ = 2-Thienyl; entry g) for which the 1,2-addition by the thienyl group also takes place[227].

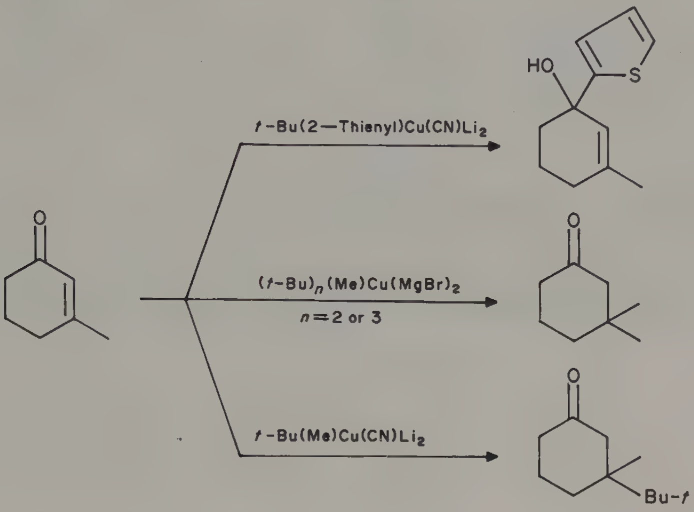
TABLE 27. Conjugate addition of a vinyl group to isophorone using various cuprates

Entry	Reagent	Yield (%)	Ref.
a	$(CH_2{=}CH)Cu(C{\equiv}C.Bu\text{-}t)Li$	52	168
b	$(CH_2{=}CH)_2CuLi.PBu_3$	60	163
c	$(CH_2{=}CH)Cu(PPh_2)Li$	64	214
d	$(CH_2{=}CH)Cu(NCp)_2Li$	18	214
e	$(CH_2{=}CH)_2Cu(CN)Li_2$	88	226
f	$(CH_2{=}CH)(Me)Cu(CN)Li_2$	>97	228
g	$(CH_2{=}CH)(Th)^a\ Cu(CN)Li_2$	49[b]	227

[a] Th = 2-Thienyl.
[b] 1, 2-addition of the thienyl group also takes place.

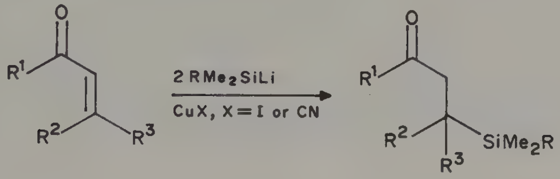
An analogous 1,2-addition of the 2-thienyl group occurs in the reactions of lithium bis(2-thienyl)cuprate with 2-cyclohexenone and benzalacetone[150].

In some cases, the auxiliary group becomes the transferred group, depending upon the nature of the organic moieties in the copper reagent (equation 36).



(36)

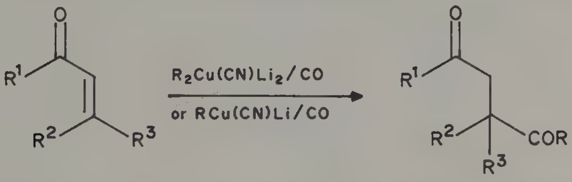
Organocopper reagents proved to be useful in the formation of β-silyl carbonyl compounds **104** (equation 37)[142,229–231].



(37)

(104)

Seyfert and Hui[232,233] described a method for direct nucleophilic acylation of enones and enals, using acylcuprates obtained by carbonylation of lower- or higher-order mixed organocuprates (equation 38).



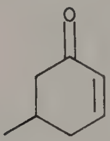
(38)

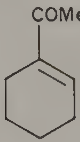
Yamamoto and coworkers described the reaction of the RCu–BF$_3$ complex with α,β-unsaturated compounds[234–236]. These organocopper–Lewis acid reagents have proved to be useful in the key steps of total synthesis of many natural products[237]. Comparative

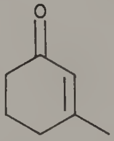
TABLE 28. Reaction of Bu_2CuLi and $BuCu–BF_3$ with α-enones

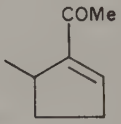
Entry	Enone	Reagent	Yield (%)		Ref.
			1,2-adduct	1,4-adduct	
a	$Me_2C{=}CHCOMe$	Bu_2CuLi	—	83	171
b	$Me_2C{=}CHCOMe$	$BuCu–BF_3$	55	45	236
c	$Me_2C{=}C(Me)COMe$	Bu_2CuLi	77	19	236
d	$Me_2C{=}C(Me)COMe$	$BuCu–BF_3$	7	14	236
e	**105**	Bu_2CuLi	—	72	236
f	**105**	$BuCu–BF_3$	—	20	236
g	**106**	Bu_2CuLi	—	74	236
h	**106**	$BuCu–BF_3$	—	90	236

results obtained from the reaction of the $RCu–BF_3$ complex and R_2CuLi with various α-enones are summarized in Table 28.


(105)


(106)


(107)


(108)

Although the mechanism by which the complex $RCu–BF_3$ reacts still remains unclear[237] (a cyclic transition state had been proposed[234–236]), it is noteworthy that this reagent is more sensitive to β,β-disubstitution than R_2CuLi (entries a and b), whereas an α substituent prevents the 1,2-addition (entries c and d). Moreover, the conjugate addition to the transoid enone **105** (entries e and f) is more effective with Bu_2CuLi than with $BuCu–BF_3$, while that to the cisoid enone **106** proceeds smoothly with the latter (entries g and h).

As shown in Table 29, the 1,4-addition of higher-order mixed organocuprates **109–111** is also largely improved by addition of $BF_3–Et_2O$. Other Lewis acids tested were ineffective[238].

$Ph_2Cu(CN)Li_2$ **(109)** $(CH_2{=}CH)(2\text{-Thienyl})Cu(CN)Li_2$ **(110)** $Me(2\text{-Thienyl})Cu(CN)LiMgBr$ **(111)**

TABLE 29. Effect of $BF_3–Et_2O$ on conjugate addition of higher-order cuprates **109–111** to α-enones

Enone	Reagent	Additive	Yield (%)	Ref.
Isophorone	**109**	—	0[a]	142
Isophorone	**109**	$BF_3–Et_2O$	95	142
Isophorone	**110**	—	49[a]	227
Isophorone	**110**	$BF_3–Et_2O$	98	238
108	**111**	—	29	228
	111	$BF_3–Et_2O$	85	228
107	**111**	—	34	228
	111	$BF_3–Et_2O$	73	228

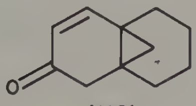
[a] 1,2-adduct is obtained in various amounts depending on the reaction temperature.

TABLE 30. Reaction of MeCu–$AlCl_3$ and Me_2CuLi with enones **76** and **112**

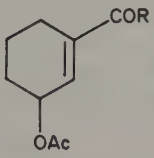
Enone	Reagent	1,4-addition	Ring opening	Overall yield (%)	Ref.
76	MeCu–$AlCl_3$	100	0	72	239
76	Me_2CuLi	48	52	—	199
112	MeCu–$AlCl_3$	100	0	75	239
112	Me_2CuLi	55	39[a]	90	182

[a] Reduction compound is also obtained (6%).

Ibuka and coworkers[239,240] have already demonstrated that organocopper(I)–Aluminium trichloride (RCu–$AlCl_3$) is a useful reagent for regio- and stereoselective 1,4-additions to the β′-cyclopropyl-α-enone **72**. Using homocuprate (Me_2CuLi), the 1,4-addition competes significantly with cyclopropane ring opening (see equation 24). Comparative results obtained in the reaction of these two reagents with enones **76** and **112** are summarized in Table 30.



(112)



R=Me **(113)**
R=Ph **(114)**

The conjugate addition of a methyl or a phenyl group has been performed by RCu–$AlCl_3$ on γ-acetoxy or γ-trialkylsilyloxy α,β-unsaturated ketones[241,242], while these ketones are reduced by lithium dimethylcuprate to give α,β- and/or β,γ-unsaturated ketones[186,188,191,241,242] **74** and **75** (see equation 27). An illustration is given in Table 31 with γ-acetoxy enones **73**, **113** and **114**.

Chlorotrimethylsilane (TMSCl) can be used in combination with organocopper reagents, and added before the α,β-unsaturated carbonyl compound. It acts not only as a simple enolate trap[143], but it accelerates and improves the 1,4-addition reactions[149,193,243–246].

As exemplified in Table 32, the addition of chlorosilanes greatly enhances the rate of conjugate addition of homocuprates. Chlorosilanes used together with an activator such as HMPA or 4-dimethylaminopyridine (DMAP) strongly promote the conjugate addition of the unreactive BuCu[245].

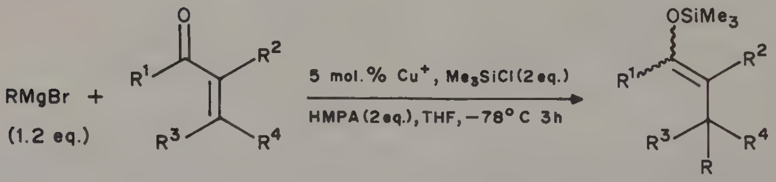
TABLE 31. Reaction of MeCu–$AlCl_3$ and Me_2CuLi with γ-acetoxy-α,β-enones **73**, **113** and **114**

Enone	Reagent	Yield (%) 1,4-addition	Yield (%) Reduction products	Ref.
73	MeCu–$AlCl_3$	82	—	241
	Me_2CuLi	—	67	186
113	MeCu–$AlCl_3$	71	—	241
	Me_2CuLi	—	39	241
114	MeCu–$AlCl_3$	81	—	241
	Me_2CuLi	—	91	241

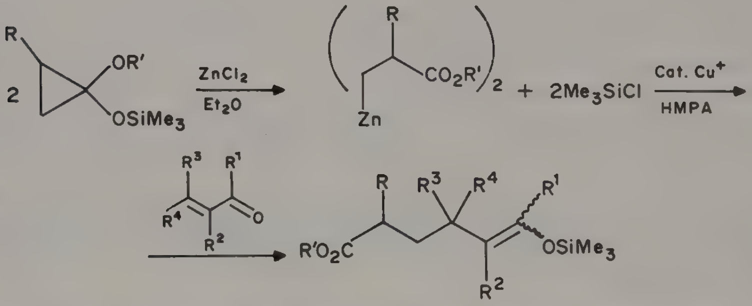
TABLE 32. Chlorosilane-assisted addition of organocopper reagents to α,β-unsaturated carbonyl compounds

Enone or enal	Reagent	Additive	Yield (%)	Ref.
Acrolein	Bu_2CuLi	—	25	206
Acrolein	Bu_2CuLi	Me_3SiCl	60	206
2-Cyclohexenone	$(EtCH{=}CH)_2CuLi$	—	65	149
2-Cyclohexenone	$(EtCH{=}CH)_2CuLi$	Me_3SiCl	86	244
3-Me-2-cyclohexenone	Bu_2CuLi	—	28	245
3-Me-2-cyclohexenone	Bu_2CuLi	Me_3SiCl	99	245
3-Me-2-cyclohexenone	Bu_2CuLi	t-$BuMe_2SiCl$	31	245
3-Me-2-cyclohexenone	Bu_2CuLi	t-$BuMe_2SiCl$/HMPA	95	245
3-Me-2-cyclohexenone	BuCu	Me_3SiCl	24	245
3-Me-2-cyclohexenone	BuCu	Me_3SiCl/HMPA	89	245

The TMSCl/HMPA mixture also promotes the conjugate addition of copper-catalyzed Grignard reagents[247] (equation 39) or zinc homoenolate[248] (equation 40) to enals and enones.

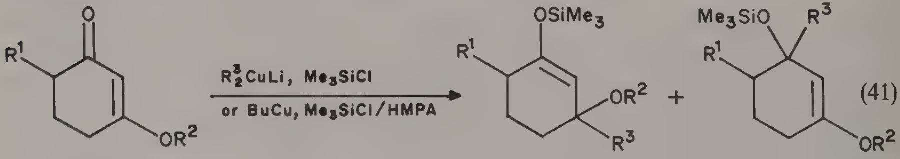


(39)



(40)

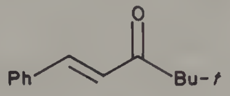
3-alkoxy-2-cyclohexenones **115**, reported to be unreactive towards organocopper species, due to their very low reduction potential ($E_{red} < -2.40$ V), react with R_2CuLi in the presence of TMSCl[244,245] or with BuCu in the presence of TMSCl/HMPA[245], although a mixture of 1,2- and 1,4-adducts is obtained (equation 41).



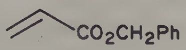
(41)

(115)

An attractive hypothesis to account for the observed rate acceleration involves coordination of TMSCl with the carbonyl oxygen which raises the reduction potential. However, several lines of evidence argue against this hypothesis: (i) ^{1}H NMR studies of a mixture of enone and TMSCl reveal no sign of such coordination[243,245], (ii) there is only a minor increase in relative reaction rate with increasing concentration of TMSCl[243], and (iii) enone **116** reacts faster with Me_2CuLi than acrylate **117** although the carbonyl of **117** would appear more basic than that of **116**[243]. Corey and Boaz[193,243] suggest that TMSCl accelerates cuprate–enone conjugate addition by trapping an initial d–π^* complex **79** and forcing conversion to β-carbon adduct **80** (see equation 31).

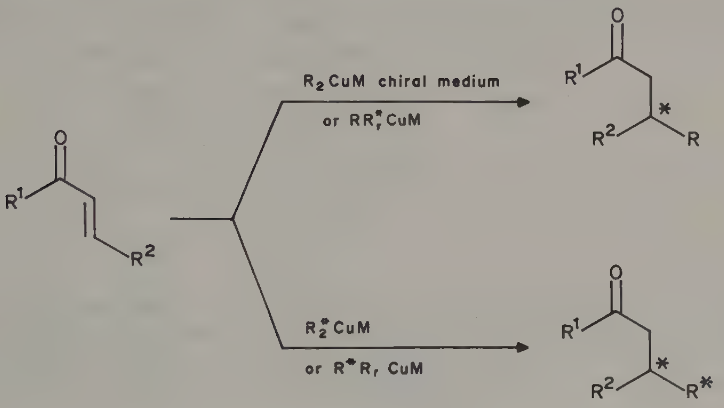


(116)



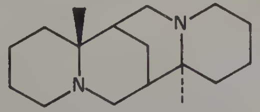
(117)

Regioselective conjugate addition of organocopper reagents to prochiral α-enones provides possibilities for asymmetric synthesis with the introduction of a new chiral centre in the β-position of the substrate. Studies have focused on two points: (i) the selective formation of one enantiomer using a chiral medium (usually in the form of a chiral coordinating ligand) or cuprates ($R_tR_r^*CuM$) containing a chiral non-transferable group, and (ii) the formation of diastereomeric products using cuprates with a chiral transferable ligand (R_2^*CuM or $R_t^*R_rCuM$) or chiral substrates (equation 42).



(42)

Asymmetric 1,4-addition of achiral magnesium or lithium dialkyl cuprates to prochiral α,β-unsaturated ketones in a chiral medium such as ($-$)sparteine (**118**)[249] or (+)-*S*,*S*-1,4-dimethylamino-2,3-dimethoxybutane (**119**)[250,251] results in low optical yields (3–6% and 6.5–15%, respectively).



(118)

$Me_2NCH_2CH(OMe)CH(OMe)CH_2NMe_2$

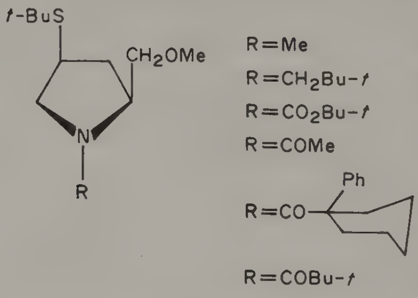
(119) (+) (*S*,*S*)

The use of 4(alkylthio)hydroxyproline derivatives **120**–**125** as bidentate ligands yields

TABLE 33. Asymmetric methylation of chalcone using Me_2CuLi in Et_2O at − 50 °C in the presence of chiral ligands **120–125**[252]

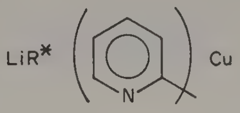
Ligand	Yield (%)	e.e. (%)	Configuration
120	98	2	*R*
121	97	7	*R*
122	95	33	*R*
123	71	33	*R*
124	93	68	*R*
125	95	75	*R*
125 + TMEDA	95	50	*R*

up to 75% of enantiomeric excess (e.e.) in the β-methylation of chalcone with lithium dimethyl cuprate[252]. As shown in Table 33, in all cases the R enantiomer is formed predominantly and the N-alkylated ligands **120** and **121** induce very low enantioselectivity, whereas the N-carboalkoxylated and N-acylated ligands **122–125** lead to much higher optical yields. The effectiveness of amide ligands in comparison with amine ligands indicates the importance of chiral ligand–lithium complexation, which is confirmed by the decrease in the enantiomeric excess upon addition of TMEDA.

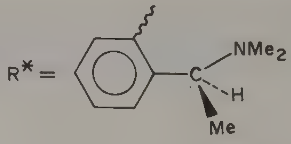


(**120**)
(**121**)
(**122**)
(**123**)
(**124**)
(**125**)

The degree of the asymmetric induction obtained in the reaction of benzalacetone with the mixed cuprate **126** is considerably higher (e.g. 84%)[253] than when a methyl group is transferred (e.e. 5%)[254,255] by cuprate **127** using the same chiral ligand. It seems probable that the pyridine nitrogen atom interacts with the metal atom in a stereodifferentiating step.

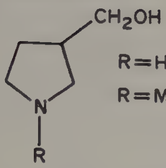


LiR*MeCu

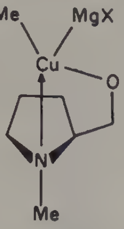


(**126**) (**127**)

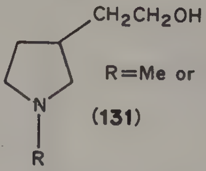
Although the heterocuprates LiR(Het)Cu (Het = R′O, R′S, R'_2N) are valuable reagents for conjugate addition, the methylation of chalcone using reagents generated from various aminoalcohols affords optical yields of 0–31%[256]. Similarly, the alkylation of 2-cyclohexenone with heterocuprates derived from chiral alcohols[257,258], thiols[258] and amines[257] and from N-methyl ephedrine[259] affords equally low optical yields. The higher enantiomeric excess (e.e. 15%) is obtained with organocopper reagents derived from the (*S*)-prolinol **128**[257] or N-methyl prolinol **129**[258].



R=H (**128**)
R=Me (**129**)



(**130**)

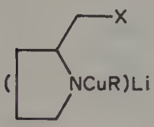


R=Me or CO_2Bu-*t*

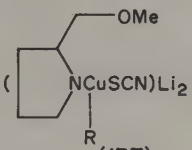
(**131**)

Imamoto and Mukaiyama have achieved *β*-methylation of chalcone in high optical yield (68%) using a large excess of chiral magnesium heterocuprate derived from (*S*)-prolinol[260]. This work was extended by Leyendecker and coworkers[261] (Table 34). Except for chalcone, the highest asymmetric induction is realized with (*S*)-prolinol. The optical yields increase on going from toluene (or benzene) to THF for the (*S*)-N-methyl prolinol derived cuprate and decrease for the (*S*)-prolinol bound cuprate. Asymmetric induction is viewed as arising from different chelation mechanisms: magnesium-arene *π*-coordination in the N-methyl system and hydrogen-carbonyl chelation in the prolinol system[261]. Higher optical yields (80%)[262] are achieved upon dilution, suggesting the importance of an internally chelated species **130** assumed to possess higher enantiodifferentiating ability. Higher homologues such as **131** proved less effective (0–2% e.e.)[262].

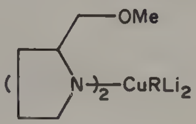
Very recently Dieter and Tokles undertook an extensive investigation of the conjugate addition of chiral organoheterocuprates **132**–**138** derived from (*S*)-prolinol[263]. The more characteristic results are summarized in Table 35.



X=OMe (**132**)
X=SMe (**133**)
X=SPh (**134**)
X= (**135**)
X=OLi (**136**)



(**137**)



(**138**)

The magnitude of the optical yields is sensitive to all the reaction parameters. The highest enantiomeric excesses are obtained at lower temperature in solvents such as Et_2O or toluene for cyclohexenone and acyclic enones using lower-order cuprates **132** or **133** and higher-order cuprate **138**. The (−)-*S*-prolinol-derived chiral cuprates induce predominant formation of either the *R*- or *S*-enantiomer depending upon the solvent, the cuprate composition and the substrate structure. The lower order cuprates **132** and **133** selectively afford the *S*-enantiomer in Et_2O and the *R*-enantiomer in THF or toluene, while higher-order cuprates **137** and **138** selectively afford the *R*-enantiomer in Et_2O or toluene, except for cyclopentenone.

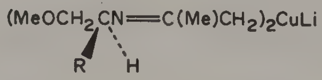
The influence of the substrate structure, the cuprate composition and the solvent upon the induced absolute stereochemistry is more difficult to understand owing to the lack of a thorough knowledge of the structure and aggregation of the cuprate reagent, and the

TABLE 34. Asymmetric induction in methylation of α-enones with $CH_3(R^*O)CuLi$ derived from **128** or **129**[261]

Enone	Alcohol inductor	Solvent	Yield (%)	e.e. (%)	Configuration
2-Cyclohexenone	**129**	PhH	64	1	*R*
2-Cyclohexenone	**129**	THF	70	5	*R*
2-Cyclohexenone	**128**	PhH	36	37	*S*
2-Cyclohexenone	**128**	THF	61	29	*S*
Benzalacetone	**129**	PhMe	80	3	*R*
Benzalacetone	**129**	THF	82	10	*S*
Benzalacetone	**128**	PhMe	36	37	*S*
Benzalacetone	**128**	THF	61	29	*S*
Chalcone	**129**	PhMe	82	2	*S*
Chalcone	**129**	THF	81	41	*S*
Chalcone	**128**	PhMe	42	20	*S*
Chalcone	**128**	THF	70	15	*S*

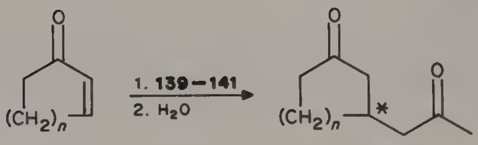
reaction mechanism. However, a simple model has been proposed to rationalize a body of data[263].

Methodologies based upon diastereoselective C—C bond formation by conjugate addition of a chiral transferable group are, in general, more successful. Interesting diastereoselectivities are observed by Yamamoto and coworkers[264,265] in the addition of chiral lithium bis(azoenolato)cuprates **139**–**141** to prochiral cyclic enones. The primary products, hydrolyzed during the workup, yield optically active 3-acetonylcycloalkanones **142** in enantiomeric excess ranging from 17 to 75% (equation 43) (Table 36).



$$(MeOCH_2\underset{R\ \ \ H}{C}N{=}C(Me)CH_2)_2CuLi$$

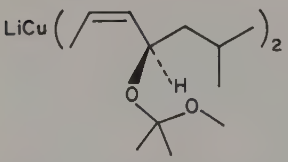
R=CH₂Ph (**139**)
R=*i*-Pr (**140**)
R=*t*-Bu (**141**)



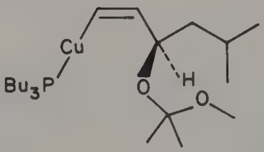
(**142**)

(43)

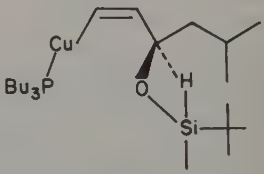
The conjugate addition of chiral organocopper reagents **143**–**145** to 2-methyl-2-cyclopentenone proceed with a high degree of stereoselectivity (Table 37)[266,267].



(**143**)



(**144**)



(**145**)

TABLE 35. Asymmetric induction from conjugate addition of chiral organo (hetero) cuprates **132**–**138** to α-enones at −78 °C[263]

Enone	Reagent	Solvent	Yield (%)	Optical yield (%)	Configuration
2-Cyclohexenone	**132** (R = Me)	Et_2O	73	75	*S*
	132 (R = Me)	PhMe	62.5	70	*R*
	132 (R = Me)	THF	60	53	*R*
	132 (R = Bu)	Et_2O	38	56	*S*
	132 (R = t-Bu)	Et_2O	25	67	*S*
	133 (R = Me)	Et_2O	68	80	*S*
	133 (R = Bu)	Et_2O	46	58	*S*
	133 (R = *t*-Bu)	Et_2O	51	69	*S*
	134 (R = Me)	Et_2O	77.5	71	*S*
	134 (R = Me)	PhMe	71	80	*R*
	134 (R = Me)	THF	70	52	*R*
	135 (R = Me)	Et_2O	39	8	*S*
	136 (R = Me)	Et_2O	54	69	*R*
	137 (R = Me)	Et_2O	57	75	*R*
	137 (R = Me)	PhMe	68	83	*R*
	138 (R = Me)	Et_2O	24	20	*R*
2-Cyclopentenone	**132** (R = Me)	Et_2O	36	23	*S*
	132 (R = Me)	PhMe	70	37	*R*
	132 (R = *t*-Bu)	Et_2O	56	35	*S*
	133 (R = Me)	Et_2O	60	33	*S*
	134 (R = *t*-Bu)	Et_2O	50.4	50	*S*
3-Penten-2-one	**132** (R = Bu)	Et_2O	36	64	*S*
	133 (R = Bu)	Et_2O	52	64	*S*
	134 (R = Bu)	Et_2O	51	61	*S*
	137 (R = Bu)	Et_2O	37	68	*R*
3-Octen-2-one	**132** (R = Me)	Et_2O	46	58	*R*
	133 (R = Me)	Et_2O	78	83	*R*
	134 (R = Me)	Et_2O	42	74	*R*
	137 (R = Me)	Et_2O	56	75	*R*

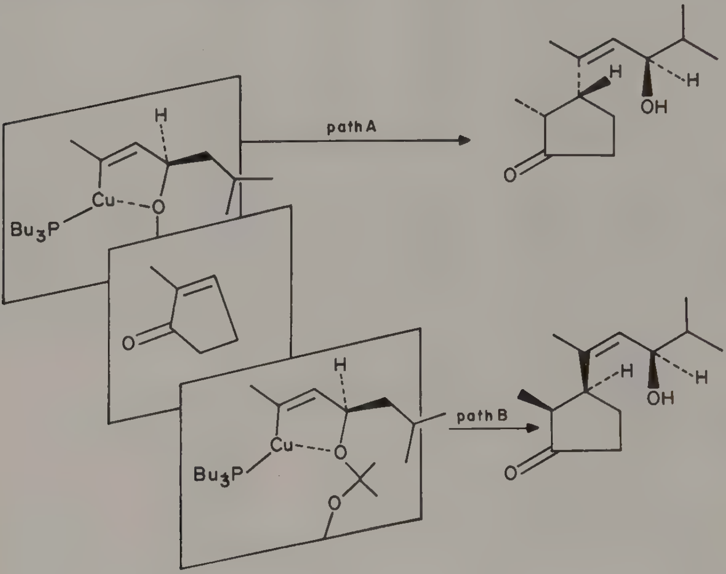
TABLE 36. Asymmetric conjugate addition of chiral reagents **139**–**141** to 2-cyclohexenone and 2-cyclopentenone (equation 43)[264]

Enone	Reagent	Yield (%)	Optical yield (%)	Configuration
2-Cyclohexenone	(*S*) **139**	21	28.6	*R*
	(*S*) **140**	46	22.5	*R*
	(*S*) **141**	30	44.2	*S*
	(*R*) **141**	31	43.6	*R*
2-Cyclopentenone	(*S*) **139**	54	16.5	*R*
	(*S*) **140**	75	26.9	*S*
	(*S*) **141**	89	75.4	*R*

TABLE 37. Relative yields of diastereomers **146** and **147** from the conjugate addition of reagents **143**–**145** to 2-methyl-2-cyclopentenone[266]

Reagent	**146**	**147**	Overall yield (%)
143	14	86	67
144	10	90	70
145	18	82	54

Owing to the interaction between the isobutyl group and the cyclopentenone ring, the addition reaction mainly proceeds through path B rather than A, giving rise preferentially to the diastereomer **147** (equation 44).



(146)

(44)

(147)

TABLE 38. Diastereomeric excess (d.e.) from conjugate addition of cuprates **148** and **149** to various enones in Et_2O at 0 °C[268]

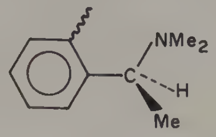
Enone	Reagent	d.e. (%)	Overall yield (%)
2-Cyclohexenone	**148**	> 98	87
2-Cyclohexenone	**149**	> 98	57
2-Cyclopentenone	**149**	84	—
MeCH=CHCOMe (*E*)	**148**	80	30
MeCH=CHCOMe (*E*)	**149**	82	70
PhCH=CHCOMe (*E*)	**148**	> 98	50
PhCH=CHCOMe (*E*)	**149**	> 98	44
PhCH=CHCOBu-*t*	**148**	76	67
PhCH=CHCOBu-*t*	**149**	> 98	42

One diastereomer is also formed in large excess (76–98%) on addition of the chiral (*S*)-2-(1-dimethylaminoethyl)phenyl group to various enones (Table 38) using the homocuprate **148** or the mixed 2-thienyl cuprate **149**[268–270].

LiR^*_2Cu **(148)**

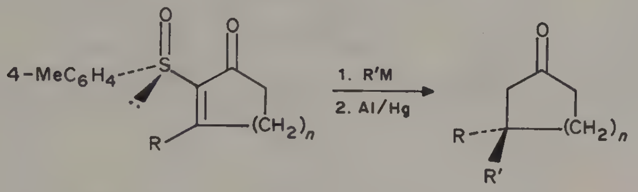
$LiR^*(2\text{-Thienyl})Cu$ **(149)**

$R^* =$



The steric outcome leading preferentially to the (*S,S*)-diastereomer is the same for all the enones, and the diastereoselectivities are of the same order of magnitude, indicating that the chelation by the dimethylaminoethyl group in the entering group is more important than the steric difference between the substrates[270].

Similarly, Posner and coworkers have introduced an elegant synthetic methodology for the enantio-controlled formation of a β C—C bond via asymmetric conjugate addition of various achiral organometallic reagents to the enantiomerically pure 2-(arylsulphinyl)cycloalkanones **150** (equation 45)[271–277].



(45)

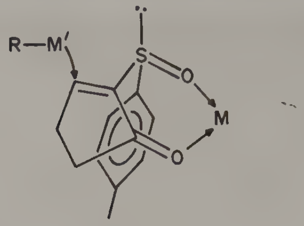
(150) $n = 1, 2$ **(151)**

The data from Table 39 on asymmetric synthesis of 3,3-disubstituted cyclopentanones **151** show that no one type of organocopper reagent is superior over the others. Although lithium dimethyl cuprate and lithium ditolylcuprate work well (entries a and f), lithium di-*n*-butyl cuprate does not (entry d).

The configuration of the opposite enantiomers resulting from the reversed sequences, i.e. the addition of a methyl group to 3-tolylcyclopentenone sulphoxide or of a tolyl group to 3-methylcyclopentenone sulphoxide, may be predicted using the chelate model **152** proposed for asymmetric conjugate addition of Grignard reagents in the presence of a complexing metal[276].

TABLE 39. Asymmetric synthesis of 3,3-disubstituted cyclopentanones **151** ($n = 1$) via equation 45 in THF[275]

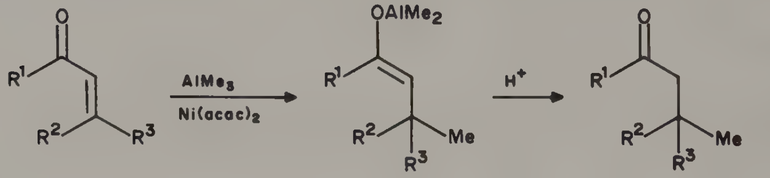
Entry	R in enone **150**	Reagent	e.e. (%)	Yield (%)	Configuration
a	4-MeC_6H_4	Me_2CuLi	78	58	*S*
b	4-MeC_6H_4	$Me(PhS)CuMgBr$	73	77	*S*
c	4-MeC_6H_4	$Me_5Cu_3Li_2$	65	44	*S*
d	4-MeC_6H_4	Bu_2CuLi	—	0	—
e	4-MeC_6H_4	$Bu(PhS)CuMgCl$	81	69	—
f	Me	$(4\text{-MeC}_6H_4)_2CuLi$	90–93	53	*R*
g	Me	$Bu(PhS)CuMgCl$	53	79	—
h	Me	$Bu(t\text{-BuO})CuMgCl$	88	61	—



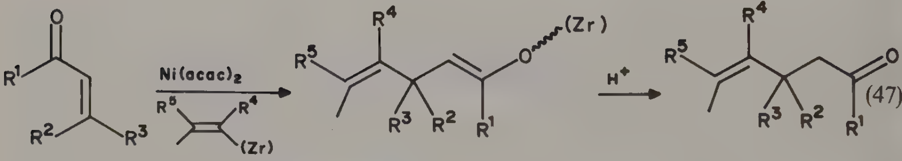
(152)

2. *Aluminium, zirconium, zinc, palladium, lanthanides*

$Ni(acac)_2$-catalyzes the conjugate methylation of several unsaturated ketones by trimethylalanes with varying degrees of success (equation 46)[277,278] and the addition of terminal alkenyl units to α-enones using alkenylzirconium(IV) complexes (equation 47)[279–282].



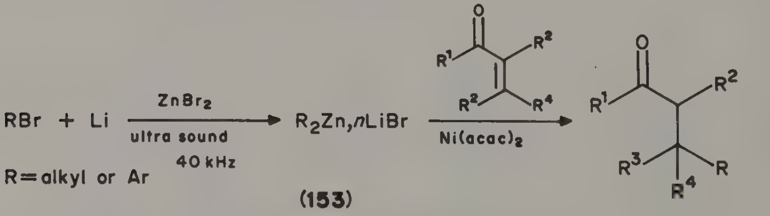
(46)



(47)

$(Zr)=Cp_2ZrCl$

Luche and coworkers used $Ni(acac)_2$ for the conjugate addition of diorganozinc reagents **153**, prepared by sonication (equation 48)[283–286].



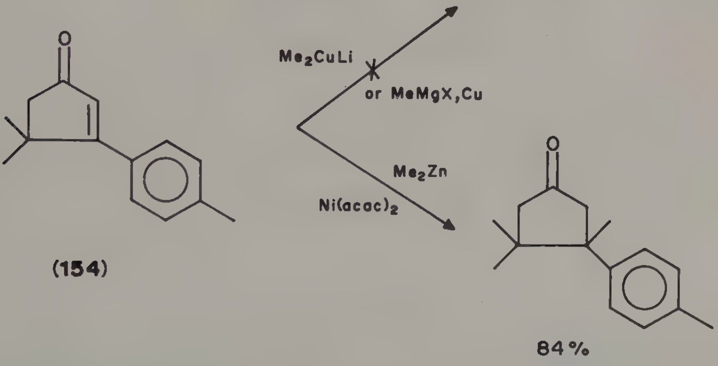
(48)

The thermal stability of these reagents allows the reaction to proceed at room temperature in many instances. Arylation or alkylation of α,β-unsaturated ketones usually proceeds well even with β,β-disubstituted-α-enones (Table 40) or with the enone **154**[287],

TABLE 40. Conjugate addition of R_2Zn reagents to α-enones[283–285]

Enone	R in R_2Zn	Yield (%)
2-Cyclohexenone	n-C_7H_{15}	88
	$Me_2C{=}CH$	83
	4-PhC_6H_4	92
	$PhCH{=}CH$	84
	$PhCH_2$	64
2-Cyclopentenone	$Me_2C{=}CH$	21
	4-MeC_6H_4	76
3-Me-2-cyclopentenone	2-MeC_6H_4	72
	4-MeC_6H_4	87
Isophorone	Me	90
	4-MeC_6H_4	94
Mesityl oxide	Ph	98

which fails to react with lithium dimethyl cuprate or in a copper-catalyzed Grignard reaction[288] (equation 49).



(154)

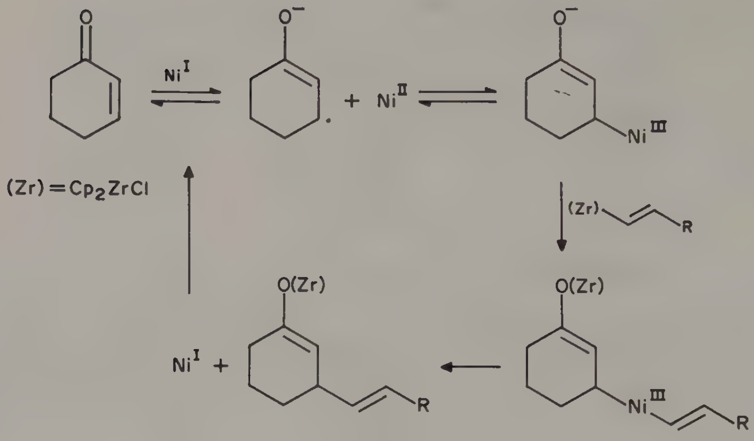
(49)

Although aryl groups are selectively transferred to the β-position of α,β-unsaturated aldehydes, the delivery of an alkyl group is not satisfactory[286].

The role of $Ni(acac)_2$ is quite important, since in its absence the reaction of $(4\text{-}MeC_6H_4)_2Zn$ with 2-cyclohexenone proceeds in a much reduced rate and the methylation of enone **154** does not occur[285]. The reaction mechanism is assumed to have some analogy to the one proposed by Schwartz and coworkers for the nickel-catalyzed organozirconium addition reactions[279–282] which involve one-electron reduction of the substrate by catalytically active reduced valent Ni(I) species (equation 50).

Triorganozincates **155** and **156** are another type of reagent that can be used to add alkyl groups in a 1,4-fashion to α,β-unsaturated ketones. They have not, however, been as extensively studied as cuprates, and the scope of their reactions remains to be established.

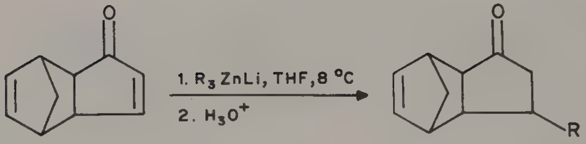
Isobe and coworkers demonstrated that R_3ZnLi, prepared in THF by mixing zinc halide (or its TMEDA complex) and alkyl lithium in a 1:3 molar ratio (equation 51), reacts with the enone **157** (equation 52) to give excellent yield of the 1,4-addition product[289].



(50)

R_3ZnM **(155)** $R'R_2ZnM$ **(156)** M=Li or MgX

$$3\,RLi \xrightarrow[ZnCl_2/TMEDA]{ZnCl_2 \text{ or}} R_3ZnLi + 2\,LiCl \tag{51}$$



(157)

(52)

The yields are dependent of the counter halide anion, the highest yields being obtained with zinc chloride. The steric effect of R in the complex has been examined using primary, secondary and tertiary butyllithium. Steric bulk does not affect the mode of addition but reduces the reaction velocity, since bulkier reagents give a lower amount of 1,4-adducts for a limited reaction period.

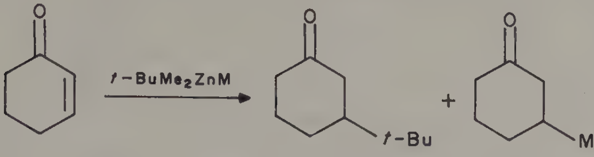
Langer and Seebach have shown that, like cuprates, the 1,4-addition reactions of zincates are enantioselective when carried out in a chiral medium[250]. More recently, Watson and Kjonaas showed that mixed triorganozincates **156** (M = Li, R = Me) selectively transfer the R′ group (R′ = *n*-Bu or *s*-Bu) rather than the methyl group[290].

Solvent effect and additive studies have been carried out by Oshima and coworkers with symmetrical and unsymmetrical triorganozincates. THF or Et_2O is the best solvent[291]. Hydrocarbon solvents are usually employed. Methylene chloride gives lower yields and unsymmetrical decreased selectivity with unsymmetrical zincates. DME and DMF suppress the reaction. Among the various additives studied it appears that the methylation of 2-cyclohexenone with Me_3ZnLi is catalyzed by cobalt complexes.

Grignard reagents have been also used in place of alkyllithium. Depending upon the halide, the 1,4-addition of R_3ZnMgX is contaminated by 1,2-addition products when

R = Ph and Me, but is essentially free of these compounds when R = *n*-Bu or *i*-Pr. Evidently, the yields are highest when X = Cl[292].

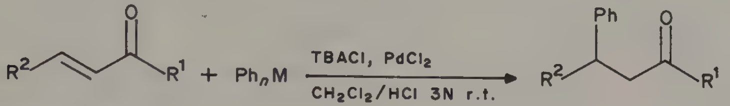
With unsymmetrical zincates, the selectivity of the transfer of the different groups is very dependent on the metal counter ion, as exemplified by the reactions of 2-cyclohexenone with 1.2 molar equivalents of *t*-$BuMe_2ZnM$ in THF at − 78 °C for one hour (equation 53).



(53)

M=MgCl	5%	68%
M=Li	20%	10% (+38% recovered enone)

Phenyl palladium compounds, generated *in situ* from phenylmercury or phenyltin compounds and palladium(II) salts, react with α,β-unsaturated ketones in a two-phase acidic system in the presence of a catalytic amount of tetrabutyl ammonium chloride (TBACl) to give the conjugate addition product (equation 54)[293–297].

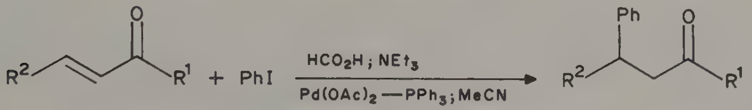


(54)

M=Sn; *n*=4

M=HgCl; *n*=1

Iodobenzene, in the presence of a catalytic amount of palladium, an excess of formic acid and triethylamine, provides a useful alternative to phenylmercury compounds (equation 55)[297,298].



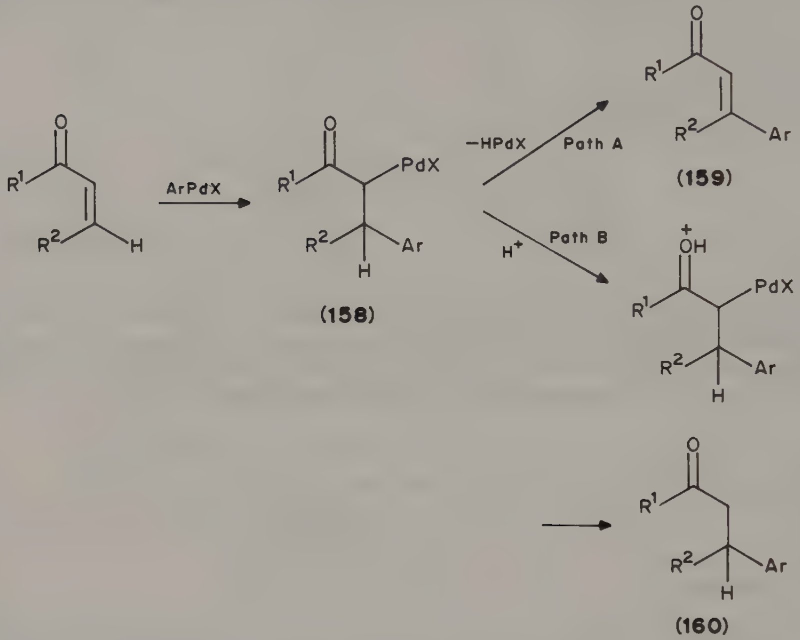
(55)

Unhindered α-enones react with these reagents, giving rise to the conjugate addition-type products. The main limitation seems to arise from the steric hindrance in the substrate. Thus, isophorone, cholest-4-ene-3-one and carvone fail to react with phenylmercury or phenyltin compounds under palladium catalysis[293].

By contrast, a wide variety of aryl units containing electron-donating and electron-withdrawing substituents, such as Me, Cl, CHO, COOMe, COOH, OH, OMe, NHCOMe and NO_2, are successfully transferred to the β-carbon of benzalacetophenone[294,298]. However, the substituent in the aryl moiety of the reagent can affect the reaction rate.

The reaction proceeds through an initial addition of the arylpalladium reagent to form the intermediate **158**, which undergoes *cis* elimination of HPdX (path A) or heterolytic fission of the palladium carbon bond (path B) giving rise to either the product of vinylic substitution **159** or the conjugate adduct **160** (equation 56).

Competition between $C_{(\alpha)}$Pd bond cleavage, coupled with the formation of $C_{(\alpha)}$H bond and *syn* elimination of HPdX, appears to be dependent upon a complex combination of steric, electronic and medium factors. An acidic medium is critical: in its absence, the percentage of the vinylic-substituted product is related to the amount of the added palladium. The formation of the aryl palladium intermediate **158** seems to be the rate-limiting step and the acid-catalyzed elimination of the Pd(II) species is faster than any other reaction pathway. The ammonium salt or triethylamine is also important.



(56)

α-enals^{299} and α, β, γ, δ-dienones^{300} give exclusively the 1,4-addition products. β, β-diaryl ketones or aldehydes **162** are obtained from aryl iodide in the presence of a palladium catalyst and β-unsubstituted α, β-carbonyl compounds (equation 57)^{301}.

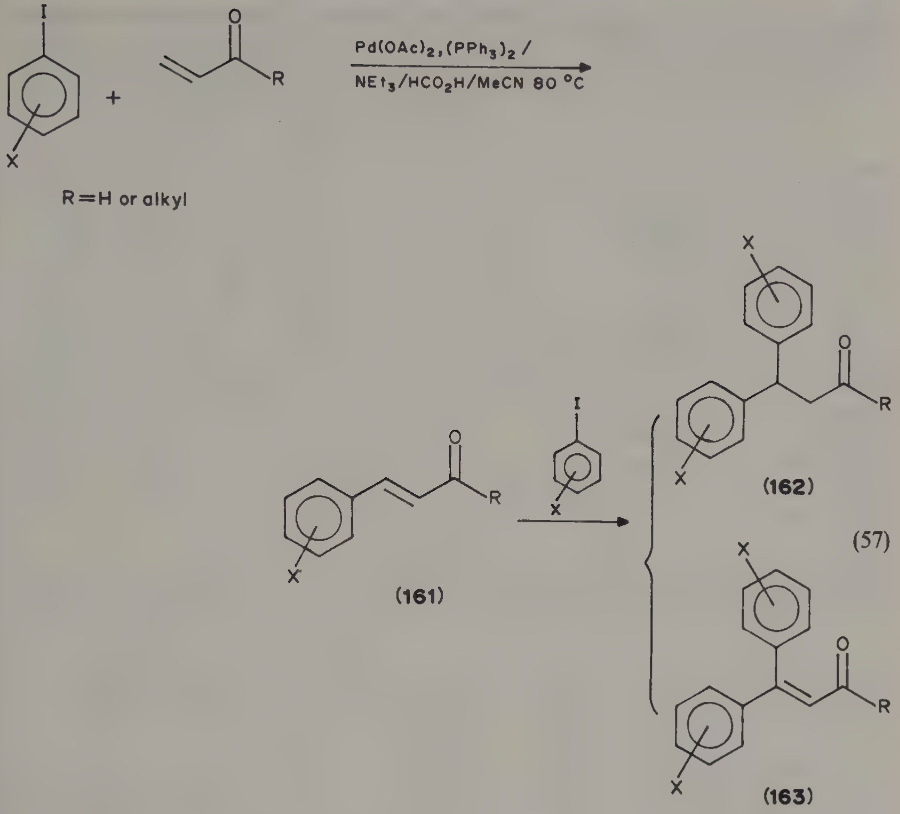
The reaction proceeds through a vinylic substitution followed by an *in situ* conjugate addition to the β-substituted α, β-unsaturated carbonyl compounds **161**. Compounds **163**, derived from a double vinylic-substitution reaction, are also obtained in variable amounts^{301}.

By contrast, benzene addition to α-substituted chalcones **164** using palladium-catalyzed reaction of benzene/acetic acid in reflux leads to the vinylic substitution. The conjugate adduct is obtained only when the α substituents are bulky and powerfully electron-withdrawing (equation 58)^{302}.

Organometallic compounds involving lanthanides are harder nucleophiles than Grignard reagents^{303,304}. Divalent organolanthanide σ-complexes (RLnI with Ln = Ce, Sm, Eu and Yb)$^{304-306}$ or organocerium(III) reagents ($RCeCl_2$)$^{307-310}$ react with α-enones to afford the 1,2-addition products in higher regioselectivity as compared to organolithium and Grignard reagents (Table 41).

The reactions of various organocerium reagents $RCeCl_2$ (R = Me, Bu, Ph) with (*E*)- and (*Z*)-1-(4-methoxyphenyl)-3-phenyl-2-propenone leads to the allylic alcohols in excellent yields without isomerization of the double bond^{310}. This selective 1,2-addition proceeds through a direct nucleophilic addition like the selective 1,2-reduction of α-enones with $NaBH_4/CeCl_3$ reagent system^{311}.

Results obtained in reactions of reagents **165**^{303} and **166**^{312} with α-enones (Table 42)

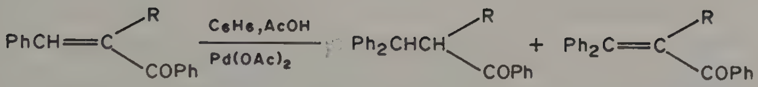


(161)

(162)

(163)

(57)



$$\mathrm{PhCH{=}C(R)COPh} \xrightarrow[\mathrm{Pd(OAc)_2}]{\mathrm{C_6H_6,AcOH}} \mathrm{Ph_2CHCH(R)COPh} + \mathrm{Ph_2C{=}C(R)COPh} \qquad (58)$$

(164)

R=H	0%	74.8%
R=Br	0%	42.6%
$R=NO_2$	20.2%	5.1 %
$R=CO_2Et$	12.2 %	56.5%
R=COPh	52.5%	8.0%

show that the 1, 2-addition is favoured over the 1, 4-addition by the presence of β-substituents on the substrate (entries a and b) the lower bulk of the organic moiety delivered (entries b and c) and by low temperatures (entries d, f and g).

$[\mathrm{Li(TMEDA)_2}][\mathrm{Lu(Bu\text{-}}t)_4]$ $[\mathrm{Li(TMEDA)}]_3[\mathrm{LnMe_6}]$ Ln = Pr or Sm

(165) **(166)**

TABLE 41. Product distribution in the reactions of organolithium, organomagnesium and organolanthanides with α-enones in THF

Enone	Reagent	Temperature (°C)	Time (min)	Yield (%) 1,2-adduct	Yield (%) 1,4-adduct	Ref.
Chalcone	PhLi	– 30	40	75	15	306
	PhMgI	20	180	—	90	306
	PhYbI	– 40	40	75	—	306
	PhCeI	– 40	40	60	—	306
	PhEuI	– 40	40	55	—	306
	PhSmI	– 40	40	65	—	306
	PhMgBr	0	60	5	81	309
	PhMgBr, $CeCl_3$	0	60	58	33	309
Benzalacetone	BuMgBr	0	60	21	69	309
	BuMgBr, $CeCl_3$	0	60	78	6	309
Cyclohexenone	*i*-PrMgCl	0	60	12	53	309
	i-PrMgCl, $CeCl_3$	0	60	91	5	309

TABLE 42. Product distribution in reactions of **165** and **166** with α-enones[303,312]

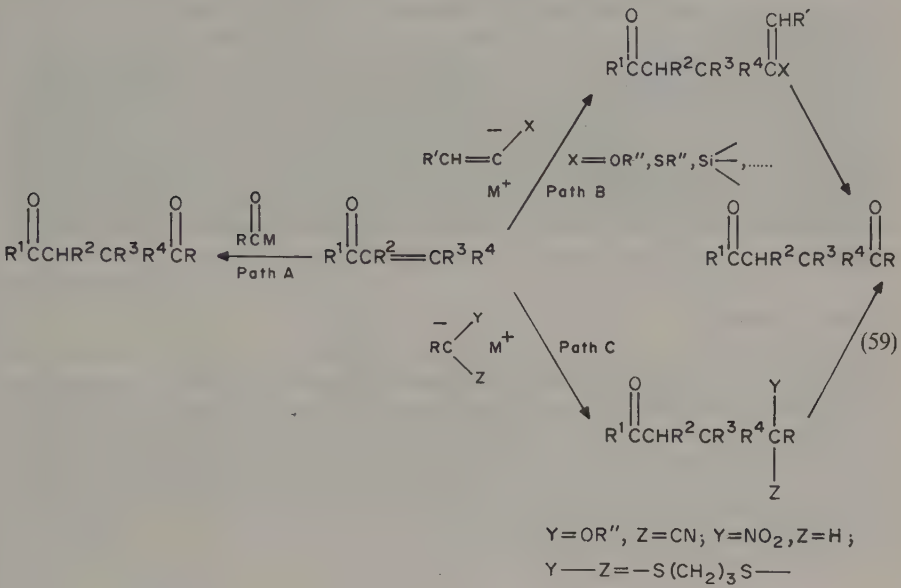
Entry	Enone	Reagent	Solvent	Temperature (°C)	Yield (%) 1,2-adduct	Yield (%) 1,4-adduct
a	CH_2=CHCOMe	**165**	Et_2O	– 78	50	50
b	Me_2C=CHCOMe	**165**	Et_2O	– 78	> 80	< 20
c	Me_2C=CHCOMe	**166**	THF	– 78	> 95	< 5
d	Cyclohexenone	**165**	Et_2O	– 78	70	30
e	Cyclohexenone	**166**	THF	– 78	> 80	< 20
f	Cyclohexenone	**165**	Et_2O	20	> 75	< 25
g	Cyclohexenone	**165**	Et_2O	34	> 66	< 33

III. NUCLEOPHILIC 1,4-ACYLATION OF ENALS AND ENONES

Among the numerous reagents which lead to a conjugate nucleophilic addition to α,β-unsaturated aldehydes or ketones, those that correspond to an acyl anion addition present a great potential interest to organic chemists. The resulting 1,4-diketones or 1,4-keto aldehydes are useful intermediates for further elaboration of natural products and related compounds involving furan and cyclopentenone ring systems[313,314].

The general area of acylation was reviewed by Seebach in 1969[315] and by Seebach and Kolb in 1974[316], and more recently by Lever[317] and Hase and Koskimies[318]. The use of acyl anion equivalents derived from cyanohydrins, protected cyanohydrins and α-dialkylaminonitriles was very well explored by Albright in 1983[12]. The more recent and valuable methods are discussed below in the peculiar case of nucleophilic 1,4-addition of acyl anion to α,β-unsaturated aldehydes and ketones. Although some methods are laboratory curiosities and/or mechanistic challenges related to the 1,2 and 1,4 competitive additions discussed above, other methods are taking their place beside classical carbonyl chemistry as important synthetic procedures.

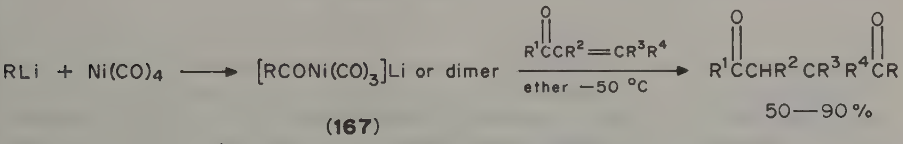
The two pathways to the formation of 1,4-dicarbonyl derivatives from nucleophilic addition to enones and enals use (i) direct nucleophilic 1,4-acylation with acylmetallic compounds (path A in equation 59) and (ii) reagents containing masked functionality to invert carbonyl reactivity of the electrophilic acyl group (equation 59, path B and C, e.g. metallated derivatives of enols and other latent carbonyl functions).



(59)

A. Acylmetallic Reagents

Acylmetallic intermediates in which the metal ion is not of the transition series have little preparative value[317]. Those of the transition series lead to compounds and reaction intermediates with higher stability and greater synthetic appeal. Corey and Hegedus[319] reported a general process in which lithium acyl tricarbonylnickelate **167**, prepared by addition of an organolithium reagent to nickel tetracarbonyl, forms Michael adducts with enones and other unsaturated carbonyl compounds, including β,β-disubstituted substrates (equation 60). The insensitivity of this reaction to steric effects is an advantage that is not shared by all nucleophilic acylating reagents which undergo conjugate additions. The high toxicity of nickel tetracarbonyl limits the usefulness of the procedure and leads to the development of other acylmetallic reagents. For example, acyllithium reagents, generated by the alkyllithium–carbon monoxide reaction, give only 1,2-addition products with 2-cyclohexenone and 2-cyclopentenone and mixtures of 1,2- and 1,4-products with other



$$\mathrm{RLi} + \mathrm{Ni(CO)_4} \longrightarrow \underset{\textbf{(167)}}{[\mathrm{RCONi(CO)_3}]\mathrm{Li} \text{ or dimer}} \xrightarrow[\text{ether } -50\ ^\circ\mathrm{C}]{\mathrm{R^1C(O)CR^2{=}CR^3R^4}} \underset{50\text{—}90\%}{\mathrm{R^1C(O)CHR^2CR^3R^4C(O)R}}$$

(60)

enones[320]. Conversely, R(CN)$CuLi_2$/CO or R(CN)CuLi/CO reagents give with α,β-unsaturated aldehydes and ketones the expected 1,4-dicarbonyl compounds in 50–90% and 70–95% yields, respectively[232,233].

B. Masked Acyl Anion Equivalents

The term *umpolung*[316] describes the inversion of reactivity which occurs when a normally electrophilic CO group is transformed into a nucleophile through the use of masked reagents. Masked acyl anion equivalent for 1,4-acylation of enals and enones must satisfy three requirements: (i) the reagent must be easy to prepare, (ii) the resulting carbanion must be highly delocalized so as to afford preferentially the 1,4-adduct either directly or from the reversibility of 1,2-addition and (iii) the masking group must be removable under gentle specific conditions. Most masked acyl anions fall into the two general classes of metallated derivatives of enols and metallated derivatives of carbon acids. Other methods use masked functionality of a different nature, e.g. the sp-hybridized cyanide and acetylide ions.

1. Cyanide ions

Conjugate addition of cyanide to α,β-unsaturated ketones produces β-cyano ketones, which can be considered as hemi-protected 1,4-dicarbonyl systems. Nagata and coworkers[321] found that side-reactions sometimes encountered in traditional procedures (e.g. KCN in aqueous alcohol) are minimized when cyanide is used in the presence of NH_4Cl[322]. They also developed organoaluminium reagents (alkylaluminium cyanide R_2AlCN or a combination of an alkylaluminium compound and HCN) for hydrocyanation of enones[323]. Conjugate addition to enones is also observed with cyanotrimethylsilane[324,325] using Lewis acid catalysts.

2. Acetylide ion

The β-acetylenic ketones are valuable synthetic precursors for 1,4-diketone formation[326], indicating that any reagent able to add an acetylenic unit on $C_{(3)}$ of enone can be considered as a masked acyl anion equivalent. Lithiated derivatives of primary acetylenes add in conjugate fashion only when the carbonyl group of α-enones is highly hindered[327,328]. The use of alkynyl copper reagents is precluded by the tenacity with which copper binds alkynyl ligands[164,168]. The regiospecific 1,2-addition of cuprate **168** to enals[153] or cyclic enones[329] can be performed in the presence of HMPA as cosolvent; without this additive, reagents of this nature are rather inactive towards either 1,2- or 1,4-additions.

Corey and Wollenberg[330] have developed an indirect method, which involves the temporary transformation of the acetylene to a vinyl-stannane derivative. The addition of the mixed cuprate **169**, and subsequent oxidative elimination of the stannyl group, results in the conjugate addition of the acetylide to the enone. Extensions of this synthesis to higher acetylenes have not been reported.

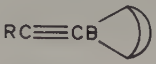
$$(RC{\equiv}C)_3CuLi_2 \qquad n\text{-}Bu_3SnCH{=}CHCuC{\equiv}CPrLi$$

(168) **(169)**

Diethylalkynyl alane **170** undergoes 1,4-addition reactions with α,β-unsaturated ketones to give γ,δ-alkynyl ketones[331,332]. The reaction may be complicated by the concurrent formation of large amounts of 1,2-addition products[332]. It is highly sensitive to the solvent and to β,β-disubstitution of the substrate. It is restricted to ketones that can achieve *s-cis*-conformation. Cyclic ketones such as 2-cyclohexenone or isophorone, in which the enone system is rigidly constrained to a transoid geometry, react with alane reagents to provide the tertiary carbinol (80–85%) derived from the 1,2- rather than 1,4-addition of the alkynyl unit[331].

$Et_2AlC\equiv CR$

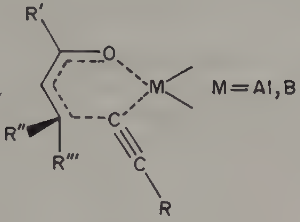
(170)



(171)

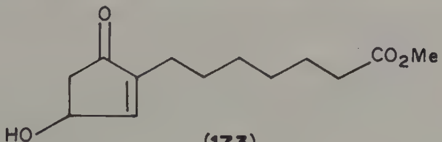
Trialkynyl boron derivatives have been successfully added to methyl vinyl ketone[333]. The use of B-1-alkynyl-9-borobicyclo[3.3.1]nonanes **(171)**[334] avoids the waste of the two residual alkynyl units. A variety of structural modifications on the acetylenic unit, including the presence of a heteroatom, can be accommodated. As for alkynylalanes, the cisoid ketones react satisfactorily to give the 1,4-addition product. The transoid ketones do not react in the desired manner, and do not lead to the 1,2-addition products.

In the cases of alanes and boron derivatives, the pathway involves the intramolecular delivery of the alkynyl group through a six-membered transition state **172** with a necessary *syn* geometry[331,334].



(172)

1,4-addition of trialkynylalane reagents was achieved in the particular case of the fixed *S-trans*-enone **173**. The *cis* stereochemistry of the hydroxyl functional group and the acetylide unit in the adduct indicates the participation of the hydroxy group in the 1,4-addition process. In addition, when the hydroxyl function is blocked by a tetrahydropyranyl group, the reaction with the aluminium reagent is prevented[335,336].



(173)

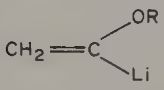
Conjugate addition of a terminal alkynyl unit has been successfully performed by Schwartz and coworkers[337,338] using diethylalkynyl alane and the complex formed by the reaction of $Ni(acac)_2$ and diisobutylaluminium hydride as catalyst. *S-cis*, *S-trans* and hindered α-enones are alkynylated in the β-position in good yields. Reactive transition-metal species are believed to be involved in the conjugate addition step[337,338].

3. Nitronate anion

Michael addition of nitronate anions to enones has been an established reaction for many years[339,340]. Recently, improved methods have been elaborated using catalysts such as amines[341,342], tertiary phosphines[343–349], barium hydroxide[350] and fluoride ion[351–357] or the combined effects of catalysts and phase-transfer[358] or high-pressure conditions[359,360]. They have been successfully used for conjugate additions of nitroalkanes to enals or enones. Moreover, a variety of mild methods are capable of efficiently converting γ-nitroketones into the corresponding 1,4-diketones[339,351,361–370] with none of the disadvantages that accompany other nitro transformation reactions[317,361] (e.g. the Nef reaction[371]).

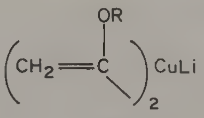
4. *Metallated enol derivatives*

Lithiated enol ethers **174** give exclusively the product of carbonyl addition with unsaturated carbonyl compounds. The copper 'ate' complexes **175** of **174** and mixed cuprates (e.g. **176**) behave as true cuprates and lead to exclusive conjugate additions to α, β-unsaturated ketones. While the yield of 1,4-adduct is not markedly affected by substitutions at $C_{(2)}$, $C_{(5)}$ or $C_{(6)}$ in 2-cyclohexenone (50–91% yields), these reagents are acutely sensitive to additional substitutions in the β- or γ-position (e.g. starting material was recovered with 3-methyl and 4-*t*-butyl-2-cyclohexenones)[215,216]. A similar effect was found with acyclic enones. Cuprate **177** proves to be strongly reactive with a variety of α, β-unsaturated ketones, including β,β-disubstituted ones (56% and 25% yields were obtained with 3-methyl and 4-*t*-butyl-2-cyclohexenones, respectively[216]).



(174)

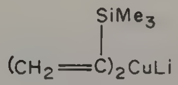
R=Me,Et



(175)

$CH_2{=}C(OEt)CuC{\equiv}CPrLi$

(176)

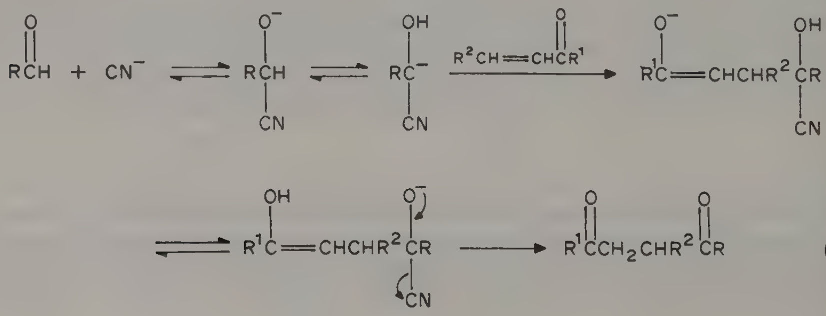


$(CH_2{=}\overset{SiMe_3}{C})_2CuLi$

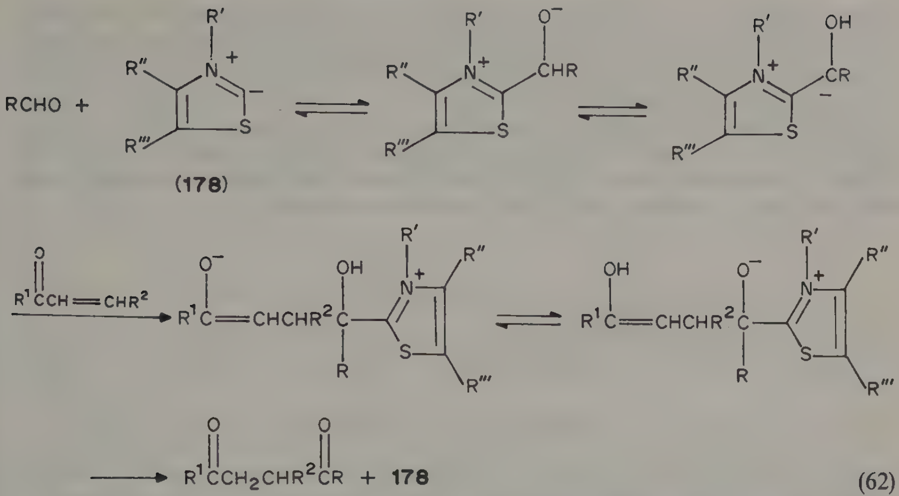
(177)

5. *Cyanohydrin carbanion and related reagents*

In formal analogy with the benzoin condensation, aromatic and heterocyclic aldehydes are added conjugatively as the corresponding acyl anion equivalents to α, β-unsaturated ketones and other activated olefines in the presence of catalytic amounts of cyanide ion (equation 61) or the conjugate base of the thiazolium salt **178** (equation 62)[372,373].



(61)



(62)

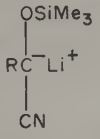
Stetter and coworkers$^{374-389}$ found that aliphatic aldehydes and various functionalized aldehydes can also be used with the latter catalyst, while the cyanide ion is too reactive to be employed with these substrates. α-keto acids are used instead of aldehydes in the thiazolium salt catalyzed addition to α-enones^{390}. Polymer attached thiazolium salts have also been used^{391}.

6. Acyl anion equivalents derived from carbon acids

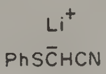
Most masked acyl reagents may be considered as metallated derivatives of carbon acids. The efficiency of the acylation method is dependent on different factors which promote the conjugate addition to enals and enones, such as the structure of nucleophiles and electrophiles, and reaction conditions. These factors have been discussed in the previous section. The masked acyl anion equivalents may be divided into two classes: (i) protected cyanohydrin anions and related reagents (e.g. α-disubstituted aminonitriles), and (ii) anions of 1, 3-dithianes, dithioacetals, diselenoacetals and derivatives.

For protected cyanohydrins, the 2-ethoxyethyl^{46,288,392,393} and the trimethylsilyl groups$^{36-38,394}$ are the most widely used. Lithiated derivatives of suitable protected cyanohydrins **179** and **180** of aliphatic, aromatic and α,β-unsaturated aldehydes undergo 1, 4-additions to cyclic and acyclic enones under favourable reaction conditions. Usually, conjugate additions predominate with bulky anions or with an enone containing a hindered carbonyl function. Demasking is obtained by successive acid and base hydrolysis^{395}. The lithium salt of phenylthioacetonitrile (**181**) can also be used for formylation^{396}.

(179)



(180)



$\overset{\text{Li}^+}{\text{PhS}\bar{\text{C}}\text{HCN}}$

(181)

In the peculiar case of benzoyl equivalents, lithiated derivatives of arylacetonitrile (**182**) have been employed successfully using THF as solvent under thermodynamic control^{23,42}

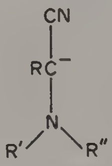
or THF–HMPA under kinetic control[14,41,397]. Demasking is obtained under phase transfer conditions with or without preliminary protection of the carbonyl group, from oxidative decyanation of the 1,4-adducts using 50% NaOH/DMSO in the presence of benzyltriethylammonium chloride[396,398].

α-disubstituted aminonitrile anions (**183**) allow easy demasking of the acyl group[12,57,399–404]. Apart from questions connected with 1,2 and 1,4 competitive additions to enones and enals, the usefulness of disubstituted amino acetonitriles is also dependent on the choice of the disubstituted amino component[12].

$\mathrm{Ar\bar{C}HCN\ Li^+}$

$\mathrm{Ar = Ph}$, $p\text{-}\mathrm{MeOC_6H_4}$

(182)

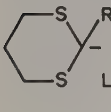


(183)

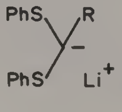
Zervos and Wartski[405] showed that the three lithiated derivatives **179** (R = Ph), **182** (Ar = Ph) and **183** (R = Ph, R′ = R″ = Me) exhibit similar reactivities towards $C_{(3)}$ unsubstituted α-cycloenones, but that **183** and other aminonitriles[12,57,405] do not react with β-disubstituted cyclohexenones.

Since the initial communication by Corey and Seebach[406], describing the use of 2-lithio-1,3-dithianes **184** as masked acyl anions, the chemistry of these reagents and other dithioacetals such as bis(phenylthio) alkyllithiums **185** has been widely explored[407–409].

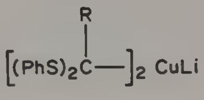
The advance in the understanding of factors influencing the regioselectivity of nucleophilic attacks on enals and enones is joined to developments of acyl anion equivalents containing sulphur. Indeed, it appeared for a time that anions of 1,3-dithianes **184** or other thiocetals **185** normally add exclusively in a 1,2 manner to α,β-unsaturated carbonyl compounds in THF or give a mixture of the two adducts[317,410–413]. Some rather complicated methods have been proposed to overcome this problem, such as the use of lithium bis[tris(phenylthio) methyl] copper **186** (R = PhS) or lithium [α,α-bis(phenylthio)benzyl] copper **186** (R = Ph)[414], lithium enolates of bis(alkylthio)acetate **187**[415–419], lithiated derivatives of thioacetal monosulphoxide **188**[420,421], tris(phenylthio)methyl **189**[422–425], trimethylsilyl- and triorganylstannyl-substituted lithio bis(methylthio) methane **190**[426,427] or lithio derivatives of (methylthio) methyl *p*-tolyl sulphone **191**[428].



(184)

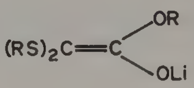


(185)

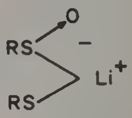


$\mathrm{[(PhS)_2C(R)-]_2\,CuLi}$

(186)



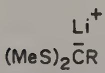
(187)



(188)

$\mathrm{(PhS)_3C^-Li^+}$

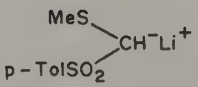
(189)



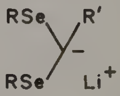
$\mathrm{(MeS)_2\bar{C}R\ Li^+}$

R=SiMe$_3$, SnR$'_3$

(190)



(191)



(192)

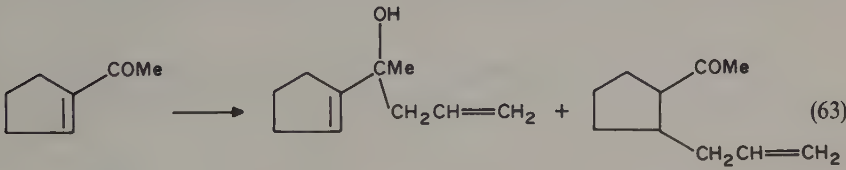
The discovery that polar solvents favour the 1,4-addition of some alkyllithiums has led to the successful reinvestigation of the reaction of the simplest acyl anion equivalents containing sulphur with enals[29,30,429,430] and enones[31,33,34,49,431]. Side by side with lithiothio derivatives, α-lithio seleno-acetals **192**[432–435] proved to be efficient acyl anion equivalents. Krief and coworkers[32] have performed an interesting comparative study of the conjugative addition of acyl anion equivalents **184**, **185** and **192** to α-enones. Among the different methods allowing the preparation of 1,4-dicarbonyl compounds from the thio- and seleno-acetal adducts, the $CuCl_2/CuO$ method was the most satisfactory[32,414,436,437].

IV. NUCLEOPHILIC ALLYLATION OF ENALS AND ENONES

Control of 1,4- versus 1,2-addition of allylic organometallic reagents to α,β-unsaturated carbonyl compounds is rather difficult compared with that of alkyl organometallic derivatives.

Conjugate addition of an allyl group is more effective with organocuprates than with Grignard reagents. The almost exclusive 1,2-addition of allyl magnesium bromide to α-enones has often been rationalized by the impossibility of achieving an eight-membered transition state[438,439]. Only one exception is reported in the case of the highly hindered mesityl vinyl ketone, where 1,4-addition is claimed but in unspecified yield[440].

The addition of lithium diallyl cuprate to an α,β-unsaturated ketone is highly substrate-dependent[441]; for example, 2-cyclohexenone reacts to give 3-allylcyclohexanone in 90% yield, whereas a more hindered substrate such as isophorone gives only the tertiary alcohol via 1,2-addition and $\Delta^{1,9}$ 2-octalone fails to undergo conjugate addition. Reaction of diallyl cuprate with acetylcyclopentene (**193**) affords a mixture of 1,2-adduct **194** (31%), 1,4-adduct **195** (29%) and recovered ketone (11–24%) while the allyl Grignard reagent gives the tertiary alcohol **194** in 83% yield (equation 63)[442].

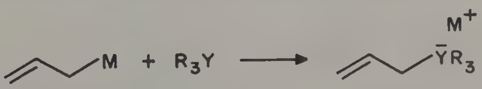


(63)

(193) **(194)** **(195)**

	(194)	(195)
$(CH_2{=}CHCH_2)_2CuLi$	31%	29%
$CH_2{=}CHCH_2MgX$	83%	

Allylic boron and aluminium 'ate' complexes **197**, prepared by addition of trialkylboranes or alanes to allylic organometallic reagents **196** (equation 64), react exclusively in a 1,2 manner with α-enals, while they react with α,β-unsaturated ketones in a competitive 1,2- and 1,4-addition[443,444]. Although the relative importance of the 1,4-addition increases with the formation of the 'ate' complex, the effect is not so noteworthy (Table 43).



(64)

(196) **(197)**

M = Li, MgX, Cu   Y = Al, B

TABLE 43. Reaction of allylic 'ate' complexes **197** with α-enones[443]

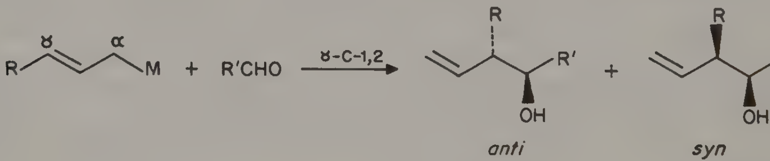
Enone	M in **196**	Additive	$C_{(1)}$ attack	$C_{(3)}$ attack	Overall yield (%)
PhCH=CHCOMe	MgCl	*n*-Bu-9-BBN	95	5	70
PhCH=CHCOMe	Li	*n*-Bu-9-BBN	83	17	72
PhCH=CHCOMe	Cu	*n*-Bu-9-BBN	75	25	62
PhCH=CHCOMe	MgCl	Et_3Al	90	10	85
CH_2=CHCOMe	Li	*n*-Bu-9-BBN	50	50	30

Allyl silanes (see Section V.B) and allyl stannanes are less reactive. Lewis acid mediated reactions of allylic stannanes with α,β-unsaturated aldehydes afford only the 1,2-adduct[445–447]. BF_3–Et_2O catalyzed allylation of quinones with allyltin reagents gives the corresponding allylhydroquinones[448].

Allylation of α-enals has also been performed with allyltin reagents under thermal[449] or hyperbaric[450] conditions. In both cases only the 1,2-adduct is obtained.

All other allylic organometallic reagents add exclusively in a 1,2 manner. These include allyl halides in the presence of manganese powder[451], cerium amalgam[307,308] or chromium(II) salts[452,453], B-allyl derivatives of 9-BBN[454–456] and dibutylallyltin chlorides[457–461].

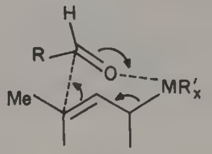
Allylic organometallic derivatives are ambident nucleophiles and, in the case of an unsymmetrical allyl group, both $C_{(\alpha)}$ and $C_{(\gamma)}$ adducts are obtained. Diastereo- and regioselectivities of $C_{(\alpha)}$ or $C_{(\gamma)}$ addition of organometallic reagents have mainly been studied with α,β-enals. In most cases, addition of an unsymmetrical allyl group to carbonyl compounds gives predominantly the product in which the allylic group is attached at the most substituted position (γ adduct) leading, in the case of 1,2-addition, to the formation of *anti* and/or *syn* homoallylic alcohols **198** and **199** (equation 65).



(198) (199)

(65)

Formation of these rearranged compounds has often been accounted for in terms of a six-membered transition state **200**, owing to the affinity of the metal atom for the carbonyl oxygen[446,449,453–455].

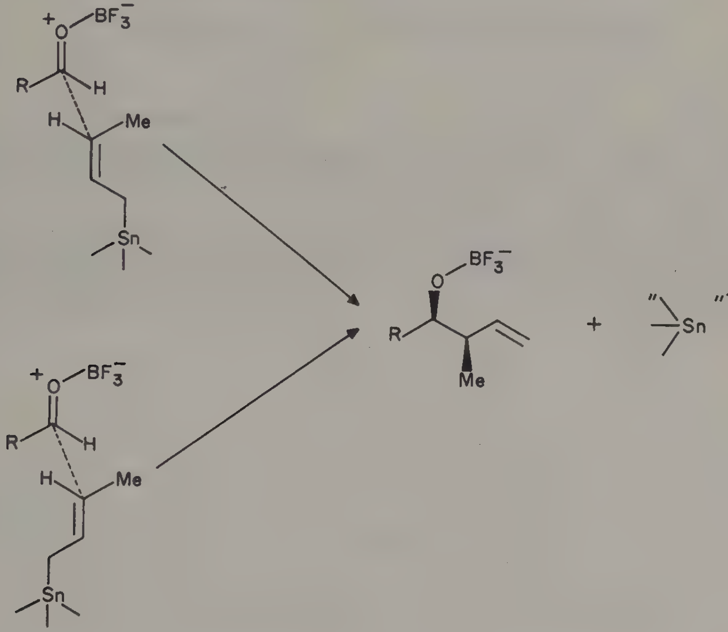


M=B,Cr,Sn

(200)

The stereochemistry of the reaction depends upon the geometry of the allylic unit; the *anti* isomer is formed predominantly from the *E* allylic metal compound, while the *Z* derivative gives preferentially the *syn* isomer[446,449,453,456,460].

By contrast, BF_3–Et_2O mediated reactions of crotyltrialkyl stannanes with α-enals produce preferentially the *syn* homoallylic alcohol, regardless of the geometry of the crotyl unit[446]. An acyclic transition state has been proposed, following activation of the carbonyl group by the Lewis acid which prevents the coordination of the Sn atom (equation 66)[446]. In such a transition state, steric interaction is minimized along the newly formed bond, and the reaction has a stereoselective course. As shown in Table 44, the nature of the Lewis acid used is important for the stereochemical convergence. In addition, in $TiCl_4$ promoted reactions, adjustment in stoichiometry can be made to favour *anti* or *syn* products. In this case, an allyltitanium reagent has been postulated as the reactive species[462]. In the presence of Bu_2SnCl_2, the *syn*/*anti* ratios of the recovered homoallylic alcohols are roughly related to the *Z*/*E* ratios of the allyltin reagents[460]. In this case, the stereochemical course of the reaction depends on the formation and redistribution *in situ* of allyltin metal compounds (equations 67–69).



(66)

TABLE 44. Addition of allylstannanes $RCH{=}CHCH_2SnBu_3$ to crotonaldehyde in the presence of Lewis acids

R in allylstannane	Lewis acid	Overall yield (%)	*syn*	*anti*	Ref.
Me (*Z*)	$BF_3 \cdot Et_2O$	83	91	9	446
Me (*Z*/*E* = 55/45)	Bu_2SnCl_2	75	56	44	460
Me (*Z*/*E* = 40/60)	Bu_2SnCl_2	70	44	56	460
$TBSO(CH_2)_3$ (*Z* + *E*)[a]	$BF_3 \cdot Et_2O$	73	90	10	447
$TBSO(CH_2)_3$ (*Z* + *E*)[a]	$TiCl_4$	47	5	95	447

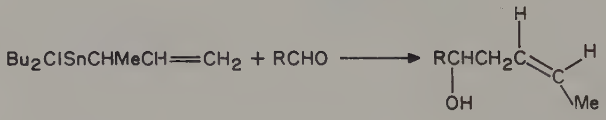
[a] TBS = *t*-Bu(Me)$_2$Si.

$$Z \text{ or } E \quad Bu_3SnCH_2CH{=}CHMe \xrightarrow{Bu_2SnCl_2} Bu_2ClSnCHMeCH{=}CH_2 + Bu_3SnCl \tag{67}$$

$$Bu_2ClSnCHMeCH{=}CH_2 \xrightarrow{Bu_2SnCl_2} (Z+E)Bu_2ClSnCH_2CH{=}CHMe \tag{68}$$

$$Z \quad Bu_2ClSnCH_2CH{=}CHMe \xrightarrow{Bu_2SnCl_2} E \; Bu_2ClSnCH_2CH{=}CHMe \tag{69}$$

The reaction of α-methylallyl substrate **201** is kinetically controlled and yields almost exclusively the linear homoallylic alcohol **202** wholly in the Z configuration (equation 70)[457].

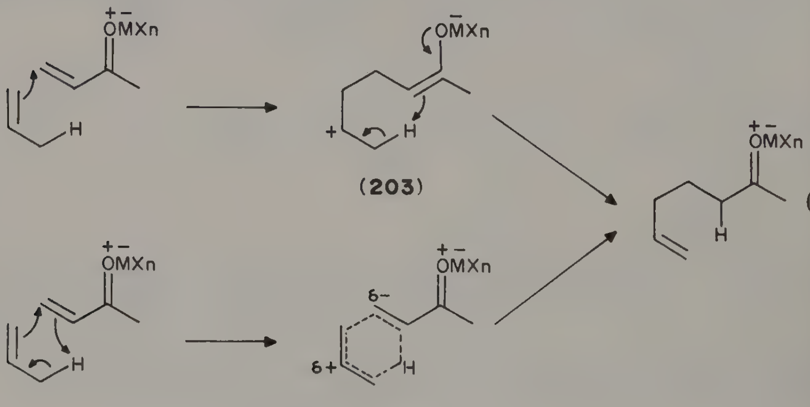


(70)

(201) **(202)**

Preferential allyl $C_{(\alpha)}$ 1,2-addition can be accomplished by crotyl magnesium bromide in the presence of $AlCl_3$, BF_3 or $EtAlCl_2$, while in the presence of $TiCl_4$, $SnCl_4$ or $SnCl_2$ the $C_{(\gamma)}$ 1,2-adduct is preferentially obtained[463].

Lewis acid catalyzed 'ene' reactions between α, β-unsaturated ketones or aldehydes and alkenes having an allylic hydrogen proceed either via a stepwise mechanism with a zwitterionic intermediate **203** or a concerted mechanism with a polar transition state **204** (equation 71)[464].



(203)

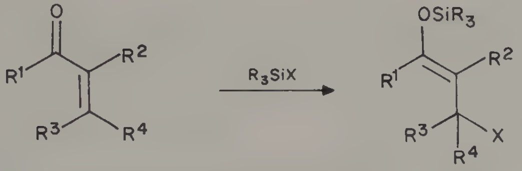
(71)

(204)

The energetics of the two mechanisms are similar and the lower energy process varies as a function of the ene, enophile and catalyst. For the 'ene' reactions of α-enals and α-enones, Me_2AlCl is a very useful catalyst[464]. This method of allylation is, however, limited to β-unsubstituted enones and enals such as acrolein, methyl vinyl ketone or isopropyl vinyl ketone. Other β-substituted enones and enals such as 3-penten-2-one or crotonaldehyde do not undergo Lewis acid catalyzed 'ene' reactions with alkenes and side-reactions are observed[465]. Even with β-unsubstituted enones or enals, depending on the structure of the ene, δ-unsaturated carbonyl derivatives or bicyclic alcohols arising from annelation are obtained[466–468].

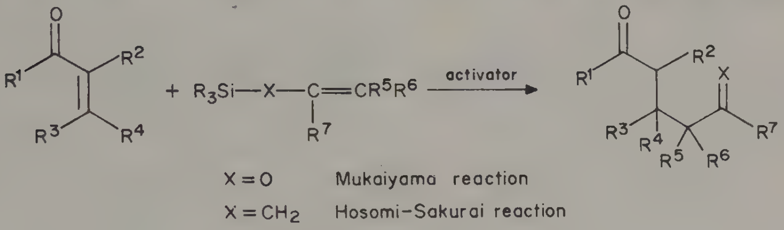
V. CARBON–CARBON BOND FORMATION FROM NUCLEOPHILIC ATTACKS OF ORGANOSILICONS

The use of organosilicons in organic synthesis has greatly increased in the last few years[469–474]. Conjugate additions of R_3SiX species to enones led to numerous silyl enol ethers and the corresponding β-substituted carbonyl compounds as synthetic intermediates[475–477] (equation 72).



(72)

Only the Mukaiyama reaction[478,479] and the Hosomi–Sakurai reaction[480,481], which exhibit similarities, will be considered here. They are shown schematically in equation 73.



(73)

A. Michael-type Reactions with Silyl Enol Ethers and Related Compounds

The Michael reactions with metal enolates are often complicated by side-reactions and concomitant 1,2-addition[482] (see Section II.B). For synthetic purposes, some of these problems are overcome by the use of silyl enol ethers as functional equivalents of enolates (equation 73). In the original procedure described by Mukaiyama and coworkers, the conjugate addition of silyl enol ethers or O-silylated ketene acetals to α-enones was promoted under mild conditions (−78 °C) by an equimolar amount of titanium tetrachloride in dichloromethane. When the enones are very sensitive to $TiCl_4$, the activation of enones is accomplished by the use of both $TiCl_4$ and $Ti(OPr\text{-}i)_4$ (Table 45).

In sharp contrast to these results, condensation of S-silylketene S,N-acetals with α-enones activated by $ClTi(OPr\text{-}i)_3$ affords exclusively 1,2-addition in good yields, while O-silylketene O,N-acetals afford a mixture of 1,2- and 1,4-additions under identical reaction conditions. 1,2-Condensation with S-silylketene S,N-acetals promoted by $ClTi(OPr\text{-}i)_3$ does not seem to involve titanium enethiolate as intermediate[486].

In the Mukaiyama reaction, the Lewis acid acts as an activator of the enone species and is used in equimolar quantities. Corriu and coworkers have elaborated two valuable methods to carry out the conjugate addition using fluoride ion activation (Lewis base activation) of the silicon atom by heterogeneous catalysis. In the former procedure, the silyl enol ether reacts with the enals or enones without solvent, between 25–80 °C in the presence of caesium fluoride which can be recovered[487] (Table 46). Cinnamaldehyde leads

TABLE 45. Michael reaction between $R^1COCR^2 = CR^3R^4$ and $R_3SiOCR^7 = CR^5R^6$ in the presence of Lewis acids at −78 °C in CH_2Cl_2

Enone				Reagent				Lewis acid				
R^1	R^4	R^2	R^3	R_3Si	R^5	R^6	R^7	$TiCl_4$ (eq./reag.)[a]	$Ti(OPr\text{-}i)_4$ (eq./reag)[a]	Time (h)	Yield (%)	Ref.
Me	Me	H	Me	Me_3Si	H	H	Ph	1	—	0.03	76	483
Me	Me	H	Me	Me_3Si	H	$—(CH_2)_3—$		1	—	0.25	66	483
Me	Me	H	Me	Me_3Si	H	CH_2Ph	OMe	1.1	—	3	72	484
Me	Me	H	Me	Me_3Si	Me	Me	OMe	1.1	—	3	72	484
Ph	H	H	Ph	Me_3Si	H	H	Me	1.0	0.5	0.5	44	483
Ph	H	H	Ph	Me_3Si	H	H	Me	1.0	0.8	0.5	63	485
Ph	H	H	Ph	Me_3Si	H	$—(CH_2)_3—$		1.0	—	0.75	85	483
Ph	H	H	Ph	Me_3Si	H	$—(CH_2)_4—$		1.0	—	1	95	483
Ph	H	H	Ph	Me_3Si	H	CH_2Ph	OMe	1.1	—	3	90	484
Ph	H	H	Ph	Me_3Si	Me	Me	OMe	1.1	—	5	>99	484
Ph	H	H	Ph	$t\text{-}BuMe_2Si$	H	H	OEt	1.1	—	3	98	484
$—(CH_2)_3—$		H	H	Me_3Si	H	Ph	Me	1.0	—	1	55	483
$—(CH_2)_3—$		H	H	Me_3Si	H	H	Ph	1.0	0.4	0.5	70	485
$—(CH_2)_3—$		H	H	Me_3Si	H	CH_2Ph	OMe	1.1	0.55	3	81	484
$—(CH_2)_3—$		H	H	Me_3Si	Me	Me	OMe	1.1	0.55	3	74	484
$—(CH_2)_3—$		H	H	Me_3Si	H	$—CH_2CH_2O—$		1.1	0.55	3	82	484
Me	H	H	H	Me_3Si	H	CH_2Ph	OMe	1.1	—	3	0	484
Me	H	H	H	Me_3Si	H	CH_2Ph	OMe	1.1	0.55	3	38	484
Me	Me	H	H	Me_3Si	H	H	Ph	1.0	0.8	0.5	56	485

[a] eq./reag. = equivalent/reagent.

TABLE 46. Reaction between $R^1COCR^2{=}CR^3R^4$ and silyl enol ethers $R_3SiOCR^7{=}CR^5R^6$ in the presence of CsF (1g/1g of silyl enol ether)[487]

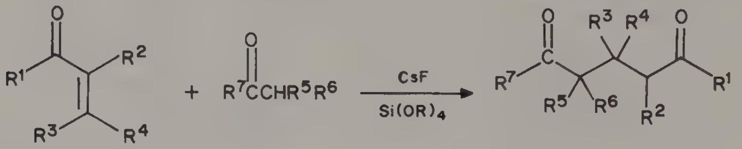
Substrate					Reagent								
R^1	R^4	R^2	R^3	(eq)[a]	R_3Si	R^5	R^6	R^7	Time (h)	Temperature (°C)	1,2-attack	1,4-attack	Overall yield (%)
Ph	Ph	H	H	(1)	Me_3Si	H	$—(CH_2)_4—$		0.5	25	0	100	80
Ph	Ph	H	H	(1)	Me_3Si	H	H	Ph	3	25	14	86	84
$—(CH_2)_3—$		H	H	(2)	Me_3Si	H	$—(CH_2)_4—$		1	80	0	100	40
$—(CH_2)_3—$		H	H	(2)	$Me(OEt)_2Si$	H	$—(CH_2)_4—$		1	80	0	100	40
$—(CH_2)_3—$		H	H	(1)	Me_3Si	H	H	Ph	4	25	0	100	55
H	Ph	H	H	(1)	Me_3Si	H	H	Ph	3	25	100	0	70
H	Ph	H	H	(1)	Me_3Si	H	H	*t*-Bu	5	80	100	0	60

[a] equivalent = mmol/mmol of silyl enol ether.

TABLE 47. Michael additions of $R^7COCHR^5R^6$ to $R^1COCR^2{=}CR^3R^4$ in the presence of $Si(OEt)_4$/CsF (Method A) or $Si(OMe)_4$/CsF (Method B)

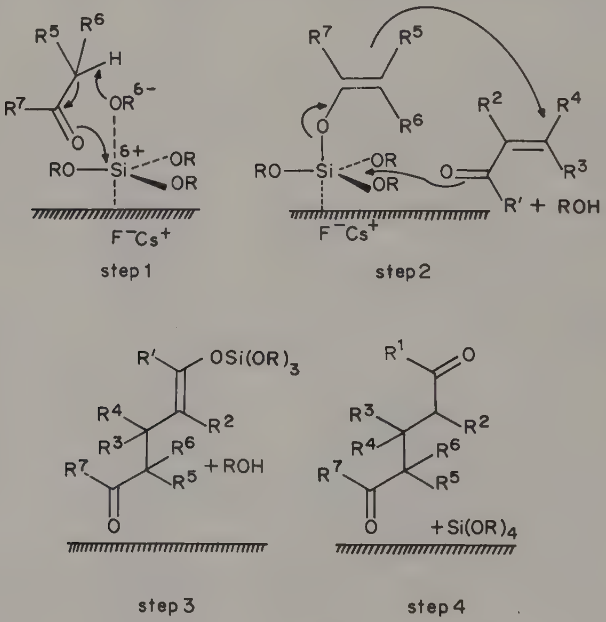
Substrate				Michael donor							
R^1	R^4	R^2	R^3	R^5	R^6	R^7	Method	Time (h)	Temperature (°C)	Yield (%)	Ref.
Ph	Ph	H	H	Me	$—(CH_2)_4—$		A	2	60	65	388
Ph	Ph	H	H	Me	$—(CH_2)_3—$		B	1	20	82	355
$—(CH_2)_3—$		H	H	Me	$—(CH_2)_4—$		A	6	25	65	488
Carvone				Me	$—(CH_2)_4—$		B	4	25	70	489
Carvone				H	$—(CH_2)_3—$		B	3	80	60	489
Carvone				H	H	Ph	B	4	70	60	355
Carvone				Me	Me	Me	B	2	80	60	355
Pulegone				H	H	Ph	B	6	80	65	489

to 1,2-additions, and the corresponding 1,3-dienes are isolated. In the latter procedure, the heterogeneous reactions are carried out without solvent and in the presence of stoichiometric amounts of caesium fluoride, tetraalkoxysilane, ketone precursor of silyl enol ether and enone[355,488–490] (equation 74). Selected results are indicated in Table 47.



(74)

The great value of this method is that it avoids preparation of the silyl enol ether. The following mechanism has been proposed (equation 75)[489]. The first step is nucleophilic activation of $Si(OR)_4$ by the fluoride ion to give a basic species able to promote enolate formation. The enolate is silylated very quickly, giving the corresponding silyl enol ether. In a second step, the salt-activated silyl enol ether promotes formation of the 1,4-adduct from the enone. The adduct reacts *in situ* with the alcohol obtained during the formation of the silyl enol ether (step 3) to give the 1,5-diketone (step 4). Hydrolysis is not necessary to give the final product[489].



(75)

The original Mukaiyama procedure has been used for the preparation of numerous key intermediates in the synthesis of natural products, particularly *via* Robinson-type annelation[491–499]. However, the synthetically valuable silyl enol ethers are not isolated in both $TiCl_4$-promoted Michael reaction and Corriu methods. The first case reported in which the silyl enol ether intermediate has been isolated is the reaction between the trimethylsilyl enol ether of cyclohexanone and α,β-unsaturated aldehydes, such as cinnamaldehyde or 2-hexenal, promoted by tetra-*n*-butylammonium fluoride (TBAF)[500]. Unfortunately, these enals give only 1,2-addition products (50–60%)[501]. Yet, Gerlach and

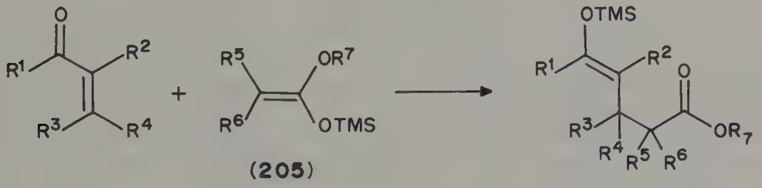
TABLE 48. Conjugate additions of trimethylsilyl ketene acetals **205** to α-enones

	Reagent							
Enone	R^5	R^6	R^7	Method[a]	Time (h)	Temperature (°C)	Yield (%)	Ref.
Cyclopentenone	Me	H	Me	A	0.5	−78	91	503
	Me	H	Me	B	18	r.t.[b]	82	503
	Me	H	Me	C	4	55	98	504
	Me	Me	Me	A	0.5	−78	61	503
	Me	Me	Me	B	18	r.t.[b]	< 5	503
Cyclohexenone	Me	H	Me	A	0.5	−78	94	503
	Me	H	Me	B	18	r.t.[b]	58	503
	Me	H	Me	C	4	55	96	504
	Me	H	Et	D	144	r.t.[b]	80	508
	Me	Me	Me	A	0.5	−78	65	503
	Me	Me	Et	D	144	50	80	508

[a] Method A: 4 mmol% TASF suspended in anhydrous THF; Method B: nitromethane only; Method C: acetonitrile only; Method D: in dichloromethane at 10 Kbar.

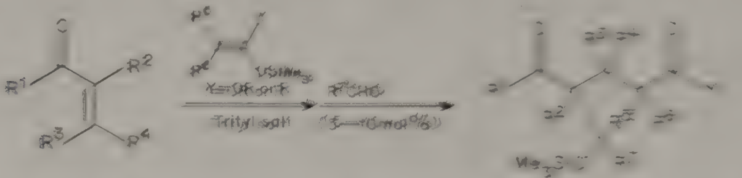
[b] r.t. denotes room temperature.

Künzler showed, using a catalytic amount (10 mol%) of TBAF, that the trimethylsilyl enol ether of S-*t*-butyl thioacetate reacts smoothly with an equimolar amount of 2-cyclopentenone in THF at low temperatures, giving the silyl enol ether of the 1,4-addition product in 72% yield[502]. Other appropriate Lewis base catalysts can be used to generate potent carbon nucleophiles from silyl enol ethers. Thus, the fluoride-catalyzed 1,4-addition of ketene trimethyl acetals to enones can be performed at low temperature using tris(dimethylamino)sulphonium difluorotrimethyl siliconate (TASF)[503] (Table 48). In fact, it has been demonstrated that direct Michael addition of silyl enol ethers can be carried out without additives using a more polar solvent such as nitromethane[504] or acetonitrile[504,505] at 20–60 °C. In these cases, it is assumed that the silyl enol ethers behave much like a Lewis acid and activate the enone for nucleophilic addition[503]. However, these thermal reactions are useful for relatively unhindered cases, and the high-pressure technique provides an alternative means of inducing silyl enol ether additions to sensitive enones having steric and conformational constraints[506–508]. Representative results of TASF-catalyzed reactions, thermal and high-pressure reactions of O-silylated ketene acetals **205** and enones (equation 76) are summarized in Table 48.



(76)

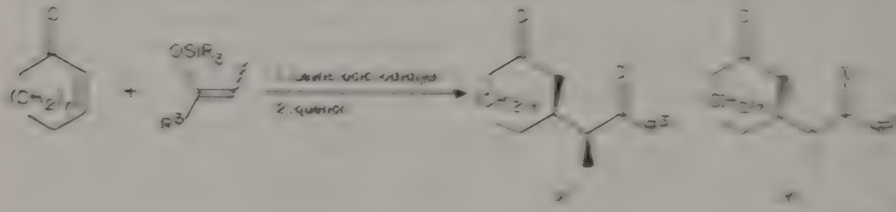
Michael reactions between enones and silyl enol ethers of ketones[509], esters[510] and thioesters[510] or siloxydienes[511] have been more recently shown to proceed smoothly at −78 °C in dichloromethane under non-basic conditions and using catalytic amounts (5–10 mol%) of trityl salts such as trityl perchlorate. The synthetically useful silyl enol ether intermediate can be isolated by quenching the reaction mixture with pyridine or 2-(hydroxymethyl)pyridine. Nevertheless, if appropriate electrophiles are added to the reaction before the quenching, it is possible to obtain the products from further reactions of the intermediate silyl enol ethers with the electrophiles, such as aldol condensation[illegible] (equation 77).



(77)

Several papers have been devoted to the interpretation of stereoselective trends of the Lewis acid promoted Mukaiyama reactions[illegible]. However, coherent transition-state hypotheses that could explain the stereoselectivity observed in particular cases of well homogeneous series are often invalidated with another series. In order to illustrate this point, we discuss below representative results among the important works of Heathcock and coworkers[illegible] and Mukaiyama and coworkers[illegible].

Table 49 shows that silyl enol ethers derived from acyclic ketones have a general tendency for *ul* selectivity, regardless of the stereostructure of the silyl ether, even if the silicon substituents play a significant role in the diastereoselectivity (equations 78 and 79). For the trityl salt promoted reactions, Mukaiyama and coworkers[illegible] explain the *ul* selectivity from the *Z* enolates by assuming the open transition state as shown in Scheme [illegible].

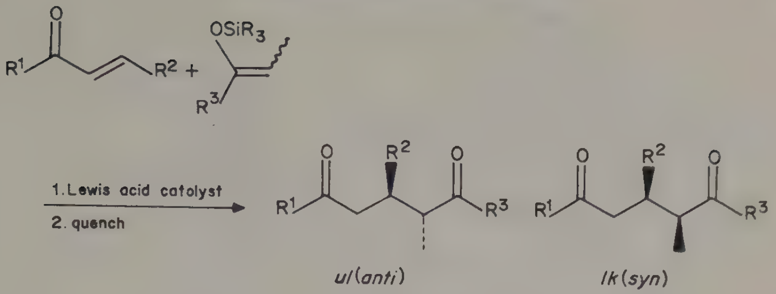


(78)

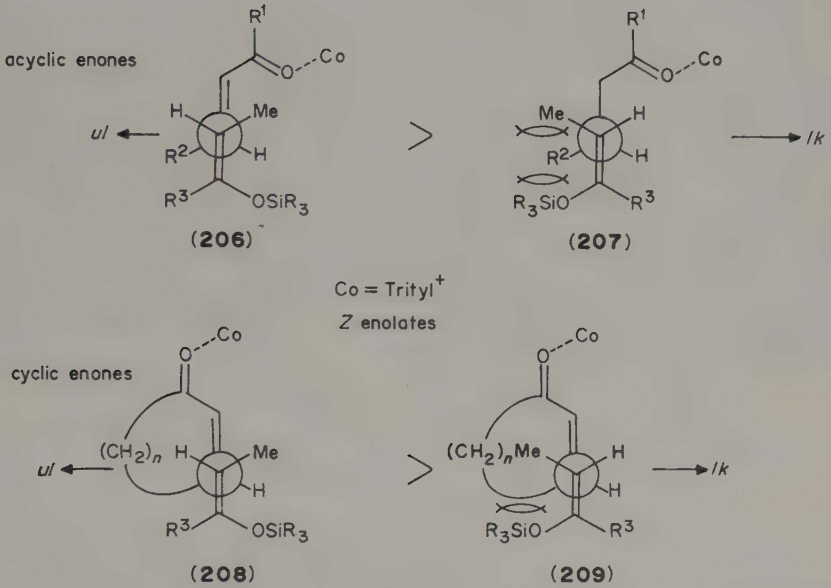
TABLE 49. Stereochemistry of additions of silyl enol ethers $R^2C(OSiR_3)=CHMe$ to enones $R^1COCH=CHR^2$ at low temperature (−45 °C to −78 °C) in dichloromethane

Enone		Silyl enol ether						
R^1	R^2	R_3	R^2	Configuration	Lewis acid[a]	*ul*	*lk*	Ref.
—(CH$_2$)$_3$—		*t*-BuMe$_2$	Ph	*Z*	TrClO$_4$	77	23	566
—(CH$_2$)$_3$—		*t*-BuMe$_2$	Ph	*Z*	TrPF$_6$	78	22	566
—(CH$_2$)$_3$—		*t*-BuMe$_2$	Ph	*Z*	TrSnCl$_5$	79	21	566
—(CH$_2$)$_3$—		*t*-BuMe$_2$	Et	*Z*	TrClO$_4$	54	46	566
Ph	Me	*t*-BuMe$_2$	Et	*Z*	TrClO$_4$	85	15	566
Ph	Me	*t*-BuMe$_2$	Et	*E*	TrClO$_4$	77	23	566
Ph	Me	Et$_3$	Et	*E*	TrClO$_4$	71	29	566
Ph	Me	Me$_3$	Et	*E*	TrClO$_4$	59	41	566
t-Bu	Me	Me$_3$	Et	*E*	SnCl$_4$	87	13	544
t-Bu	Me	Me$_3$	Et	*Z*	SnCl$_4$	89	11	544
t-Bu	Me	Me$_3$	Et	*Z*	TiCl$_4$	88	12	544

[a] Tr = Trityl.



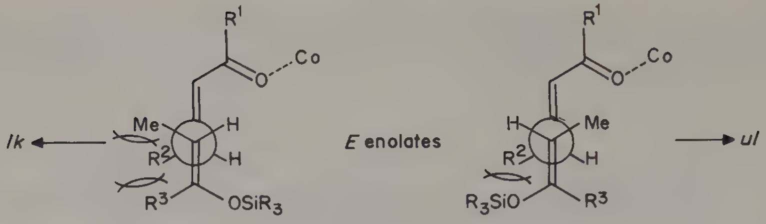
(79)



SCHEME 1

The sterically large trityl cation initially interacts with the enone, and the activated enone is attacked by the silyl enol ether with its bulky siloxy group in such a way that the steric hindrance between trityl cation and the trialkylsiloxy group can be minimized. Transition state **206** is favoured over transition state **207** for an acyclic enone and transition state **208** is preferred to transition state **209** for a cyclic enone, because of both the gauche interaction between R^2 and Me and the steric hindrance between R^2 and the siloxy group[516]. Transposition of this hypothesis to the *E* enolates leads to the transition states shown in Scheme 2. Since an *ul* selectivity is also observed, the transition state **211** must be favoured. Questions that remain are: (i) why are the gauche interactions between Me, R^2 and R^3 in **210** greater than those between R^2 and the siloxy group in **211**? and (ii) why is the *ul* diastereomer favoured when the size of the siloxy group increases (Table 49)?

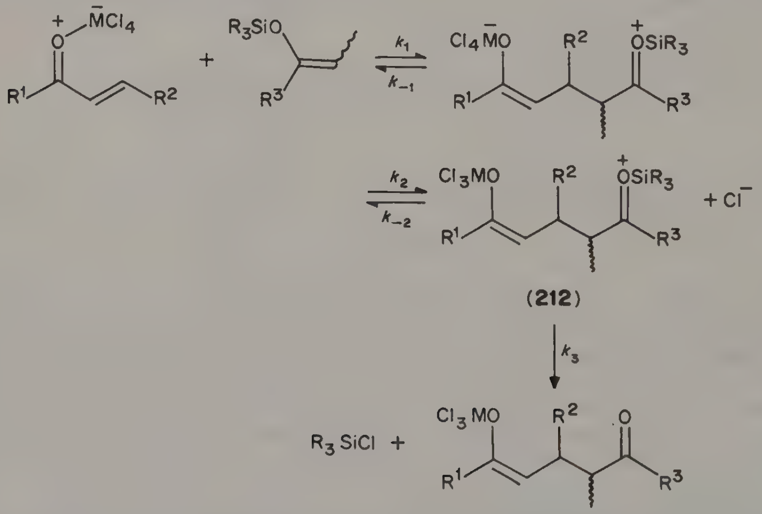
In contrast to the Mukaiyama results[516], Heathcock and coworkers presume that the reactions of the silyl enol ether in the presence of $TiCl_4$ or $SnCl_4$ are under some degree of thermodynamic control, due to Michael reversion before loss of the silyl group from the



(210) **(211)**

SCHEME 2

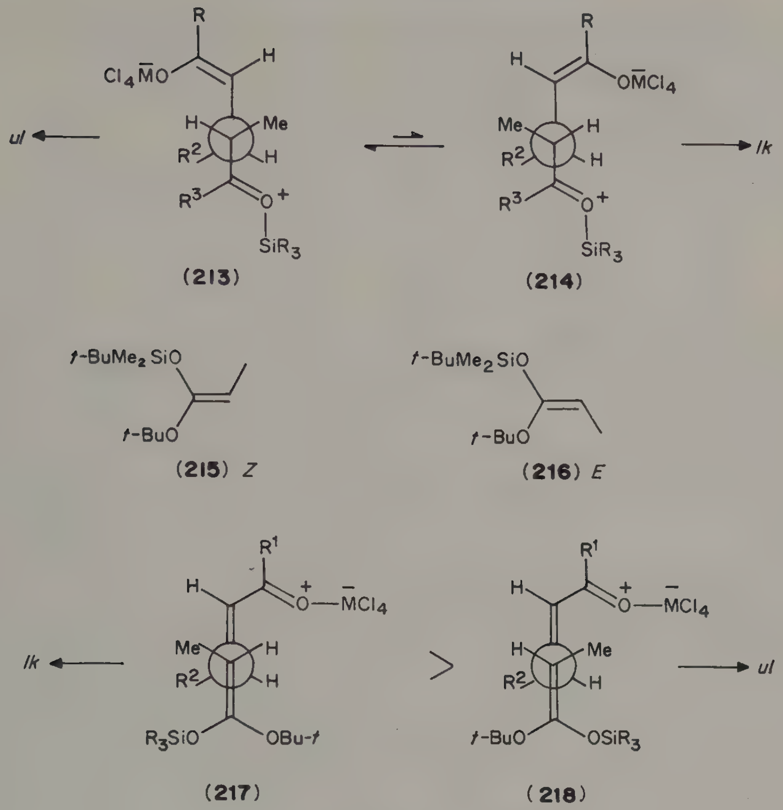
oxygen atom of the new carbonyl group[514] (equation 80). It seems that the initial equilibrium is not very favorable, and the retro-Michael reaction competes with desilylation of **212**. It is possible that *anti* stereochemistry predominates because gauche interactions are minimized in conformation **213**, relative to **214** (Scheme 3). This hypothesis explains the fact that stereoselectivity is largely independent of the silyl enol ether stereostructure. The mechanism shown in equation 80 also provides an explanation for the *lk* selectivity observed with the silyl ketene acetals **215** and **216** (Table 50). With the ketene acetals, Heathcock and coworkers[514] proposed that the initial equilibrium in equation 80 lies far to the right because the oxonium ion is delocalized. Desilylation of the (trialkylsilyl) oxonium ion is fast, relative to the retro-Michael reaction. Therefore, the stereochemistry observed with **215** and **216** seems to be the result of interactions in the isomeric transition states leading to *lk* and *ul* diastereomers. The *lk* selectivity will be the result of a preference for transition-state conformation **217** relative to **218**. We note that similar transition states (such as **206** and **218** or **207** and **217**) have been used to explain the generation of opposed stereoselectivities.



(80)

In addition, results obtained from silyl enol ethers of methyl esters and thioesters in the presence of trityl salts show that *E* silyl enol ethers tend towards a *lk* selectivity whereas *Z* silyl enol ethers tend towards *ul* selectivity[510] (Table 51).

Finally, the stereochemistry observed for additions of silyl enol ethers derived from ketones and esters to chiral enones is hardly reconcilable with the mechanistic



SCHEME 3

interpretation proposed by Heathcock and Uehling[515]. In fact, the stereochemistry of Lewis acid mediated Michael additions of silyl enol ethers to enones is very dependent on several reaction parameters, such as the solvent, the reaction temperature, the nature of silyl enol ether and the siloxy group, the geometry of the enolate and the nature and

TABLE 50. Stereochemistry of reactions of silyl ketene acetals **215** and **216** with $R^2CH{=}CHCOR^1$ at $-78\,°C$ in dichloromethane in the presence of $TiCl_4$[514]

Enone				
R^1	R^2	Reagent	*ul*	*lk*
—$(CH_2)_3$—		**215**	25	75
—$(CH_2)_3$—		**216**	38	62
t-Bu	*i*-Pr	**215**	4	96
t-Bu	*i*-Pr	**216**	2	98

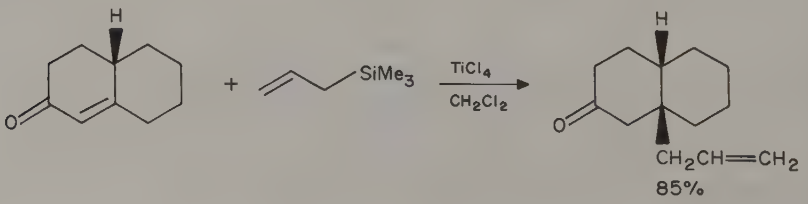
TABLE 51. Stereochemistry of reactions of silyl enol ethers $XC(OSiR_3)=CHMe$ with enones $R^2CH=CHCOR^1$ at $-78\,°C$ in dichloromethane in the presence of Trityl perchlorate[510]

Enone		Silyl enol ether				
R^1	R^2	X	R_3	Configuration	*ul*	*lk*
Ph	Me	OMe	t-BuMe$_2$	*Z*	62	38
Ph	Me	SBu-t	Me$_3$	*Z*	71	29
Ph	Me	SBu-t	t-BuMe$_2$	*Z*	95	5
Ph	Me	SBu-t	t-BuMe$_2$	*E*	31	69
Me	Me	SBu-t	t-BuMe$_2$	*Z*	>95	<5
$—(CH_2)_2—$		SBu-t	t-BuMe$_2$	*Z*	66	34
$—(CH_2)_2—$		SBu-t	Me$_3$	*E*	23	77

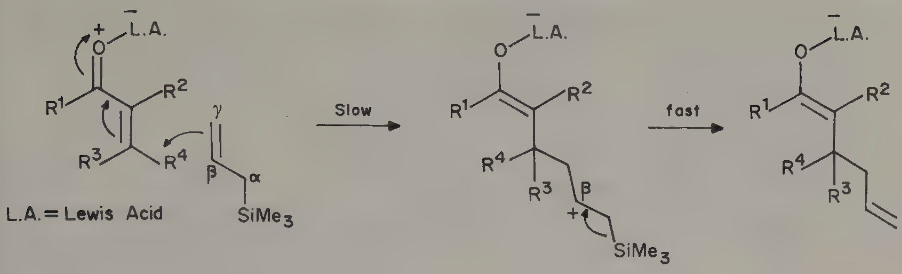
amount of the catalyst. To date, the rationalization of these effects has not yet been realized.

B. Michael-type Reactions with Allylsilanes

Allylsilanes are versatile reagents for the allylation of a variety of electrophiles with regiospecific transposition of the allylic part[473,474]. There is a striking parallel in the evolution of the methodologies of Mukaiyama and Hosomi–Sakurai reactions[480,481]. Calas and coworkers[517,518] were the first to demonstrate that allylsilanes add to activated carbonyl compounds such as chloroacetone in the presence of Lewis acids. Soon afterwards, Hosomi and Sakurai reported that many carbonyl compounds react with allylsilanes, provided that the carbonyl function is activated with titanium tetrachloride[519]; then, they showed that allylsilanes undergo regiospecific conjugate addition to an α-enone when activated by strong Lewis acid catalysts[520], and they also reported the first stereoselective introduction of an angular allyl group into a fused α-enone by using this procedure (equation 81). House and coworkers[442] showed the superior conjugate allylation capabilities of the allyltrimethylsilane–titanium tetrachloride procedure, as compared with allylmagnesium bromide–copper(I) salts and lithium diallylcuprate[441]. The Hosomi–Sakurai procedure was reviewed in 1982. Although the detailed mechanism is not yet clear, it seems that the Lewis acid first interacts with the carbonyl oxygen and activates the carbonyl compound to a regiocontrolled nucleophilic attack of the allylsilane. The γ-carbon of the allylsilane nucleophilically attacks the enone and induces positive-charge development at the β-carbon; the β-silyl carbenium ion undergoes rapid loss of the silyl group. The rate-limiting step is assumed to be the nucleophilic attack of the allylsilane double bond on the Lewis acid coordinated enone[521] (equation 82).



(81)



(82)

Among the usual Lewis acids, $TiCl_4$ is generally the most efficient as shown in Table 52. The initial Hosomi–Sakurai addition procedure has been widely exploited in annelation, particularly for natural product synthesis[480,495,499,523–531]. Usually, a stoichiometric amount of Lewis acid is required for the completion of the allylation. From their previous results on trityl salt mediated Michael addition of silyl enol ethers, Hayashi and Mukaiyama showed that catalytic amounts of trityl perchlorate promote the conjugate allylation of α-enones with allyltrimethylsilane to afford the corresponding adducts in good yields[532].

α-Enals fail to give conjugate addition with Lewis acid–allylsilane procedure. There is no reaction when $TiCl_4$ is used with cinanamaldehyde or α-methylcinnamaldehyde. 1,2-addition products are observed with BF_3–Et_2O. In the case of $TiCl_4$, it seems that the highly reactive enal functionality is rapidly consumed by a Lewis acid-catalyzed 1,2-addition of chloride ion, leading to a hemichloroacetal, which is hydrolyzed back to the aldehyde upon aqueous workup[533,534].

The $TiCl_4$-mediated Hosomi–Sakurai reaction has been used for allylation of quinones. Usually, *p*-quinones react to produce allyl-substituted hydroquinones; 2,6-disubstituted *p*-quinones produce *p*-allylquinols regioselectively in 50–90% yield[480,535].

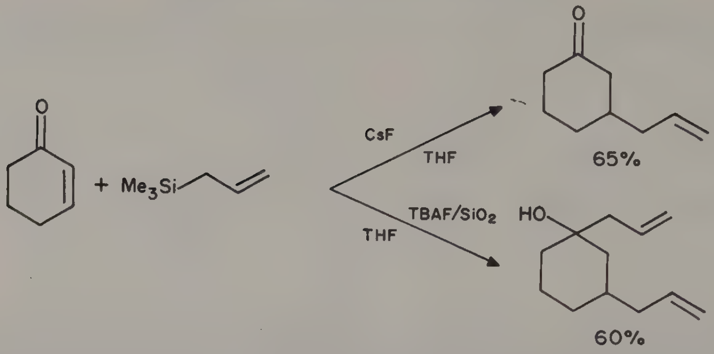
Fluoride ion catalysis can be used as an alternative to the Lewis acid-mediated allylation[536]. Although its mechanism is not clearly established, it seems that addition of a fluoride salt to an allylsilane probably occurs via the rapid formation of a non-basic pentacoordinate organosilicon nucleophile[537].

The regioselectivity of the reaction of the allylsilane with an α-enone appears to depend on the catalyst. For instance, when a silica-supported tetrabutylammonium fluoride ($TBAF/SiO_2$) is used with cyclohexenone, conjugate addition takes place along with 1,2-addition, affording the product of double allylation. With CsF, only the expected product of conjugate addition is formed[538] (equation 83).

TABLE 52. Allyltrimethylsilane addition to 5-phenyl-3-hexen-2-one in dichloromethane[522]

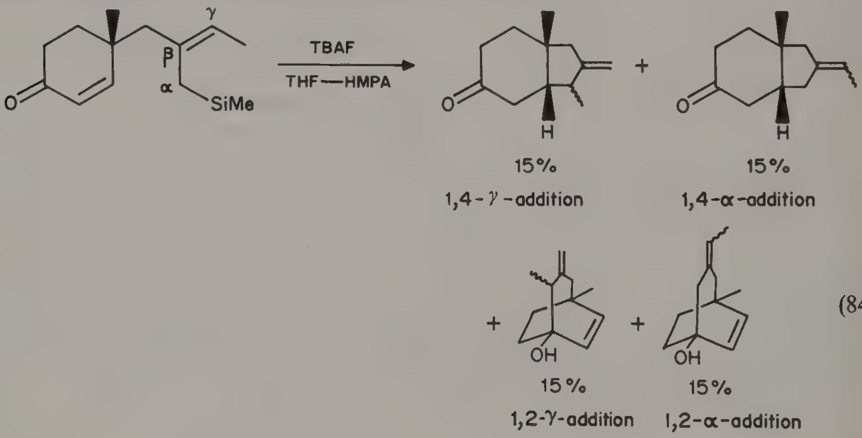
Lewis acid	Temperature (°C)	Time (h)	Yield (%)
$TiCl_4$	−78	1	74
BF_3–Et_2O	−78 to 25	24	< 50
BF_3	−78 to 25	24	no reaction
BCl_3	−78	32	< 20
$ZnCl_2$[a]	−78	72	no reaction

[a] A 1:1 mixture of ether and dichloromethane was used as solvent.

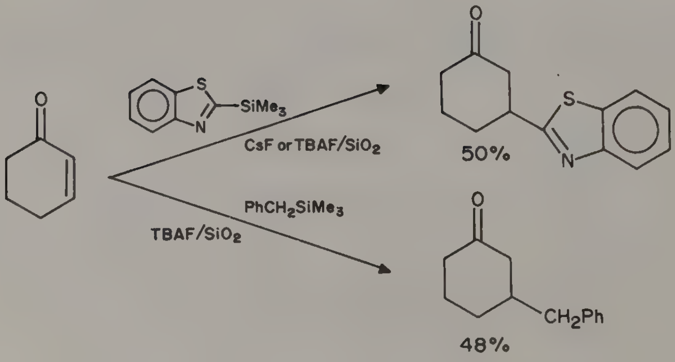


(83)

Majetich and coworkers compared the relative efficiency of fluoride ion and Lewis acids for annelation reactions[539–543]. They showed that the stereochemical outcome for intramolecular Hosomi–Sakurai reactions was dependent on the choice of catalyst, and that the fluoride ion-catalyzed allylation is highly substrate-dependent. Complex mixtures of 1,2- and 1,4-addition products are obtained with carbon–carbon bond formation with both the α and γ atoms of the allyl moiety (equation 84)[537]. It is noteworthy that the easy fluoride ion-catalyzed desilylation of organosilicon compounds containing a carbon–silicon bond has been developed into a general method for the transfer of carbanions other than allyl to the β-position of α-enones[538] (equation 85).



(84)



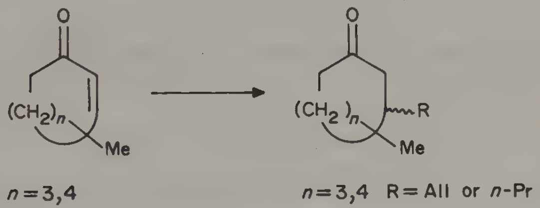
(85)

TABLE 53. Conjugate additions of allyltrimethylsilane and *n*-propylmagnesium bromide to methyl-substituted cyclic enones[521]

	$CH_2{=}CHCH_2SiMe_3$, $TiCl_4$ CH_2Cl_2, −78 °C			*n*-PrMgBr, CuI THF, −20 °C		
Enone	yield (%)	*trans*[b]	*cis*[b]	yield (%)	*trans*[b]	*cis*[b]
4-Methyl-2-cyclohexen-1-one	76	32	68	78	80	20
5-Methyl-2-cyclohexen-1-one	83	>98	<2	81	93	7
4-Methyl-2-cycloheptenone-1-one	71	35	65	65[a]	83[a]	17[a]
5-Methyl-2-cycloheptenone-1-one	76	98	2	74	82	18
6-Methyl-2-cycloheptenone-1-one	71	11	89	71	37	63

[a]Data given for conjugate addition of the di-*n*-propylcopper boron trifluoride complex.
[b]In the product.

In a comparative stereochemical study of allylation and alkylation reactions of methylated cyclohexenones and cycloheptenones from the $TiCl_4$-mediated additions and the CuI-promoted addition of Grignard reagents (Table 53) (equation 86), Blumenkopf and Heathcock have shown that the stereoselectivity for both reactions can be fully explained by stereoelectronic and steric hindrance considerations. Nevertheless, it appears that the allylsilane addition product is the stereoelectronically preferred one. In the cuprate additions there is a significant steric hindrance effect, which reduces the amount of the stereoelectronically favoured isomer[521].



(86)

VI. CARBON–CARBON DOUBLE BOND FORMATION FROM WITTIG-TYPE REACTIONS

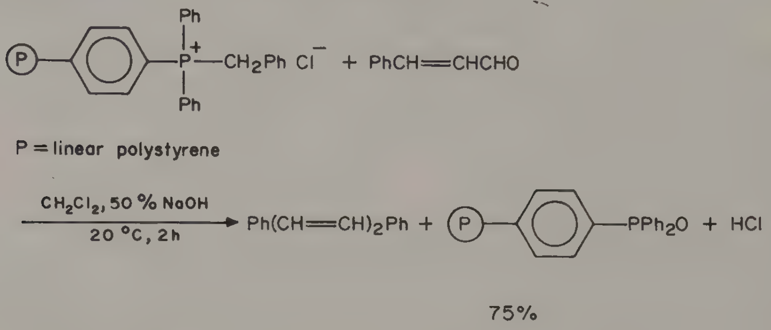
Among the usual approaches to the synthesis of olefins from a carbonyl compound, such as Knoevenagel condensations[544,545] or Peterson olefinations[474,546–548], Wittig-type reactions seem to be the most general and the most easily applicable to α,β-unsaturated aldehydes and ketones. In fact, the papers that have recently been published on olefination reactions and their synthetic use were not specifically devoted to enals and enones but rather to aldehydes and ketones[549–555]. Some of the reagents and processes that have recently been developed can be successfully applied to α-enals and α-enones and will be discussed with particular attention to the stereoselectivity. As expected, enals are more reactive than enones.

A. Olefination with Phosphoranes (Wittig reactions)

Usually, double or triple bonds conjugated with the carbonyl do not interfer in the Wittig reactions, the attack being at the carbonyl double bond.

As an example of new methodologies, polymer-supported Wittig reactions have been successfully applied to α-enals and α-enones such as cinnamaldehyde and cholest-4-en-3-

one[556]. They may be associated to phase-transfer-catalyzed reactions. Phase-transfer-catalyzed polymer-supported Wittig reactions have been performed with cinnamaldehyde, while ketones failed to react[557] (equation 87).



(87)

Palladium-catalyzed Wittig-type olefinations have been achieved in a one-pot process by mixing allylic alcohols, enals, triphenylphosphine and palladium in the form of $Pd(acac)_2$[558] (equation 88).

$$PrCH{=}CHCHO + Ph_3P + CH_2{=}CHCH(OH)C_5H_{11}\text{-}n \xrightarrow[\text{refluxing dioxane 88 h}]{5\%\ Pd(acac)_2} Pr(CH{=}CH)_3C_5H_{11}\text{-}n + Ph_3PO + H_2O \qquad (88)$$

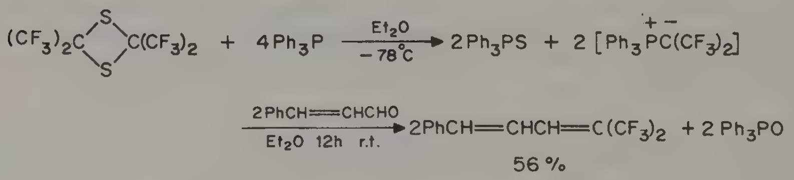
27%

Potassium fluoride supported on alumina also catalyzes Wittig reactions, without any organic solvent (equation 89)[559].

$$PhCH{=}CHCHO + Ph_3\overset{+}{P}CH_2Ph\ Cl^- \xrightarrow[\text{20°C 18h}]{KF/Al_2O_3(0.3g/mmol\ enal)} Ph(CH{=}CH)_2Ph + Ph_3PO + HCl \qquad (89)$$

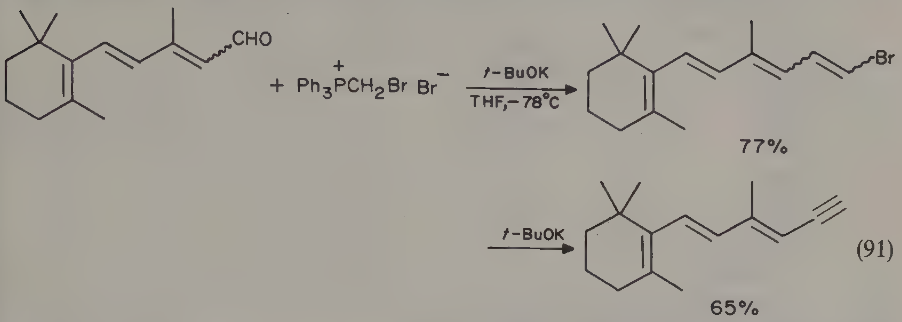
70%

Among the new Wittig reagents, it is noteworthy that a phosphonium analog of Middleton's phosphorane is generated *in situ* from tetrakis(trifluoromethyl)-1,3-dithietane and triphenylphosphine, and reacts with cinnamaldehyde giving the resultant *bis*-trifluoromethyl olefin in 56% isolated yield (equation 90)[560]. Ketones fail to give olefins under these conditions, since decomposition of the ylide occurs faster than olefination of the ketone.



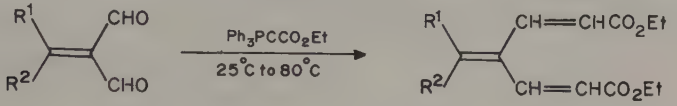
(90)

Enals are easily converted to 1-bromoolefins or terminal acetylenes by the use of Wittig reaction of bromomethylenetriphenylphosphorane, which is prepared from bromomethyltriphenylphosphonium bromide with potassium *t*-butoxide as exemplified by reaction with *β*-ionilidene acetaldehyde (equation 91)[561].



(91)

A double Wittig reaction can be performed on 2-ene-1,3-dial[562,563] with functionalized phosphorane in good yields (equation 92)[564].



(92)

R^1=H or Ph R^2=Ph or Ar

An acylylidene group can be added to enals from the Wittig reaction of phosphorane **219**, obtained from the Grignard reaction between ketenylidenetriphenylphosphorane **220** and alkyl or aryl magnesium halide (equation 93)[565].

$$\underset{(\mathbf{220})}{\mathrm{Ph_3P{=}C{=}C{=}O}} \xrightarrow[2.\ \mathrm{H_2O}]{1.\ \mathrm{RMgX}} \underset{(\mathbf{219})}{\mathrm{Ph_3P{=}CHCOR}}$$

$$\xrightarrow{\mathrm{Me(CH_2)_2CH{=}CHCHO}} \mathrm{Me(CH_2)_2(CH{=}CH)_2COR} + \mathrm{Ph_3PO} \qquad (93)$$

R = Ph yield = 48%

B. Olefination with Phosphonates and Phosphine Oxides (Wittig–Horner or Horner–Emmons or Wadsworth–Emmons Reactions)

Phosphonates, are considered to react poorly with *α,β*-unsaturated ketones, except *β*-ionone[566–570], due to the smaller electrophilicity of the carbonyl carbon atom and to the competitive Michael addition. Nevertheless among other possibilities[571–578] (see Section II.A), one can perform Horner–Emmons reactions of diethyl cyanomethylphosphonate with various 3-substituted-5,5-dimethyl-2-cyclohexen-1-ones using sodium hydride as base and THF as solvent (equation 94) (Table 54)[579,580].

Under the same experimental conditions, these ketones lead to very poor yields (except when X = OEt, 79%) with triethyl phosphonoacetate, and polymerizations arise when the reaction time is increased.

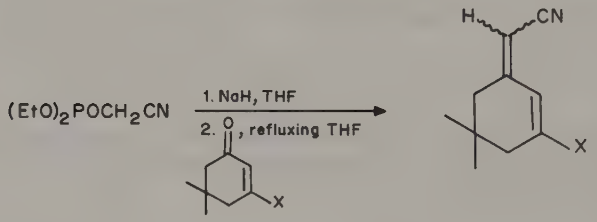
Cinnamaldehyde is converted into the corresponding *α,β-γ,δ*-dienic ester using triethyl phosphonate and a weaker base such as triethylamine in the presence of lithium bromide

TABLE 54. Horner–Emmons reaction between diethyl cyanomethylphosphonate and 3-substituted-5, 5-dimethyl-2-cyclohexen-1-ones in refluxing THF using NaH as base[579,580]

3-X substituent in the ketone	Time (h)	Isolated yield (%)	Product Z	Product E
H	18[a]	28	40	60
Me	24	56	46	54
Ph	24	55	63	37
Cl	24	47	40	60
Br	24	80	50	50
OEt	16	92	62	38
SEt	24	90	35	65
CH_2Ph	48[a]	82	44	56
p-$NO_2C_6H_4$	24	70	47	53

[a] Reactions performed at room temperature.

(equation 95)[581]. Apart from cyclohexanone, simple ketones fail to react under these conditions.

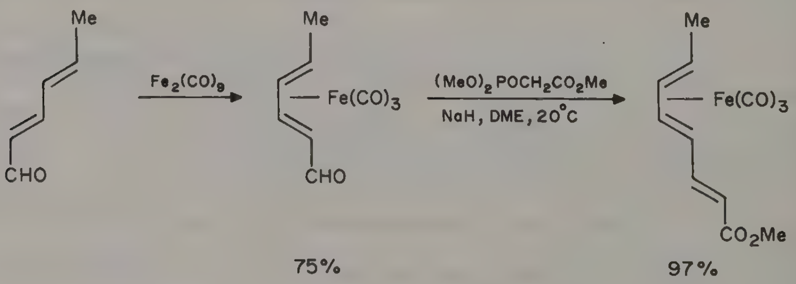


(94)

$$PhCH{=}CHCHO + (EtO)_2POCH_2CO_2Et + LiBr \xrightarrow[CH_3CN,\ 25\,^{\circ}C,\ 12\,h]{Et_3N} \underset{65\%}{Ph(CH{=}CH)_2CO_2Et} \qquad (95)$$

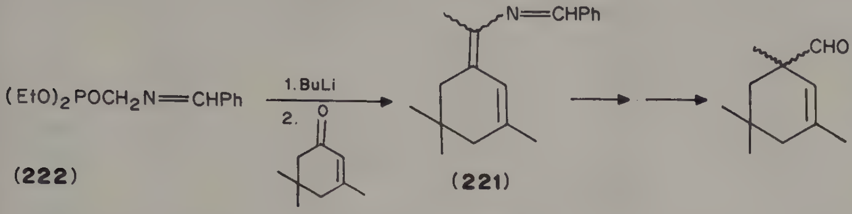
The polymer-supported phosphonate technique has also been successfully used with enals and β-ionone in THF at room temperature[582].

Sorbic aldehyde reacts in excellent yield with trimethyl phosphonoacetate in DME at 20 °C with NaH as base, when complexed by $Fe_2(CO)_9$ (equation 96)[583].



(96)

In order to perform geminal acylation-alkylation at the carbonyl carbon via regiospecifically generated metalloenimines, Martin and coworkers[584] have used the initial conversion of isophorone into the substituted 2-azatriene **221** by a Horner–Emmons reaction with diethyl N-benzylidenamino phosphonate **222** in THF (equation 97).



(222) **(221)** (97)

α,β-γ,δ-unsaturated sulphones and sulphoxides can be prepared via the Horner–Emmons reaction of α-enals and α-enones with α-phosphoryl sulphones **223** and sulphoxides **224** (equation 98). Selected results are presented in Table 55[585].

$$RSO_nCH_2PO(OEt)_2 + R^1COCH{=}CHR^2 \xrightarrow[THF]{BuLi} RSO_nCH{=}CR^1CH{=}CHR^2 \qquad (98)$$

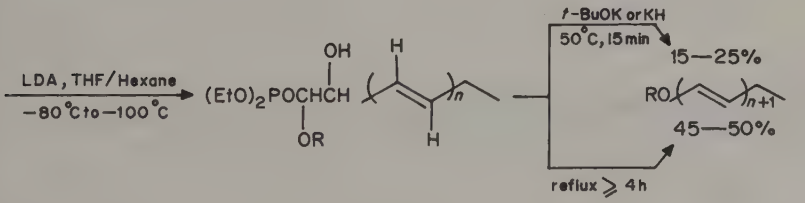
$n = 2$ **(223)**

$n = 1$ **(224)**

Vo-Quang and coworkers have described a convenient and highly stereoselective method for the synthesis of polyenic enol ethers by the reaction of polyenals with the carbanion of diethyl alkoxymethylphosphonate **225** (equation 99)[586].

R = Me, Et, PhCH$_2$, MeOCH$_2$CH$_2$OCH$_2$

(225)



(99)

Enals and β-ionone can be converted into their homologous ketene O, O-acetals by a Horner–Emmons reaction with dialkyloxymethyldiphenylphosphine oxides, while reactions with phosphonates usually fail (equation 100)[587].

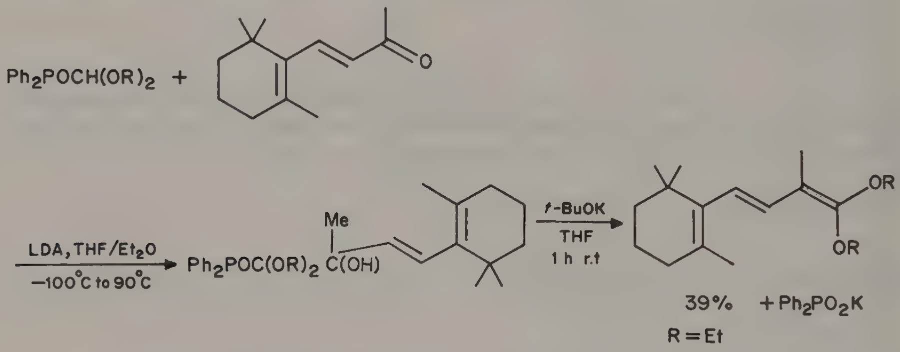
Cyanopolyenes can be prepared in a one-step route based on the Peterson reaction and the Horner–Emmons olefination of diethyl 2-cyano-2-trimethylsilylethanephosphonate **226** as exemplified by reaction with cinnamaldehyde (equation 101)[558].

Olefinations with phosphonates or phosphine oxides are seldom highly stereoselective. However, the stereochemistry with α,β-unsaturated aldehydes tends towards an *E*

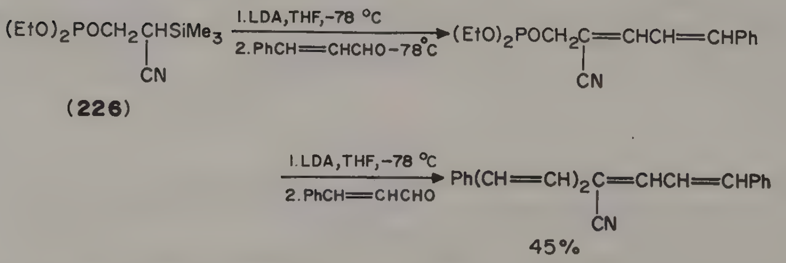
TABLE 55. Reaction of phosphoryl sulphones **223** and phosphoryl sulphoxides **224** with $R^1COCH{=}CHR^2$ at −78 °C[585]

Substrate				Isolated yield	Product	
R^1	R^2	Reagent	R	(%)	*Z*	*E*
H	H	**223**	Me	10	0	100
H	H	**223**	Ph	68	0	100
H	H	**224**	Ph	45	43	57
H	Ph	**223**	Me	80	0	100
H	Ph	**223**	Ph	80	0	100
H	Ph	**224**	Ph	64	42	58
—$(CH_2)_3$—		**223**	Me	30	61	39
—$(CH_2)_3$—		**224**	Ph	40	59	41

selectivity[582–591]. Several efforts have been made to rationalize the various factors influencing the stereoselectivity (structure of the anionic reagents and carbonyl compounds, the nature of the solvent and reaction temperature), to increase the *E* stereoselectivity or to reverse the selectivity[582–602].



(100)



$$(EtO)_2POCH_2\underset{CN}{CHSiMe_3} \xrightarrow[2.\ PhCH{=}CHCHO\ -78\,^\circ C]{1.\ LDA,THF,-78\,^\circ C} (EtO)_2POCH_2\underset{CN}{C}{=}CHCH{=}CHPh$$

(226)

$$\xrightarrow[2.\ PhCH{=}CHCHO]{1.\ LDA,THF,-78\,^\circ C} Ph(CH{=}CH)_2\underset{CN}{C}{=}CHCH{=}CHPh \qquad (101)$$

45%

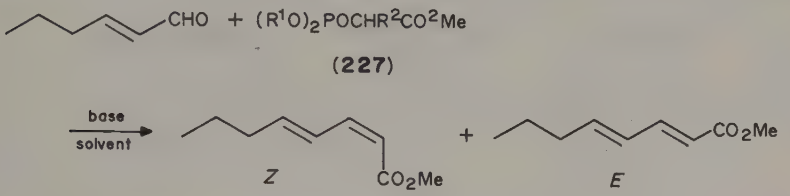
As exemplified in Table 56 with phosphonate **227**, the stereoselectivity depends upon the degree of substitution of the carbon α to phosphorus (entries a and b) as well as upon the nature of alkoxy groups bonded to phosphorus (entries a and c or d, or b and e) (equation 102)[592].

TABLE 56. Reactions between phosphonoesters **227** and 2-hexenal (*E*) under various conditions[592]

	227				Product	
Entry	R^1	R^2	Conditions[a]	Overall yield (%)	*Z*	*E*
a	Me	H	A	50	22	78
b	Me	Me	A	59	60	40
c	CF_3CH_2	H	A	87	>98	<2
d	CF_3CH_2	H	B	65	94	6
e	CF_3CH_2	Me	A	79	>98	<2

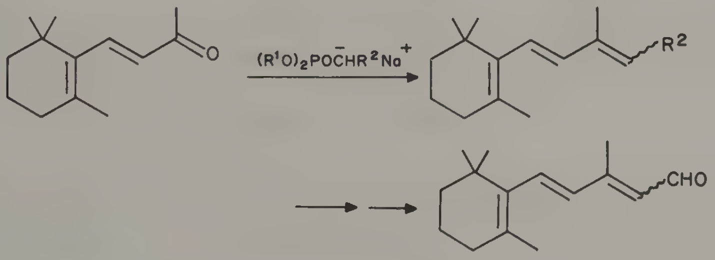
[a] Conditions: (A) KN $(TMS)_2$/18-crown-6/THF; (B) K_2CO_3/18-crown-6/Toluene.

The generally improved *Z* stereoselection with added substituents to carbon α to phosphorus is typical of Horner–Emmons olefinations[603]. As pointed out by Seyden-Penne and coworkers, the use of base system having minimally complexing counter-ions is important in facilitating elimination and thus maintaining *Z* stereoselection[593,595,597,598].



(102)

The influence of the nature of the phosphoric group and of the electron-withdrawing substituent bonded to the α-carbon is also demonstrated by the results observed with the intermediates used for preparation of the β-ionylideneacetaldehyde **228** (equation 103).



(103)

(228)

	Z : *E*		Ref.
R^1=Et, R^2=CN	33	67	567
R^1=Et, R^2=CO_2Et	6	94	604
R^1=*i*-Pr, R^2=CN	18	82	605

In order to perform the highest *E*-stereoselection, Etemad-Moghadam and Seyden-Penne compared the reactivities of diethyl cyanomethylphosphonate (**229**), diisopropyl

TABLE 57. Reaction of carbonyl compounds **232–236** with reagents **229–231**[606]

Carbonyl compound	Method[a] (*T* °C)	**229** Yield (%)	**229** *Z*	**229** *E*	**230** Yield (%)	**230** *Z*	**230** *E*	**231** Yield (%)	**231** *Z*	**231** *E*
232	A(−78)	60	25	75	—		—		*b*	
232	A(20)	50	40	60	—		—		*b*	
233	A(−78 or 20)	70	20	80	—		—		*c*	
233	B(20)	70	20	80	60	20	80		*c*	
234	B(20)	—	—	—	—		—	85	≤5	≥95
235	B(20)	95	25	75	95	20	80	95	≤5	≥95
236	B(20)	—	—	—	90	25	75	70	5	95

[a] Methods: (A) *n*-BuLi/THF; (B) *t*-BuOK/THF.
[b] No reaction takes place; the starting materials are recovered unchanged.
[c] No olefin detected.

cyanomethylphosphonate (**230**) and diphenyl cyanomethylphosphine oxide (**231**) with enals **232–235** and *β*-ionone (**236**) in various media[606] (Table 57).

R_2POCH_2CN

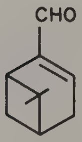
R = EtO (**229**)
R = *i*-PrO (**230**)
R = Ph (**231**)

$MeCH{=}CHCHO$

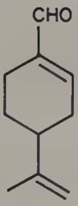
(**232**)

$CH_2{=}CMeCHO$

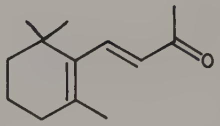
(**233**)



(**234**)



(**235**)



(**236**)

$PhCH{=}CHCHO$

(**237**)

Whereas the *E* stereoselectivity obtained with **231** is higher than with **229** and **230** when the olefination occurs, it appears that the phosphine oxide is less reactive than the phosphonates.

Comparable results are obtained with reaction between diethyl 1-carbomethoxyethylphosphonate (**238**), 1-carbomethoxyethylphosphine oxide (**239**) and enals **232**, **234**, **235** and **237**[607] (Table 58). On the other hand, the *E* stereoselectivity from diethyl phosphono-α-fluoroacetate (**240**) is higher than from the corresponding diphenyl phosphine oxide **241**[608] (Table 58). These results are in line with previous interpretations which take into account the electron density and steric hindrance around the phosphorus atom[608].

$(EtO)_2POCHMeCO_2Me$ (**238**)

$Ph_2POCHMeCO_2Me$ (**239**)

$(EtO)_2POCHFCO_2Me$ (**240**)

$Ph_2POCHFCO_2Me$ (**241**)

TABLE 58. Olefination reactions of enals and β-ionone with phosphonates **238**, **240** and phosphine oxides **239**, **241**[607,608]

Carbonyl compound	Method[a] (*T* °C)	Reagent	Yield (%)	*Z*	*E*
232	A(−78)	**238**	85	10	90
	A(20)	**239**	60	10	90
	A(−78)	**240**	76	⩽2	⩾98
	A(0)	**241**	85	83	17
234	A(20)	**238**	75	10	90
	B(20)	**239**	75	⩽5	⩾95
	A(20)	**240**	50	⩽2	⩾98
	B(20)	**241**	75	40	60
235	A(20)	**238**	90	10	90
	B(20)	**239**	65	⩽5	⩾95
	A(20)	**240**	75	⩽15	⩾85
	B(20)	**241**	75	70	30
236	A(20)	**240**	90	30	70
	B(20)	**241**	85	50	50
237	A(−78)	**238**	65	10	90
	B(20)	**239**	—	⩽5	⩾95
	A(−78)	**240**	75	⩽2	⩾98
	B(20)	**241**	80	70	30

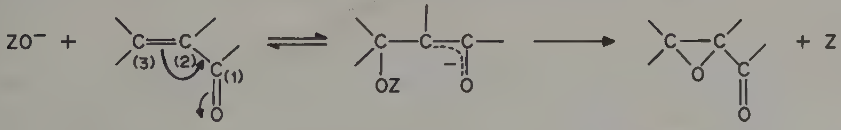
[a] Methods: (A) *n*-BuLi/THF; (B) *t*-BuOK/DMF.

VII. NUCLEOPHILIC EPOXIDATIONS

A. Formation of Epoxides from the Carbon–Carbon Double Bond

Nucleophilic epoxidation of α-enones is generally accomplished with hydrogen peroxide, *t*-butyl hydroperoxide or hypochlorite salts such as NaOCl or KOCl, where the attacking nucleophiles are respectively HOO^-, *t*-BuO^- and ClO^-[9,609]. Hydrogen peroxide and *t*-butyl hydroperoxide are often used in protic or aprotic media with strong bases (i.e. NaOH, KOH, LiOH, Triton B)[609–613], but they can also be used in an aprotic solvent using fluorides, particularly Bu_4NF[614].

The well-established mechanism of alkaline epoxidation with H_2O_2[609,615,616] (Weitz–Scheffer reaction)[617] can be extended to *t*-butyl hydroperoxide and hypochlorite salts[609,612,618]. It proceeds by an initial nucleophilic attack of ZO^- ($Z = HO$, *t*-BuO, Cl) at $C_{(3)}$ in **242** to give the intermediate **243** and then the epoxide **244** by an intramolecular substitution of the carbanionic $C_{(2)}$ on the oxygen (equation 104). The reaction with $Z = OH$[615] or Cl[618] is first order both in α-enone and in ZO^-[619,620].



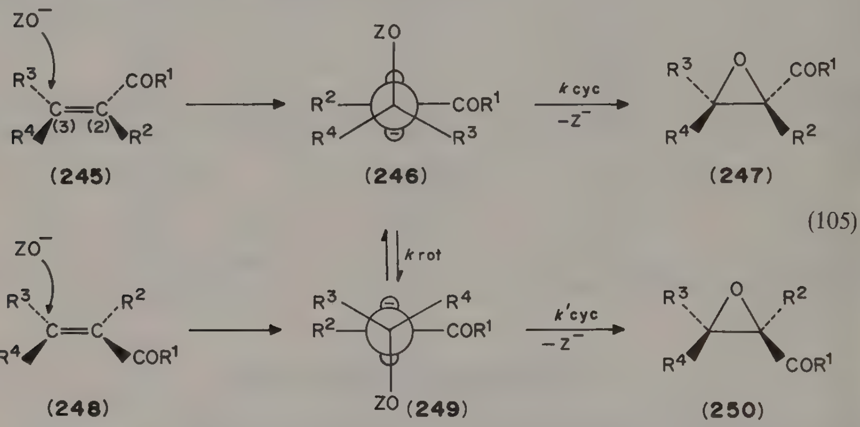
(242) **(243)** **(244)**

(104)

1. Stereochemistry of the nucleophilic epoxidation

The stereochemistry of the epoxidation depends on the nature of both the nucleophile and the enone. Acyclic enones and cyclic enones should be distinguished.

a. Stereochemistry of epoxidation of acyclic enones. Oxidation of acyclic enones with alkaline H_2O_2 is usually stereoselective but not stereospecific, giving the same single epoxide from both *E* and *Z* precursors[609,616,621,622]. For *t*-butyl hydroperoxide, the stereochemistry seems similar to that with hydrogen peroxide[614] whereas epoxidation with the hypochlorite ion is mostly stereospecific giving a high proportion of the retained epoxide[623,624]. In the two-step carbanionic mechanism, the ZO^- nucleophile approaches the enone **245** or **248** in a plane perpendicular to the molecular plane. The carbanion is therefore formed initially in a perpendicular conformation **246** or **249** where the 2p(C^-)-C-OZ hyperconjugation is maximal[625] (equation 105).



Usually, the stereochemistry of nucleophilic epoxidation is determined by the relative activation energies for rotation around the $C_{(3)}$-$C_{(2)}$ bond and for cyclization. The reaction is highly stereospecific if internal rotation in **246** or **249** (cf. k_{rot}) is significantly slower (i.e. the rotation barrier is high) than nucleophilic displacement of Z^- (cf. k_{cyc}, k'_{cyc}). A pair of *E* and *Z* enones should then give two different retained isomeric epoxides (i.e. **245** → **247**, **248** → **250**). However, if the rotation **246** ⇄ **249** is faster than ring closure and the **246** ⇄ **249** equilibrium is established before nucleofuge expulsion, then complete stereoconvergence (i.e. formation of identical **247**:**250** mixtures from either **245** or **248**) should be observed.

The rotation barriers **246** ⇄ **249** are determined by the hyperconjugating ability (HCA) of the C—OZ, C—R^3 and C—R^4 bonds, by the nature of COR^1 and R^2 and by the eclipsing steric interactions of the α- and β-substituents[625]. If steric effects are relatively small, then the stereochemistry of nucleophilic epoxidation can be explained by the following points:

(i) The higher the stereospecificity of epoxidation for a particular set of substituents R^1, R^2, R^3, R^4, the higher the HCA of the C—OZ bond. The dependence of stereospecificity on the nucleofuge decreases in the order $ClO^- > HOO^- \sim t\text{-}BuO^-$.

(ii) α-Substituents R^2 that stabilize the carbanion, reduce the rotation barrier in **246** or **249**, increase k_{rot}, and decrease the stereospecificity of epoxidation with a particular nucleophile.

(iii) The better the nucleofugality of *Z*, the higher is k_{cyc} and the higher is the stereospecificity. Both HCA (C—OZ) and the nucleofugality of Z are related to the electronegativity of Z and in most cases they change in a parallel fashion[625]. HO^- is a poor nucleofuge as compared to Cl^-, $k_{rot} > k_{cyc}$ and the product ratio is determined exclusively by the relative energies of the transition states leading to the diastereomeric epoxides. Stereoselectivity but not stereospecificity is often observed[609,621]. If HCA(C—OOBu-*t*) ~ HCA(C—OOH), *t*-BuO^- is a poor nucleofuge as compared to HO^- due to electron donation by the alkyl group. Lower stereospecificity is therefore observed in epoxidation with *t*-$BuOO^-$ comparatively to HOO^-[614].

(iv) The degree of stereospecificity is in most cases nearly independent of the alkyl or aryl substituents R^3 and R^4 (except when they are very bulky) because HCA(C—OZ) ≫ HCA(C—R^3), HCA(C—R^4).

b. Stereochemistry of epoxidation of cyclic enones. The stereochemistry of epoxidation of cyclic enones has been extensively studied for the Weitz–Scheffer reaction. In the case of an enone with an exocyclic double bond, the stereochemistry is comparable to those of acyclic enones due to the possibility of rotation of the hydroperoxyalkyl side-chain in the intermediate carbanion. The hydroperoxy group is capable of fulfilling the stereoelectronic requirements for the maximum orbital overlap at both sides of the carbanionic sp^2 carbon. The stereochemistry is then dependent on the relative conformational stabilities of the two conformers of the carbanionic intermediate. A mixture of diastereomeric epoxides is obtained, the sterically more favoured and therefore the more stable isomer being dominant (Table 59)[626,627].

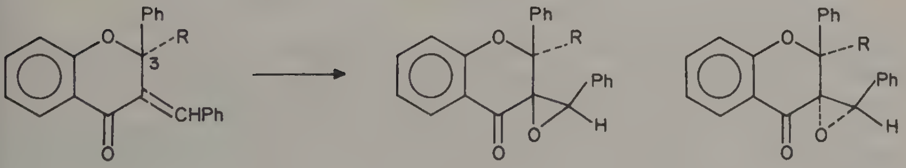
The exclusive formation of epoxide **252** from *cis* and *trans* enones **251** (equation 106)[628] and of the mixture of **254** and **255** from *cis* and *trans* **253** (equation 107)[629] with basic H_2O_2 agrees with the rule that the keto-epoxide with the least-hindered carbonyl group is preferentially obtained. When the interaction between the side-chain phenyl and the substituents on $C_{(3)}$ becomes too large (e.g. **256**) epoxidation is not observed.

(106)

cis and *trans*

(251)

(252)



cis and *trans*

(253) R = H

(256) R = Ph

(254) R = H

(255) R = H

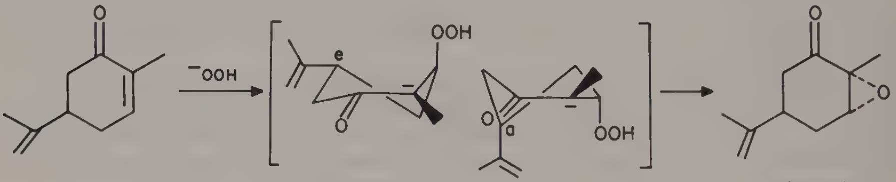
(107)

In the case of an enone with an endocyclic double bond, the alkaline H_2O_2 epoxidation can be entirely stereoselective. Thus, carvone gives only epoxide **257**[626] and 4-menthen-3-one gives only **258**[630] (equations 108 and 109). This is in accordance with the fact that the hydroperoxy group must be as close to axial as possible near the transition state for the cyclization step. Of the two axial conformations of the anions derived from carvone, the

TABLE 59. Stereochemistry of the Weitz–Scheffer reactions of cyclic enones[626,627]

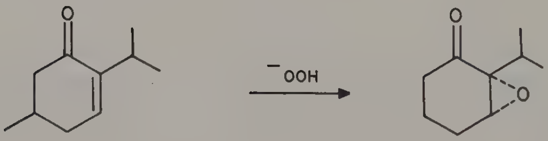
Enone	Product isomers	*trans*/*cis* ratio
(+)-(1*R*)-Pulegone	(−)-(1*R*:4*R*)-*trans*	64.5
	(+)-(1*R*:4*S*)-*cis*	35.5
(+)-(1*S*:5*R*)-Pinocarvone	(−)-(1*R*:2*S*:5*R*)-*trans*	35.5
	(+)-(1*R*:2*R*:5*R*)-*cis*	64.5
(+)-(1*R*:2*S*)-isopropylidene camphor	(−)-(1*R*:3*S*:4*S*)-*trans*	67
	(+)-(1*R*:3*R*:4*S*)-*cis*	33

one with the equatorial isopropenyl group (leading to **257**) will be definitely more reactive than the one with the axial isopropenyl group[627].



(257)

(108)



(109)

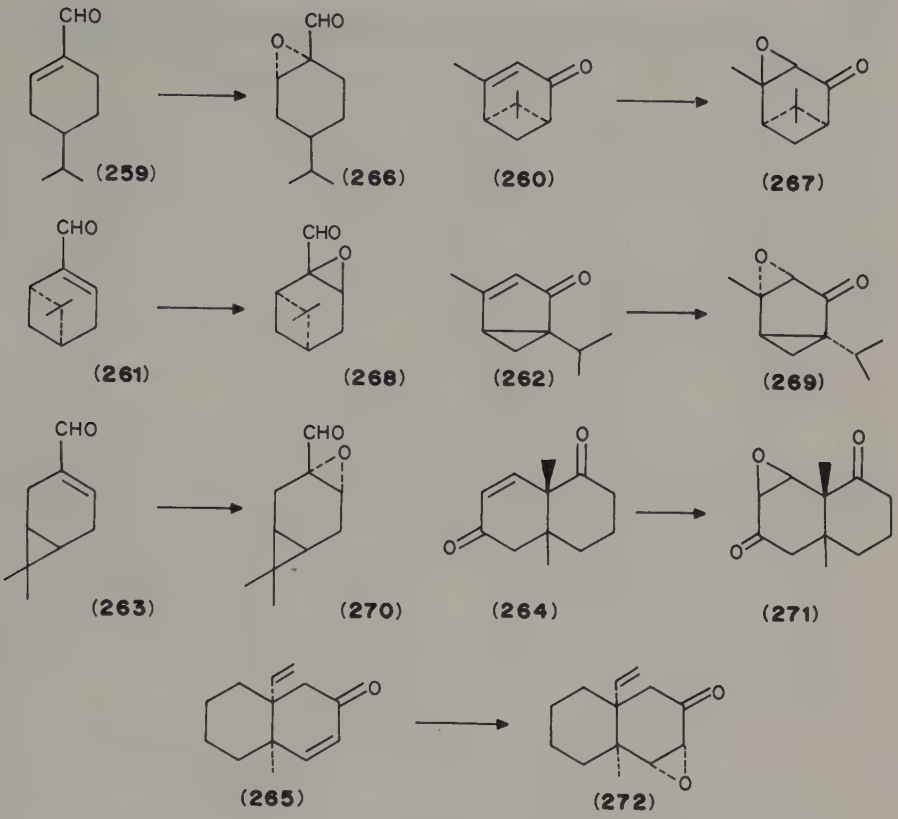
(258)

For the terpenic enals and enones **259**–**261**[626], **262**[631], **263**[632] and the decalones **264**[614], **265**[633], the exclusive formation of epoxides **266**–**272** can be explained by the theory of overlap control[627], as for carvone and 4-menthen-3-one (Scheme 4).

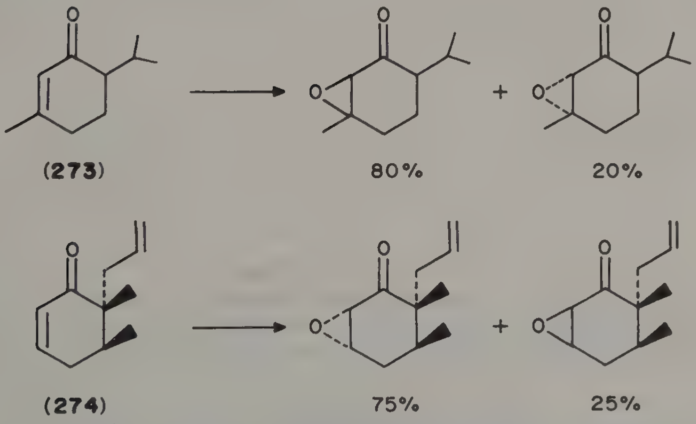
In the case of the epimerizable piperitone **273**[627] and 5, 6, 6-trisubstituted cyclohexenone **274**[634], a mixture of diastereomeric epoxides is obtained, but the product distributions are in agreement with the relative conformational stabilities of the intermediates (Scheme 5).

For the few cases studied, the stereochemistry of cyclic enone epoxidation with *t*-butyl hydroperoxide and with hydrogen peroxide are similar[614].

The stereochemistry of epoxidation with ZOH (Z = OH or *t*-BuO) in the steroid series has been explained in terms of the above mechanism for simple mono or bicyclic enones[609,612,635]. In some cases, the use of *t*-butyl hydroperoxide instead of hydrogen peroxide permits an increase of stereoselectivity, probably due to increase of the steric effect of Z[612], as exemplified in peroxide oxidation of 17-substituted Δ^4-3-ketosteroids **275** (equation 110) (Table 60).



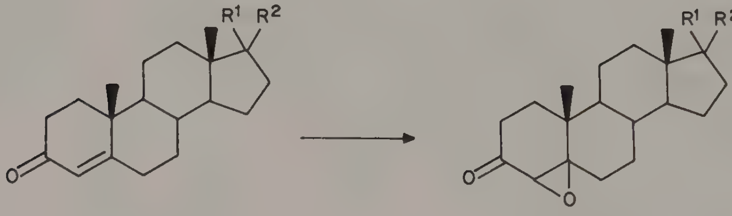
SCHEME 4



SCHEME 5

TABLE 60. Product distribution of peroxide oxidations of 17-substituted Δ^4-3-ketosteroids **275**[612]

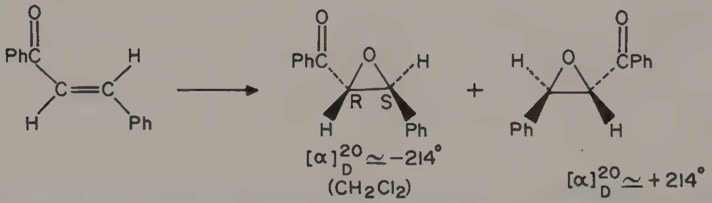
275				Epoxides **276**	
R^1	R^2	Oxidant	Base	α	β
β-C_8H_{17}	α-H	H_2O_2	NaOH	1	5
		H_2O_2	LiOH	1	6
		t-BuO_2H	LiOH	β only	
β-$COCH_3$	α-H	H_2O_2	NaOH	1	2.5
		H_2O_2	LiOH	1	3
		t-BuO_2H	LiOH	β only	
β-OH	α-H	H_2O_2	NaOH	1	2.3
		t-BuO_2H	LiOH	β only	
=O		H_2O_2	NaOH	1	3
		t-BuO_2H	LiOH	β only	



(275) α or β **(276)** (110)

2. *Catalytic asymmetric induction in nucleophilic epoxidation*

In order to optimize the optical yields of enantioselective epoxidation of enones, several attempts have been carried out with *trans*-chalcone, principally by two groups: Wynberg and coworkers using phase-transfer conditions, and Julia, Colonna and coworkers using three-phase systems (equation 111).



(111)

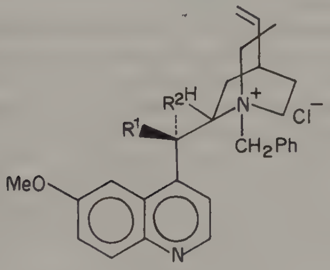
Owing to the many factors involved in the asymmetric epoxidation (structure and amount of the catalyst, solvent, temperature and nature of the oxidant), it is difficult to rationalize the occurrence of asymmetric induction. Nevertheless, some inferences can be made.

As exemplified by the Weitz–Scheffer reaction with hydrogen peroxide and the most efficient catalysts **277**–**283** (Table 61), appropriate poly-α-amino acids, such as poly(*S*)alanine **279** or poly(*S*)leucine **280** and poly(*S*)isoleucine **281**, lead to a high

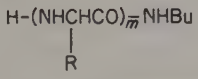
TABLE 61. Enantioselective oxidation of *trans*-chalcone with alkaline H_2O_2 in toluene

Catalyst	Yield (%)	$[\alpha]_D^{20}$ in CH_2Cl_2 (deg)	e.e. (%)	Ref.
277	99	−51	24	636, 637
278	—	+49	23	636, 637
279 $m = 10$ (L)	75	−199.5	93	638, 639
279 $m = 10$ (D)	53	+193.5	90	638, 639
279 $m = 30$ (L)	77	−205.4	96	638, 639
280 $m = 10$ (L)	60	−182.2	84	638, 639
280 $m = 30$ (L)	44	−189.8	88	638, 639
281 $m = 10$ (L)	76	−204.5	95	638, 639
282	69	−79	37	640
283	81	+4	2	640

stereospecificity. Other polypeptides such as poly(*S*)valine, polyglutamate or polyaspartate lead to lower chemical and optical yields[639,641].

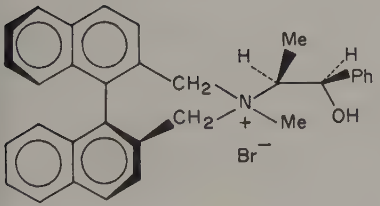


(**277**) R¹=OH, R²=H
(**278**) R¹=H, R²=OH

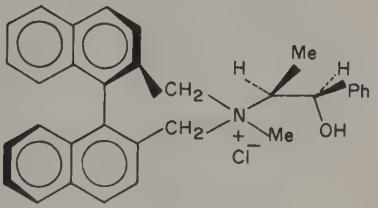


$\text{H-}(\underset{\underset{\text{R}}{|}}{\text{NHCHCO}})_{m}\text{NHBu}$

(**279**) R = Me
(**280**) R = CH_2CHMe_2
(**281**) R = $CHMeCH_2Me$



(**282**) (1*R*,2*S*,*S*)



(**283**) (1*R*,2*S*,*R*)

The opposite specific rotations of epoxychalcone obtained from the two antipodes (L and D) of **279** are easily comprehensive. By contrast, results obtained from the diastereomeric quininium and quinidinium benzyl chlorides (**277** and **278**), and the ephedrinium salts **282** and **283** are unaccountable.

Other catalysts such as quininium salts anchored to a polystyrene matrix in toluene[642], α and β cyclodextrins[643,644] or bovine serum albumin (BSA)[645] have been tested with alkaline hydrogen peroxide. They give poor chemical yield and enantiomeric excess. In the

TABLE 62. Effect of the oxidants on the asymmetric induction in chalcone epoxidation

Oxidant	Catalyst	Solvent	$[\alpha]_D^{20}$ in CH_2Cl_2 (deg)	e.e. (%)	Ref.
30% H_2O_2/NaOH	**277**	PhMe	−51	24	636
85% *t*-BuO_2H/NaOH	**277**	PhMe	+24	14	636
28% NaOCl	**277**	PhMe	+53	25	646
30% H_2O_2/NaOH	**279** *m* = 10 (L)	PhMe	−199.5	93	638,639
80% *t*-BuO_2H/NaOH	**279** *m* = 10 (L)	PhMe	+38.5	18	647
30% H_2O_2/NaOH	BSA[a]	H_2O, pH 11	−25.5	12	645
80% *t*-BuO_2H/NaOH	BSA[a]	H_2O, pH 11	+27	13	645

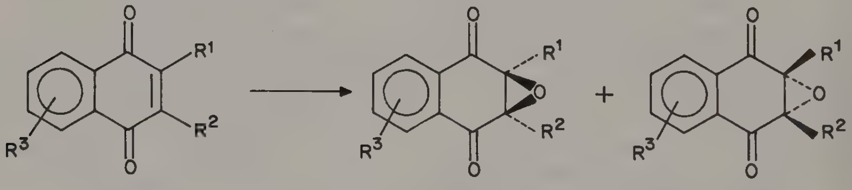
[a] BSA = Bovin Serum Albumin.

case of cyclodextrins, the use of sodium hypochlorite instead of hydrogen peroxide leads to 10% enantiomeric excess (e.e.) of epoxychalcone (0% e.e. with H_2O_2). This result can be explained through the initial formation of cyclodextrin hypochlorite[643].

With the catalysts for which the three usual oxidative reagents (hydrogen peroxide, *t*-butyl hydroperoxide, sodium hypochlorite) lead to an optical activity of epoxide mixture, optical activity is very dependent on the oxidant (Table 62).

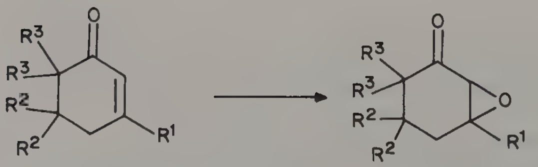
The degree of asymmetric induction in epoxidation of chalcone or substituted chalcones is influenced by the solvent. Toluene or carbon tetrachloride seems to be the solvents of choice when quininium benzyl chloride or poly-α-amino acids are used as catalysts[638,647,648]. However, no direct correlation exists between the classical solvent parameters such as the dielectric constant, and the enantiomeric excess[647,649].

The enantioselectivity is also very sensitive to minor structural variation in the substrates, as exemplified (i) by the reactions of mono or disubstituted 1,4-naphthoquinones **284** in the presence of BSA[639,645] or quininium benzyl chloride[636,637,650–652] (equation 112) (Table 63), and (ii) by the epoxidation reaction of substituted cyclohexenones **285**[636,639,653] (equation 113) (Table 64).



(284) (+)(2*S*,3*R*) **(286)** (−)(2*R*,3*S*) **(287)**

(112)



(285) **(288)**

(113)

TABLE 63. Substituent effects on enantioselective epoxidation of mono and disubstituted 1,4-naphthoquinones **284**[a]

284						
R^1	R^2	R^3	Oxidizing agent	Catalyst	[α]	e.e. (%)
Me	H	H	H_2O_2	BSA	(+)	3
			H_2O_2	**277**	(−)	9
			t-BuO_2H	BSA	(−)	20
			t-BuO_2H	**277**	(−)	6
Et	H	H	H_2O_2	BSA	(+)	15
			H_2O_2	**277**	(−)	10
			t-BuO_2H	BSA	(+)	5
i-Pr	H	H	H_2O_2	BSA	(+)	15
			H_2O_2	**277**	(−)	31
			t-BuO_2H	BSA	(+)	21
i-Bu	H	H	H_2O_2	BSA	(+)	8
			H_2O_2	**277**	(−)	16
			t-BuO_2H	BSA	(−)	77
t-Bu	H	H	H_2O_2	BSA		0
			H_2O_2	**277**	(+)	23
			t-BuO_2H	BSA		0
Ph	H	H	H_2O_2	BSA	(−)	~0
			H_2O_2	**277**	(−)	45
			t-BuO_2H	BSA	(−)	50
			t-BuO_2H	**277**	(+)	78
4-$MeO_2CC_6H_4$	H	H	*t*-BuO_2H	**277**	(+)	78
CH_2Ph	H	H	H_2O_2	BSA	(−)	15
			H_2O_2	**277**	(−)	23
			t-BuO_2H	BSA	(−)	12
n-Hex	H	H	H_2O_2	BSA	(+)	2
			H_2O_2	**277**	(+)	39
			t-BuO_2H	BSA	(−)	70
Me	Et	H	H_2O_2	BSA	(−)	11
			H_2O_2	**277**		0
			t-BuO_2H	BSA	(−)	54
Me	*n*-Bu	H	H_2O_2	BSA		0
			H_2O_2	**277**	(−)	~0
			t-BuO_2H	BSA	(−)	48
Me	H	5-Me	H_2O_2	**277**	(−)	18
Me	H	5-OMe	H_2O_2	**277**	(+)	12

[a] Reactions with Bovin Serum Albumine (BSA) are performed in pH 11 buffer solution and those with **277** under phase-transfer conditions with toluene.

TABLE 64. Substituent effects on enantioselective epoxidation of substituted cyclohexenones **285**

Cyclohexenone								
R^1	R^2	R^3	Oxidizing agent	Catalyst	Chemical yield (%)	$[\alpha]^{RT}$ in CH_2Cl_2	e.e. (%)	Ref.
H	H	H	H_2O_2	**279** $m = 10$	100	0	0	639
H	H	H	t-BuO_2H	**277**	54	-39	20	653
H	Me	H	t-BuO_2H	**277**	59	$+9$	16	653
Me	Me	H	NaOCl	**277**	23	-4	—	636
H	H	Me	t-BuO_2H	**277**	60	-15	15	653

3. *Epoxidation by electrogenerated superoxide*

Excellent yields of the epoxides of enones are obtained by treating the enones contained in the cathode chamber of an electrochemical cell with *in situ* electrogenerated superoxide in the presence of an auxiliary carbon acid, such as diphenylacetonitrile or diethyl methylmalonate (the nucleophilic species are $Ph_2C(CN)OO^-$ and $MeC(CO_2Et)_2OO^-$)[654] (Table 65).

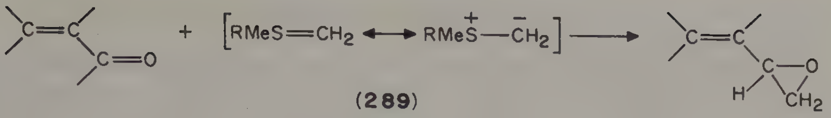
TABLE 65. Epoxidation of α-enones with electrogenerated superoxide and carbon acids[654]

Enone (5 mmol)	Carbon acid (mmol)		Faradays/ mol of enone	Yield of epoxide (%)	Recovered enone (%)
2-Cyclohexen-1-one	Ph_2CHCN	(5)	0.90	67	18
	Ph_2CHCN	(10)	1.80	89	trace
4,4-Dimethyl-2-cyclohexen-1-one	Ph_2CHCN	(10)	1.80	trace	85
	Ph_2CHCN	(10)	0.45	31	59
	$MeCH(CO_2Et)_2$	(20)	0.88	56	38
	$MeCH(CO_2Et)_2$	(40)	1.80	90	trace
4,4,6,6-Tetramethyl-2-cyclohexen-1-one	Ph_2CHCN	(10)	1.80	0	85
Mesityl oxide	Ph_2CHCN	(5)	0.90	15	64
	Ph_2CHCN	(10)	1.90	42	35
	Ph_2CHCN	(20)	3.70	85	trace
Chalcone	Ph_2CHCN	(5)	0.70	23	65
	Ph_2CHCN	(10)	1.60	42	39
	Ph_2CHCN	(20)	3.20	84	trace

B. Formation of Epoxides from the Carbon–Oxygen Double Bond

The carbonyl group of unsaturated aldehydes and ketones is converted into the unsaturated oxirane in good yields by methylene insertion with sulphur ylides **289**, generated from alkyl dimethylsulphonium salts such as trimethylsulphonium halides[655,656], dodecyl dimethylsulphonium chloride or dodecyl dimethylsulphonium methyl sulphate and base[657] (equation 114).

For enones containing other base-sensitive groups, the original conditions developed by Corey and Chaykovsky[655], using dimethyl sulphonium methylide ($R = Me$) prepared



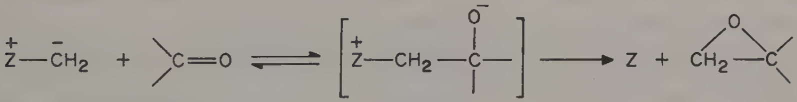
(114)

from trimethylsulphonium iodide and sodium hydride in dry dimethyl sulphoxide, are preferred. Thus, several compounds were converted to the corresponding oxiranes by selective addition of methylene to the carbonyl group, for instance benzalacetophenone (87% yield), carvone (89%), eucarvone (93%), pulegone (90%)[655], 2, 5, 6-trimethyl-2-cyclohexen-1-one (79%)[656], β-ionone (94%) and 3, 7-dimethyl-2, 6-octadienal (79%)[657]. Phase-transfer conditions using trimethylsulphonium chloride or fluoride, or dodecyldimethyl sulphonium salts (chloride or methyl sulphate), are more convenient when the substrates and products are base stable[657].

It is noteworthy that saturated ketones give oxirane formation with dimethyl oxosulphonium methylide **290**, whereas α, β-unsaturated ketones give only cyclopropanes (see Section VIII).

(290)

The stereochemical difference in the behaviour of **289** and **290** is attributed to formation of the betaine **291** (equation 115), being reversible for Z = $Me_2S{=}O$ but not for the less stable alkyldimethyl sulphonium methylide, so that the more hindered product is the result of kinetic control and the less hindered product results from thermodynamic control[658]. The stability of the sulphur ylide is an important factor in formation of the vinyl oxirane from enones. Substitution of a carboethoxy group on the methylene of dimethylsulphonium methylide dramatically increases ylide stability; consequently reversion of any kinetically favoured betaine to ylide and substrate is enhanced and cyclopropanation is observed (equation 116). As for the oxosulphonium ylides, the carbonyl stabilized ylide is a better 'leaving group'[658].

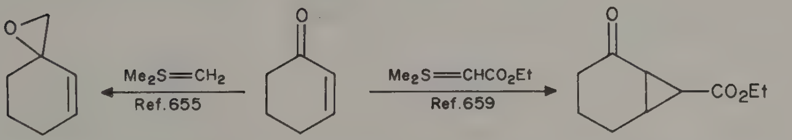


(289) Z = RMeS

(290) Z = $Me_2S{=}O$

(291)

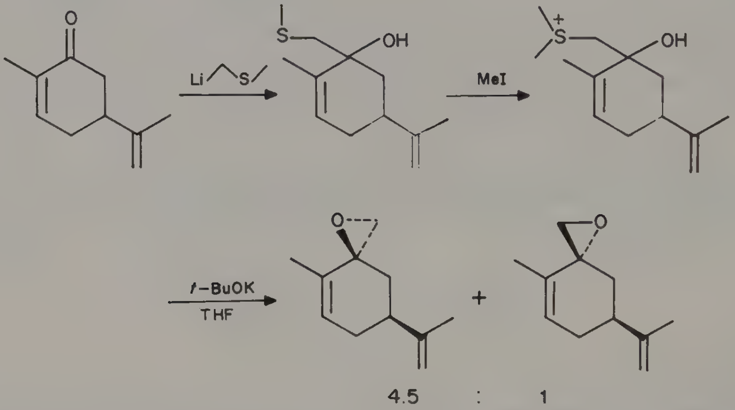
(115)



(116)

In the same way as for dimethylsulphonium methylide epoxidation, the oxirane formation is performed from an unstabilized arsonium ylide. The reaction can be highly stereoselective; for instance, with 2-butenal and triphenylarsonium *n*-butylide, the *E* epoxide is obtained in 75% yield[660].

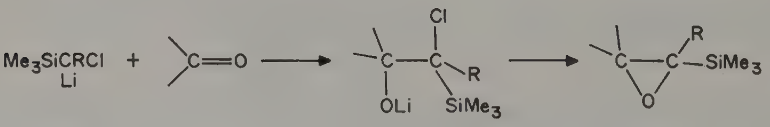
An alternative to the sulphur ylide route for the vinyl spiro epoxide formation from cyclenones, using sulphur compounds as starting materials, is the addition of [(methylthio)methyl] lithium on the carbonyl group, followed by methylation and closure of the hydroxysulphonium salt. Using this method, 2-methyl-2-cyclopenten-1-one, 2-cyclohexen-1-one and piperiton **273** might give single spiro epoxides in excellent yields (80–90%). Carvone gives a mixture of epoxides in 92% yield (equation 117)[661].



(117)

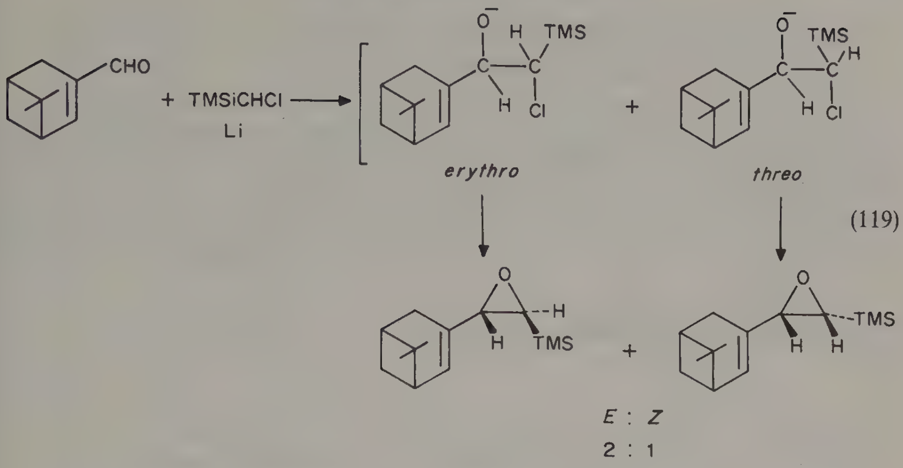
The Darzens reaction[609], i.e. the base-induced addition of a compound of type X-CHR-Y bearing halogen X and an electron-withdrawing substituent Y on the same carbon atom, to a carbonyl group, can be applied to enones to obtain α-functionalized vinyl oxiranes[609,662,663]. Taking into account the ambident electrophilic nature of α-enones, the choice of reagent is as important as that of the sulphur ylide. When the carbanion XC^-RY is pyramidal (hard), the 1,2-addition is preferred and the oxirane is obtained, whereas an inverted regioselectivity is observed with delocalized negative-charge carbanions leading to 1,4-addition and cyclopropanation. 4-phenyl-3-buten-2-one reacts with the anions derived from methyl chloroacetate and chloroacetonitrile (which are of the charge localized type, 'hard') at the carbonyl group to give equal amounts of the corresponding *Z* and *E* oxiranes. The same ketone reacts with the anions derived from methyl phenylchloroacetate and phenylchloroacetonitrile (the negative charge of which is delocalized) to give cyclopropanes by attack at the carbon–carbon double bond[20,664].

Another alternative to the Darzens reaction is the addition of reagents of the form **292** to aldehydes or ketones (equation 118)[665]. The product **293** is an α,β-epoxysilane which is a masked carbonyl group. 2-cyclohexen-1-one, carvone and myrtenal lead to the corresponding unsaturated oxiranes in 52, 76 and 95% yield, respectively. When the α,β-epoxytrimethylsilanes are formed as epimers at the carbon bearing the trimethylsilyl group (TMS), the epimer having the TMS group in the least sterically encumbered environment is predominant (equation 119)[666].



(118)

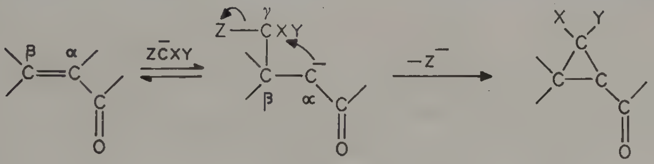
(292) **(293)**



(119)

VIII. NUCLEOPHILIC CYCLOPROPANATION

Nucleophilic cyclopropanation of the carbon–carbon double bond of α-enones closely parallels nucleophilic epoxidation both in the mechanism and the reagent of type $ZC^{-}XY$, where Z is a nucleofuge. It is established that cyclopropanation proceeds via the carbanion **294**, which cyclizes to **295** by an internal S_N2 reaction with expulsion of Z, which may be a neutral leaving group when the nucleophile is an ylide, or a halogen (equation 120)[20,625].

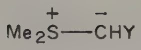


(120)

(294) **(295)**

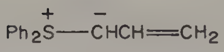
A more common nucleophilic cyclopropanation involves nucleophilic ylides, especially sulphur ylides, where intermediate **294** is a zwitterion and the nucleofuge is neutral[658]. Of the sulphonium ylides which permit methylene insertion on the ethylenic double bond of α-enones, dimethyloxosulphonium methylide **290** is the most useful[655,667]. It presents a convenient balance between reactivity and stability. Furthermore, the precursor, trimethyloxosulphonium iodide, is easily available by the S methylation of dimethyl sulphoxide. Unfortunately, S-alkylation of sulphoxides is not a general reaction, and with trivial exceptions[668] it is not possible to obtain salts in the trialkyloxosulphonium series. This limits the ylides in the series to methylide, and other sulphur ylides, e.g. **296** (Y = acyl[669–671], carboethoxy[659]), **297**[672] and **298**[673], which transfer CHY, CH-vinyl and cyclopropylidene, respectively, have also been used. CHR and CRR′ can be added in a similar manner with certain nitrogen-containing compounds[674]. For example, the ylides **299**[675], **300**[676], **301**[677] and **302**[678], and the carbanions **303** and **304**[675], have been used.

Similar reactions have been performed with nitrogen ylides such as cyanotrimethylammonium methylide[679] and substituted pyridinium phenacylides[680]. Many substituted cyclopropanes can also be made by treatment of α-enones with $ZC^{-}XY$ in which Z is Cl or



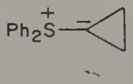
$Me_2\overset{+}{S}-\overset{-}{C}HY$

(296)

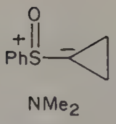


$Ph_2\overset{+}{S}-\overset{-}{C}HCH{=}CH_2$

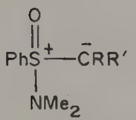
(297)



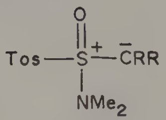
(298)



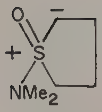
(299)



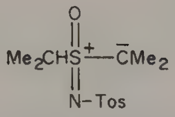
(300) R = H , R′ = Me
R = R′ = Me



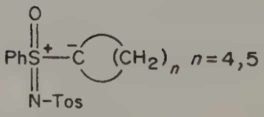
(301) R = H , R′ = Me
R = R′ = Me



(302)

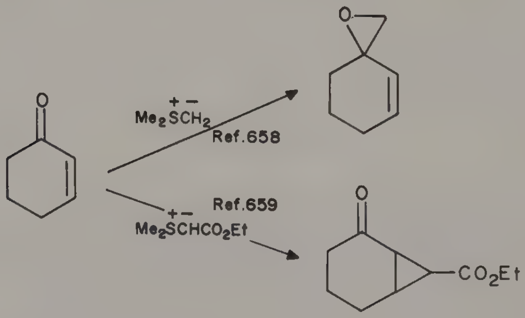


(303)

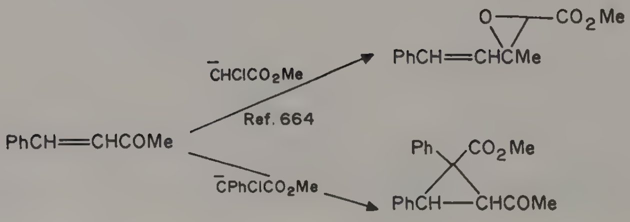


(304)

Br, X = Ph, Cl or CO_2R and Y = CO_2R, CN or COR[20,681–684]. As for sulphonium methylide[658], the stability of the ZC^-XY carbanion is very important for cyclopropanation. When X = H or alkyl, cyclopropane formation by a Michael-type addition competes with oxirane formation by 1,2-addition, since the charge-localized pyramidal carbanion (hard) ZC^-H(or alkyl)Y preferentially attacks the carbonyl group (equations 121 and 122).



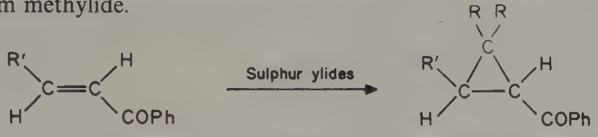
(121)



(122)

The stereochemistry of cyclopropanation with the reagents cited above is illustrated by three cases:

(*i*) *A CH_2 or CR_2 insertion into acyclic enones.* This is the case of sulphur ylides, in which intermediate **294** is a zwitterion. In most cases, a single isomeric precursor (e.g. *trans*-chalcone **8**, or *trans*-1,4-diphenyl-2-butene-1,4-dione (**305**) gives a single cyclopropane in an apparent stereoselective reaction (**8** → **306**, **305** → **307**) (equation 123)[668,673,675–677,685,686]. In contrast to these studies, Corey and Chaykovsky[655] observed a *cis–trans* mixture of cyclopropanes from *trans*-chalcone and dimethyloxosulphonium methylide.



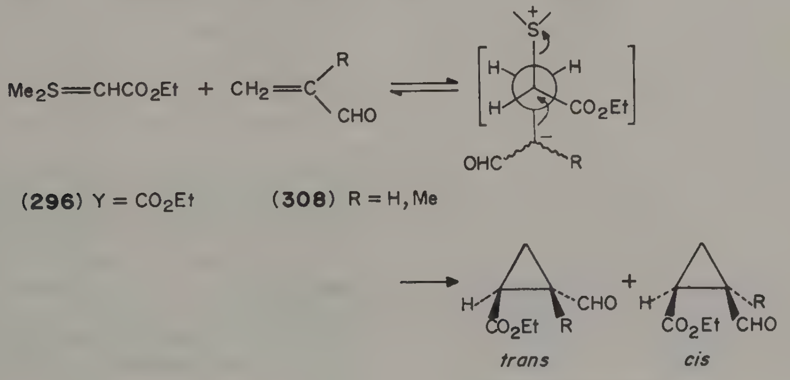
(123)

(8) R′ = Ph
(305) R′ = COPh

(306) R′ = Ph
(307) R′ = COPh

In fact, there are not sufficient data to distinguish between stereospecific and stereoselective behaviour. Computation results using the hyperconjugating ability (HCA) concept show that cyclopropanation with sulphur ylides may exhibit stereospecificity. However, this prediction is expected *a priori* to be less reliable than prediction for epoxidations of the ethylenic double bond of enones. This is because the computational experience with zwitterions is very limited, and because the extrapolation of the gas-phase results to solution is less reliable, since solvation is probably more important for zwitterions than for carbanions[625].

(*ii*) *β-Unsubstituted unsaturated aldehydes or ketones, $CH_2{=}CR^2COR^1$; sulphur ylides $>S{=}CR^3R^4$ and halogenocarbanions ZC^-XY.* The stereochemistry of the cyclopropane formed reflects both steric and electronic substituent factors and solvent effects. With sulphur ylides, this can be exemplified with acrolein **308** (R = H) and methacrolein **308** (R = Me) as substrates and **296** (Y = ethoxycarbonyl) as reagent (equation 124, Table 66).



(296) Y = CO₂Et

(308) R = H, Me

(124)

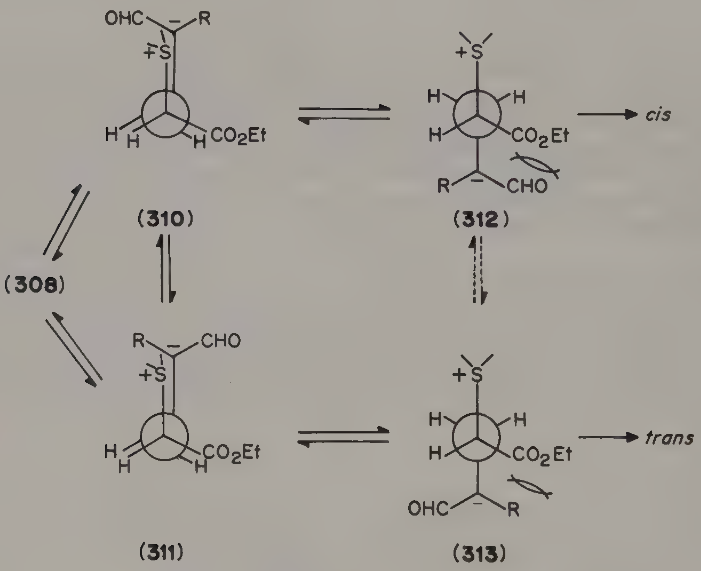
(309) R = H, Me

In all cases, predominant *trans* cyclopropanation to give **309** was observed. Electrosta-

TABLE 66. Stereochemistry of cyclopropanation of **308** by ethyl (dimethysulphuranylidene) acetate

		Product distribution		
R in **308**	Solvent	*cis*	*trans*	Ref.
H	PhH	8.5	91.5	671
H	Me_2CO	17	83	659
Me	PhH	32	68	671
Me	Me_2CO	45	55	659

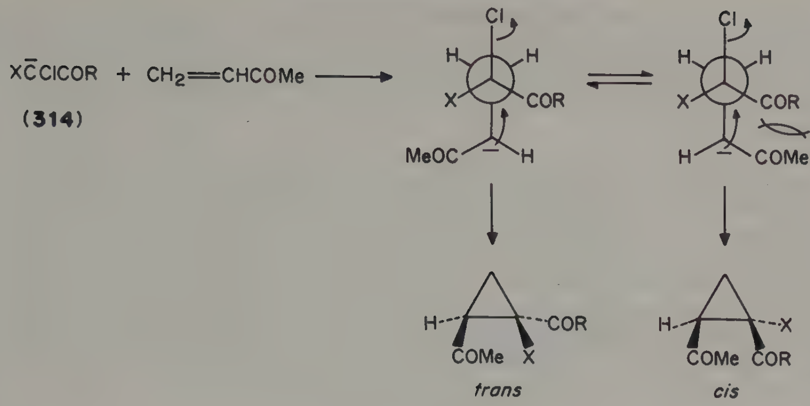
tic interactions favour initial formation of the eclipsed betaines **310** and **311** (equation 125)[550,625].



(125)

Subsequent collapse to cyclopropanes *via anti* conformers **312** and **313** is retarded in solvents of low dielectric constant such as benzene, that are less capable of solvating the proposed internal ion-pair. These solvents promote the equilibration of **310** and **311**, resulting in preferential formation of the favoured *trans* product. In solvents of higher dielectric constant such as acetone, the rate of cyclopropane formation increases. The betaine equilibration is precluded and increasing proportion of *cis* cyclopropane is formed. Comparatively to acrolein, the *trans* stereoselectivity of methacrolein decreases, due to the competitive steric interactions between the methyl and aldehyde groups and the ethoxycarbonyl group in **312** and **313**[671].

This interpretation also accounts for the stereoselectivity of cyclopropanations using carbanions ZC^-XY, as exemplified by the reaction of methyl vinyl ketone and carbanion **314** derived from α-chloroketones with NaH in benzene/HMPA (equation 126)[684].



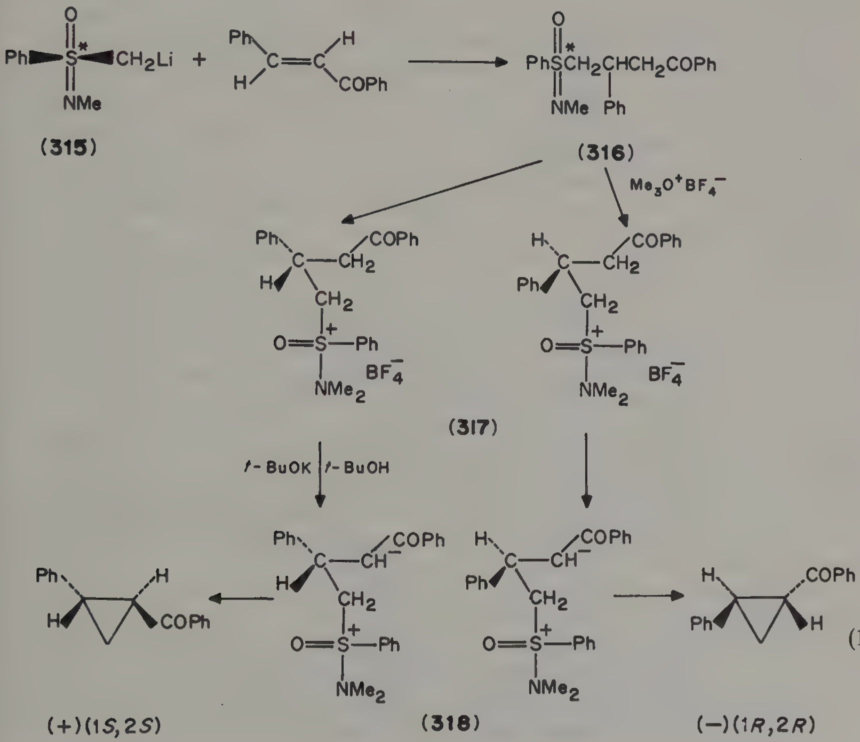
(126)

$R = Me, X = Ph$ 75 : 25

$R = Me, X = Me_2CH$ 65 : 35

$R - X = -(CH_2)_4$ >90 : <10

When acyclic enones are β-substituted (e.g. chalcone), the stereochemistry of cyclopropanation with both ylides and carbanions is difficult to explain due to the presence of several factors[20,669,672,679].



(127)

(*iii*) *A CH_2 or CR_2 insertion into substituted cyclic enones.* Few data are available for discussing the stereochemistry of cyclopropanation[655,673,686,687]. With carvone, a single isomer is obtained with dimethyloxosulphonium methylide[655], whereas *cis* and *trans* (40:60) isomers are observed with pulegone and (diethylamino)methyloxosulphonium methylide[686].

Some attempts to synthesize optically active cyclopropanes have been made by Johnson and coworkers with *trans*-chalcone and *trans*-1,4-diphenyl-2-buten-1,4-dione and chiral oxosulphonium methylides derived from sulphoximines salts. Usually the optical purities are low[676,677]. In contrast, the two pure enantiomers of *trans*-1-benzoyl-2-phenylcyclopropane are obtained by a conjugate addition of the lithium anion of (+)-(*S*)-*N*,*S*-dimethyl-*S*-phenylsulphoximine **315** to *trans*-chalcone. After separation, the two diastereomeric adducts **316** are methylated with trimethyloxonium fluoroborate, and the betaines **318**, generated by treatment of **317** with potassium *t*-butoxide-*t*-butyl alcohol, collapse to give the optically pure cyclopropanes (equation 127)[688].

IX. REFERENCES

1. Z. Arnold, V. Kral, G. V. Kryshtal and L. A. Yanovskaya, *Synthesis*, 974 (1984).
2. T. Eicher, in *The Chemistry of the Carbonyl Group* (Ed. S. Pataï), Interscience, London, 1966, pp. 621–693.
3. G. Klopman, *J. Am. Chem. Soc.*, **90**, 223 (1968).
4. O. Eisenstein, J. M. Lefour, C. Minot, Nguyen Trong Anh and G. Soussan, *C. R. Acad. Sci. Paris, Ser. C.*, **274**, 1310 (1972).
5. J. Bottin, O. Eisenstein, C. Minot and Nguyen Trong Anh, *Tetrahedron Lett.*, 3015 (1972).
6. B. Deschamps, Nguyen Trong Anh and J. Seyden-Penne, *Tetrahedron Lett.*, 527 (1973).
7. J. Durand, Nguyen Trong Anh and J. Huet, *Tetrahedron Lett.*, 2397 (1974).
8. P. Metivier, A. J. Gushurst and W. L. Jorgensen, *J. Org. Chem.*, **52**, 3724 (1987).
9. S. Patai and Z. Rappoport, in *The Chemistry of Alkenes* (Ed. S. Patai), Interscience, London, 1964, pp. 469–584.
10. B. J. Wakefield, *Chemistry of Organolithium Compounds*, Pergamon Press, Oxford, 1974, p. 133.
11. A. Krief, *Tetrahedron*, **36**, 2531 (1980).
12. J. D. Albright, *Tetrahedron*, **39**, 3207 (1983).
13. L. A. Yanovskaya, G. V. Kryshtal and V. V. Kulganeck, *Russ. Chem. Rev.*, **53**, 744 (1984); *Chem. Abstr.*, **101**, 190667x (1984).
14. L. Wartski, M. El-Bouz, J. Seyden-Penne, W. Dumont and A. Krief, *Tetrahedron Lett.*, 1543 (1979).
15. L. Wartski, M. El-Bouz and J. Seyden-Penne, *J. Organomet. Chem.*, **177**, 17 (1979).
16. G. V. Kryshtal, K. Y. Burshtein, V. V. Kulganeck and L. A. Yanovskaya, *Izv. Akad. Nauk. SSRR, Ser. Khim.*, 2541 (1984); *Chem. Abstr.*, **102**, 94993a (1985).
17. A. Roux, M. C. Roux-Schmitt and J. Seyden-Penne, *Tetrahedron*, **26**, 2649 (1970).
18. B. Deschamps and J. Seyden-Penne, *Tetrahedron*, **27**, 3959 (1971).
19. M. C. Roux-Schmitt, J. Seyden-Penne and S. Wolfe, *Tetrahedron*, **28**, 4965 (1972).
20. G. Kyriakakou, M. C. Roux-Schmitt and J. Seyden-Penne, *Tetrahedron*, **31**, 1883 (1975).
21. R. Sauvêtre and J. Seyden-Penne, *Tetrahedron Lett.*, 3949 (1976).
22. K. Popandova-Yambolieva, A. Dobrev and C. Ivanov, *Synth. Commun.*, **11**, 335 (1981).
23. R. Sauvêtre, M. C. Roux-Schmitt and J. Seyden-Penne, *Tetrahedron*, **34**, 2135 (1978).
24. M. Cossentini, B. Deschamps, Nguyen Trong Anh and J. Seyden-Penne, *Tetrahedron*, **33**, 409 (1977).
25. B. Deschamps and J. Seyden-Penne, *Tetrahedron*, **33**, 413 (1977).
26. B. Deschamps, *Tetrahedron*, **34**, 2009 (1978).
27. B. Deschamps, M. C. Roux-Schmitt and L. Wartski, *Tetrahedron Lett.*, 1377 (1979).
28. A. Loupy, J. M. Lefour, B. Deschamps and J. Seyden-Penne, *Nouv. J. Chim.*, **4**, 121 (1980).
29. L. Wartski and M. El-Bouz, *Tetrahedron*, **38**, 3285 (1982).
30. M. El-Bouz and L. Wartski, *Tetrahedron Lett.*, **21**, 2897 (1980).
31. T. Mukhopadhyay and D. Seebach, *Helv. Chim. Acta*, **65**, 385 (1982).

32. J. Lucchetti, W. Dumont and A. Krief, *Tetrahedron Lett.*, 2695 (1979).
33. C. A. Brown and A. Yamaichi, *J. Chem. Soc., Chem. Commun.*, 100 (1979).
34. D. J. Ager and M. B. East, *J. Org. Chem.*, **51**, 3983 (1986).
35. J. M. Lefour and A. Loupy, *Tetrahedron*, **34**, 2597 (1978).
36. S. Hünig and G. Wehner, *Chem. Ber.*, **113**, 302 (1980).
37. S. Hünig and G. Wehner, *Chem. Ber.*, **113**, 324 (1980).
38. S. Hünig and M. Oller, *Chem. Ber.*, **114**, 959 (1981).
39. C. Minot and Nguyen Trong Anh, *Tetrahedron Lett.*, 3905 (1975).
40. G. Stork and L. Maldonado, *J. Am. Chem. Soc.*, **96**, 5272 (1974).
41. M. C. Roux, L. Wartski and J. Seyden-Penne, *Tetrahedron*, **37**, 1927 (1981).
42. M. C. Roux-Schmitt, L. Wartski and J. Seyden-Penne, *Synth. Commun.*, **11**, 85 (1981).
43. M. C. Roux-Schmitt, J. Seyden-Penne, G. V. Baddeley and E. Wenkert, *Tetrahedron Lett.*, **22**, 2171 (1981).
44. M. C. Roux-Schmitt and J. Seyden-Penne, *Bull. Soc. Chim. Fr.*, 109 (1986).
45. J. Lucchetti and A. Krief, *J. Chem. Soc., Chem. Commun.*, 127 (1982).
46. N. Seuron and J. Seyden-Penne, *Tetrahedron*, **40**, 635 (1984).
47. W. Dumont, J. Lucchetti and A. Krief, *J. Chem. Soc., Chem. Commun.*, 66 (1983).
48. S. Yamagiwa, N. Hoshi, H. Sato, H. Kosugi and H. Ada, *J. Chem. Soc., Perkin Trans. 1*, 214 (1978).
49. P. C. Ostrowski and V. V. Kane, *Tetrahedron Lett.*, 3549 (1977).
50. M. El-Bouz, M. C. Roux-Schmitt and L. Wartski, *J. Chem. Soc., Chem. Commun.*, 779 (1979).
51. J. Lucchetti and A. Krief, *Tetrahedron Lett.*, 2697 (1978).
52. J. Canceill, J. Gabard and J. Jacques, *Bull. Soc. Chim. Fr.*, 231 (1968).
53. F. Barbot and P. Miginiac, *J. Organomet. Chem.*, **132**, 445 (1977).
54. R. A. Benkeser, M. P. Siklosi and E. C. Mozden, *J. Am. Chem. Soc.*, **100**, 2134 (1978).
55. J. M. McIntosh, P. Mishra and M. A. Siddiqui, *J. Org. Chem.*, **49**, 1036 (1984).
56. M. C. Roux-Schmitt, L. Wartski and J. Seyden-Penne, *J. Chem. Res.* (*S*), 346 (1980); (*M*), 4141 (1980).
57. H. Ahlbrecht and H. M. Kompter, *Synthesis*, 645 (1983).
58. M. Zervos, L. Wartski and J. Seyden-Penne, *Tetrahedron*, **42**, 4963 (1986).
59. M. Zervos and L. Wartski, *Tetrahedron Lett.*, **27**, 2985 (1986).
60. J. Bertrand, L. Gorrichon, P. Maroni and R. Meyer, *Tetrahedron Lett.*, **23**, 3267 (1982).
61. F. E. Ziegler, U. R. Chakraborty and R. T. Wester, *Tetrahedron Lett.*, **23**, 3237 (1982).
62. F. E. Ziegler and J. J. Mencel, *Tetrahedron Lett.*, **24**, 1859 (1983).
63. M. R. Binns, R. K. Haynes, A. A. Katsifis, P. A. Schober and S. C. Vonwiller, *Tetrahedron Lett.*, **26**, 1565 (1985).
64. M. R. Binns, O. L. Chai, R. K. Haynes, A. A. Katsifis, P. A. Schober and S. C. Vonwiller, *Tetrahedron Lett.*, **26**, 1569 (1985).
65. M. R. Binns, R. K. Haynes, T. L. Houston and W. R. Jackson, *Tetrahedron Lett.*, **21**, 573 (1980).
66. M. R. Binns and R. K. Haynes, *J. Org. Chem.*, **46**, 3790 (1981).
67. G. A. Kraus and K. Frazier, *Synth. Commun.*, **8**, 483 (1978).
68. B. M. Trost, N. R. Schmuff and M. J. Miller, *J. Am. Chem. Soc.*, **102**, 5979 (1980).
69. M. Hirama, *Tetrahedron Lett.*, **22**, 1905 (1981).
70. S. De Lombaert, I. Nemery, B. Roekens, J. C. Carretero, T. Kimmel and L. Ghosez, *Tetrahedron Lett.*, **27**, 5099 (1986).
71. M. R. Binns, R. K. Haynes, T. L. Houston and W. R. Jackson, *Aust. J. Chem.*, **34**, 2465 (1981).
72. L. L. Vasileva, V. I. Melnikova, E. T. Gainullina and K. K. Pivnitskii, *Zh. Org. Khim.*, **16**, 2618 (1980); *Chem. Abstr.*, **94**, 191837b (1981).
73. L. L. Vasileva, V. I. Melnikova, E. T. Gainullina and K. K. Pivnitskii, *Zh. Org. Khim.*, **19**, 941 (1983); *Chem. Abstr.*, **99**, 104825h (1983).
74. L. L. Vasileva, V. I. Melnikova and K. K. Pivnitskii, *Zh. Org. Khim.*, **20**, 690 (1984); *Chem. Abstr.*, **101**, 170928e (1984).
75. K. S. Kyler, M. A. Netzel, S. Arseniyadis and D. S. Watt, *J. Org. Chem.*, **48**, 383 (1983).
76. B. Lesur, J. Toye, M. Chantrenne and L. Ghosez, *Tetrahedron Lett.*, 2835 (1979).
77. S. De Lombaert, B. Lesur and L. Ghosez, *Tetrahedron Lett.*, **23**, 4251 (1982).
78. F. E. Ziegler and C. C. Tam, *Tetrahedron Lett.*, 4717 (1979).
79. F. E. Ziegler, J. J. Fang and C. C. Tam, *J. Am. Chem. Soc.*, **104**, 7174 (1982).
80. D. A. Evans and A. M. Golob, *J. Am. Chem. Soc.*, **97**, 4765 (1975).

81. D. A. Evans, D. J. Baillargen and J. V. Nelson, *J. Am. Chem. Soc.*, **100**, 2242 (1978).
82. A. Fischer and G. N. Henderson, *Tetrahedron Lett.*, **21**, 701 (1980).
83. A. Fischer and G. N. Henderson, *Tetrahedron Lett.*, **24**, 131 (1983).
84. D. A. Evans, J. M. Hoffman and L. K. Truesdale, *J. Am. Chem. Soc.*, **95**, 5822 (1973).
85. D. Liotta, M. Saindane and C. Barnum, *J. Org. Chem.*, **46**, 3369 (1981).
86. D. Liotta, M. Saindane, U. Sunay, W. C. L. Jamison, J. Grossman and P. Phillips, *J. Org. Chem.*, **50**, 3243 (1985).
87. H. O. House, R. A. Auerbach, M. Gall and N. P. Peet, *J. Org. Chem.*, **38**, 514 (1973).
88. A. G. Pinkus, J. G. Lindberg and A. B. Wu, *J. Chem. Soc., Chem. Commun.*, 1350 (1969).
89. P. Fellmann and J. E. Dubois, *Tetrahedron Lett.*, 247 (1977).
90. R. Meyer, L. Gorrichon and P. Maroni, *J. Organomet. Chem.*, **C7**, 129 (1977).
91. J. Bertrand, L. Gorrichon, P. Maroni, R. Meyer and L. Viteva, *Tetrahedron Lett.*, **23**, 1901 (1982).
92. L. M. Jackman and N. M. Szevernyi, *J. Am. Chem. Soc.*, **99**, 4954 (1977).
93. L. M. Jackman and B. C. Lange, *Tetrahedron*, **33**, 2737 (1977).
94. R. Amstutz, W. B. Schweizer, D. Seebach and J. D. Dunitz, *Helv. Chim. Acta*, **64**, 2617 (1981).
95. H. O. House, A. V. Prabhu and W. V. Phillips, *J. Org. Chem.*, **41**, 1209 (1976).
96. J. Bertrand, L. Gorrichon and P. Maroni, *Tetrahedron*, **40**, 4127 (1984).
97. J. Mulzer, G. Hartz, U. Kühl and G. Brüntrup, *Tetrahedron Lett.*, 2949 (1978).
98. C. Goasdoue, N. Goasdoue, M. Gaudemar and M. Mladenova, *J. Organomet. Chem.*, **226**, 209 (1982).
99. M. W. Rathke, *J. Am. Chem. Soc.*, **92**, 3222 (1970).
100. G. Stork, G. A. Kraus and G. A. Garcia, *J. Org. Chem.*, **39**, 3459 (1974).
101. A. Pochini, G. Puglia and R. Ungaro, *Tetrahedron Lett.*, 3897 (1979).
102. Y. Tamaru, T. Harada, S. Nishi, M. Mizutani, T. Hioki and Z. Yoshida, *J. Am. Chem. Soc.*, **102**, 7806 (1980).
103. Q. B. Cass, A. A. Jaxa-Chamiec and P. G. Sammes, *J. Chem. Soc., Chem. Commun.*, 1248 (1981).
104. C. H. Heathcock, M. A. Henderson, D. A. Oare and M. A. Sanner, *J. Org. Chem.*, **50**, 3019 (1985).
105. C. H. Heathcock and D. A. Oare, *J. Org. Chem.*, **50**, 3022 (1985).
106. H. O. House and K. A. J. Snoble, *J. Org. Chem.*, **41**, 3076 (1976).
107. P. Maroni, in *Organométalliques fonctionnels ambidents*, Recl. Comm. Colloque Franco-Bulgare, Tryavna, Bulgarie, 1980, pp. 75–99; *Chem. Abstr.*, **95**, 60732m (1981).
108. P. Metzner and R. Rakotonirina, *Tetrahedron*, **41**, 1289 (1985).
109. A. G. Schultz and Y. K. Yee, *J. Org. Chem.*, **41**, 4044 (1976).
110. P. Metzner, *J. Chem. Soc., Chem. Commun.*, 335 (1982).
111. P. Metzner and R. Rakotonirina, *Tetrahedron Lett.*, **24**, 4203 (1983).
112. L. Gorrichon-Guigon and S. Hammerer, *Tetrahedron*, **36**, 631 (1980).
113. S. H. Bertz, L. W. Jelinski and G. Dabbagh, *J. Chem. Soc., Chem. Commun.*, 388 (1983).
114. S. Berrada, P. Metzner and R. Rakotonirina, *Bull. Soc. Chim. Fr.*, 881 (1985).
115. H. O. House and M. J. Lusch, *J. Org. Chem.*, **42**, 183 (1977).
116. J. Bertrand, N. Cabrol, L. Gorrichon-Guigon and Y. Maroni-Barnaud, *Tetrahedron Lett.*, 4683 (1973).
117. L. Gorrichon-Guigon, Y. Maroni-Barnaud, P. Maroni and J. D. Bastide, *Bull. Soc. Chim. Fr.*, 291 (1975).
118. J. Bertrand, L. Gorrichon and P. Maroni, *Tetrahedron Lett.*, 4207 (1977).
119. J. M. Fang, *J. Org. Chem.*, **47**, 3464 (1982).
120. Y. Stefanovsky, Tz. Gaspidova and L. Viteva, *Tetrahedron*, **42**, 5355 (1986).
121. D. A. Oare and C. H. Heathcock, *Tetrahedron Lett.*, **27**, 6169 (1986).
122. K. Kpegba, P. Metzner and R. Rakotonirina, *Tetrahedron Lett.*, **27**, 1505 (1986).
123. J. Mulzer, A. Chucholowski, O. Lammer, I. Jibril and G. Huttner, *J. Chem. Soc., Chem. Commun.*, 869 (1983).
124. W. Oppolzer, R. Pitteloud, G. Bernardinelli and K. Baetting, *Tetrahedron Lett.*, **24**, 4975 (1983).
125. L. Viteva and Y. Stefanovsky, *Monatsh. Chem.*, **113**, 181 (1982).
126. R. Häner, T. Laube and D. Seebach, *Chimia*, **38**, 255 (1984).
127. E. J. Corey and R. T. Peterson, *Tetrahedron Lett.*, **26**, 5025 (1985).
128. I. Casinos and R. Mestres, *J. Chem. Soc., Perkin Trans. 1*, 1651 (1978).
129. I. Casinos, R. Mestres and M. Valero, *An. Quim.*, **76C**, 70 (1980).
130. I. Casinos and R. Mestres, *An. Quim.*, **78C**, 368 (1982).

131. P. Beslin and A. Dlubala, *Tetrahedron Lett.*, **27**, 1687 (1986).
132. P. Ballester, A. Garcia-Raso, A. Gomez-Solivellas and R. Mestres, *Tetrahedron Lett.*, **26**, 2485 (1985).
133. T. L. Ho, *Tetrahedron*, **40**, 1 (1985).
134. G. A. Posner, *Org. React.*, **19**, 1 (1972).
135. G. H. Posner, *An Introduction to Synthesis using Organocopper Reagents*, John Wiley and Sons, New York, 1980.
136. J. F. Normant, *Synthesis*, 63 (1972).
137. J. F. Normant, *J. Organomet. Chem. Library*, **1**, 219 (1976).
138. A. Alexakis, C. Chuit, M. Commerçon-Bourgain, J. P. Foulon, N. Jabri, P. Mangeney and J. F. Normant, *Pure Appl. Chem.*, **56**, 91 (1984).
139. A. E. Jukes, in *Advances in Organometallic Chemistry*, Vol. 12 (Eds. F. A. Stone and R. West), Academic Press, New York, 1974, pp. 215–322.
140. J. P. Marino, *Ann. Rep. Med. Chem.*, **10**, 327 (1975); *Chem. Abstr.*, **84**, 105676n (1976).
141. B. H. Lipshutz, R. S. Wilhelm and J. A. Kozlowski, *Tetrahedron*, **40**, 5005 (1984).
142. B. H. Lipshutz, *Synthesis*, 325 (1987).
143. R. J. K. Taylor, *Synthesis*, 364 (1985).
144. J. Drouin, F. Leyendecker and J. M. Conia, *Nouv. J. Chim.*, **2**, 267 (1978).
145. F. Leyendecker, J. Drouin and J. M. Conia, *Nouv. J. Chim.*, **2**, 271 (1978).
146. J. Drouin and G. Rousseau, *J. Organomet. Chem.*, **289**, 223 (1985).
147. J. P. Gorlier, L. Hamon, J. Levisalles and J. Waghon, *J. Chem. Soc., Chem. Commun.*, 88 (1973).
148. E. C. Ashby, J. J. Lin and J. J. Watkins, *J. Org. Chem.*, **42**, 1099 (1977).
149. A. Alexakis, G. Cahiez and J. F. Normant, *Tetrahedron*, **36**, 1961 (1980).
150. E. L. Lindstedt and M. Nilsson, *Acta Chem. Scand.*, **B40**, 466 (1986).
151. H. Riviere and P. W. Tang, *Bull. Soc. Chim. Fr.*, 2455 (1973).
152. F. Leyendecker, J. Drouin, J. J. Debesse and J. M. Conia, *Tetrahedron Lett.*, 1591 (1977).
153. C. Chuit, J. P. Foulon and J. F. Normant, *Tetrahedron*, **37**, 1385 (1981).
154. M. Bourgain-Commerçon, J. P. Foulon and J. F. Normant, *J. Organomet. Chem.*, **228**, 321 (1982).
155. D. L. J. Clive, V. Farina and P. L. Beaulieu, *J. Org. Chem.*, **47**, 2572 (1982).
156. S. R. Krauss and S. G. Smith, *J. Am. Chem. Soc.*, **103**, 141 (1981).
157. H. Malmberg and M. Nilsson, *Tetrahedron*, **38**, 1509 (1982).
158. S. Bertz and G. Dabbagh, *J. Org. Chem.*, **49**, 1119 (1984).
159. J. P. Marino and J. S. Farina, *Tetrahedron Lett.*, 3901 (1975).
160. Y. Kojima, S. Wakita and N. Kato, *Tetrahedron Lett.*, 4577 (1979).
161. E. Piers and B. W. A. Yeung, *J. Org. Chem.*, **49**, 4567 (1984).
162. H. O. House and W. F. Fischer, Jr., *J. Org. Chem.*, **33**, 949 (1968).
163. J. Hooz and R. B. Layton, *Can. J. Chem.*, **48**, 1626 (1970).
164. E. J. Corey and D. J. Beames, *J. Am. Chem. Soc.*, **94**, 7210 (1972).
165. W. H. Mandeville and G. M. Whitesides, *J. Org. Chem.*, **39**, 400 (1974).
166. M. Suzuki, T. Suzuki, T. Kawagishi and R. Noyori, *Tetrahedron Lett.*, **21**, 1247 (1980).
167. M. Suzuki, T. Suzuki, T. Kawagishi, Y. Morita and R. Noyori, *Isr. J. Chem.*, **24**, 118 (1984).
168. H. O. House and M. J. Umen, *J. Org. Chem.*, **38**, 3893 (1973).
169. R. G. Pearson and G. D. Gregory, *J. Am. Chem. Soc.*, **98**, 4098 (1976).
170. E. C. Ashby and J. J. Watkins, *J. Am. Chem. Soc.*, **99**, 5312 (1977).
171. H. O. House and J. M. Wilkins, *J. Org. Chem.*, **43**, 2443 (1978).
172. B. H. Lipshutz, J. A. Kozlowski and C. M. Breneman, *Tetrahedron Lett.*, **26**, 5911 (1985).
173. H. O. House and C. Y. Chu, *J. Org. Chem.*, **41**, 3083 (1976).
174. K. R. Stewart, J. R. Lever and M. H. Whangho, *J. Org. Chem.*, **47**, 1472 (1982).
175. C. Ouannes, G. Dressaire and Y. Langlois, *Tetrahedron Lett.*, 815 (1977).
176. H. O. House, W. H. Respess and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966).
177. H. O. House, D. D. Traficante and R. A. Evans, *J. Org. Chem.*, **28**, 348 (1963).
178. C. P. Casey and R. A. Boggs, *Tetrahedron Lett.*, 2455 (1971).
179. G. M. Whitesides and P. E. Kendall, *J. Org. Chem.*, **37**, 3718 (1972).
180. H. O. House, *Acc. Chem. Res.*, **9**, 59 (1976).
181. H. O. House and P. D. Weeks, *J. Am. Chem. Soc.*, **97**, 2770 (1975).
182. J. A. Marshall and R. A. Ruden, *J. Org. Chem.*, **37**, 659 (1972).
183. H. O. House, W. C. McDaniel, R. E. Sieloff and D. Vanderveer, *J. Org. Chem.*, **43**, 4316 (1978).

184. R. A. J. Smith and D. J. Hannah, *Tetrahedron Lett.*, **21**, 1081 (1980).
185. D. J. Hannah, R. A. J. Smith, I. Teoh and R. T. Weavers, *Aust. J. Chem.*, **34**, 181 (1981).
186. R. A. Ruden and W. E. Litterer, *Tetrahedron Lett.*, 2043 (1975).
187. G. Stork and E. W. Logusch, *Tetrahedron Lett.*, 3361 (1979).
188. E. W. Logusch, *Tetrahedron Lett.*, 3365 (1979).
189. D. Liotta, M. Saindane and L. Waykole, *J. Am. Chem. Soc.*, **105**, 2922 (1983).
190. D. J. Hannah and R. A. J. Smith, *Tetrahedron Lett.*, 187 (1975).
191. P. M. Wege, R. D. Clark and C. H. Heathcock, *J. Org. Chem.*, **41**, 3144 (1976).
192. W. R. Roush and B. M. Lesur, *Tetrahedron Lett.*, **24**, 2231 (1983).
193. E. J. Corey and N. W. Boaz, *Tetrahedron Lett.*, **26**, 6015 (1985).
194. C. Jallabert, H. Riviere and P. W. Tang, *J. Organomet. Chem.*, **104**, 1 (1976).
195. P. Four, H. Riviere and P. W. Tang, *Tetrahedron Lett.*, 3879 (1977).
196. J. Berlan, J. P. Battioni and K. Koosha, *Tetrahedron Lett.*, 3355 (1976).
197. J. Berlan, J. P. Battioni and K. Koosha, *Bull. Soc. Chim. Fr.*, 183 (1979).
198. R. A. J. Smith and D. J. Hannah, *Tetrahedron*, **35**, 1183 (1979).
199. C. P. Casey and M. C. Cesa, *J. Am. Chem. Soc.*, **101**, 4236 (1979).
200. C. Frejaville and R. Jullien, *Tetrahedron Lett.*, 2039 (1971).
201. C. Frejaville, R. Jullien, H. Stahl-Lariviere, M. Wanat and D. Zann, *Tetrahedron*, **38**, 2671 (1982).
202. R. Jullien, H. Stahl-Lariviere and D. Zann, *Tetrahedron*, **37**, 3159 (1981).
203. E. J. Corey and N. W. Boaz, *Tetrahedron Lett.*, **25**, 3063 (1984).
204. G. Hallnemo and C. Ullenius, *Tetrahedron*, **39**, 1621 (1983).
205. B. H. Lipshutz, R. S. Wilhelm and J. A. Kozlowski, *J. Org. Chem.*, **49**, 3938 (1984).
206. C. Chuit, J. P. Foulon and J. F. Normant, *Tetrahedron*, **36**, 2305 (1980).
207. D. L. J. Clive, V. Farina and P. Beaulieu, *J. Chem. Soc., Chem. Commun.*, 643 (1981).
208. H. O. House and M. J. Umen, *J. Am. Chem. Soc.*, **94**, 5495 (1972).
209. H. O. House, L. E. Huber and M. J. Umen, *J. Am. Chem. Soc.*, **94**, 8471 (1972).
210. J. P. Marino and D. M. Floyd, *Tetrahedron Lett.*, 3897 (1975).
211. C. Chuit, R. Sauvêtre, D. Masure and J. F. Normant, *Tetrahedron*, **35**, 2645 (1979).
212. C. J. Kowalski, A. E. Weber and K. W. Fields, *J. Org. Chem.*, **47**, 5088 (1982).
213. J. E. McMurry and S. J. Isser, *J. Am. Chem. Soc.*, **94**, 7132 (1972).
214. S. H. Bertz, G. Dabbagh and G. M. Villacorta, *J. Am. Chem. Soc.*, **104**, 5824 (1982).
215. R. K. Boeckman, Jr. and K. J. Bruza, *J. Org. Chem.*, **44**, 4781 (1979).
216. C. G. Chavdarian and C. H. Heathcock, *J. Am. Chem. Soc.*, **97**, 3822 (1975).
217. C. P. Casey, D. F. Marten and R. A. Boggs, *Tetrahedron Lett.*, 2071 (1973).
218. G. H. Posner and D. J. Brunelle, *J. Chem. Soc., Chem. Commun.*, 907 (1973).
219. E. Piers and I. Nagakura, *J. Org. Chem.*, **40**, 2694 (1975).
220. R. M. Christie, M. Gill and R. W. Rickards, *J. Chem. Soc., Perkin Trans. 1*, 593 (1981).
221. A. B. Smith, III, B. A. Wexler and J. S. Slade, *Tetrahedron Lett.*, **21**, 3237 (1980).
222. W. C. Still and T. L. McDonald, *Tetrahedron Lett.*, 2659 (1976).
223. G. H. Posner, C. E. Whitten and J. J. Sterling, *J. Am. Chem. Soc.*, **95**, 7788 (1973).
224. E. J. Corey, D. Floyd and B. H. Lipshutz, *J. Org. Chem.*, **43**, 3418 (1978).
225. R. K. Boeckman, Jr., and M. Ramaiah, *J. Org. Chem.*, **42**, 1581 (1977).
226. B. H. Lipshutz, R. S. Wilhelm and J. Kozlowski, *Tetrahedron Lett.*, **23**, 3755 (1982).
227. B. H. Lipshutz, J. A. Kozlowski, D. A. Parker, S. L. Nguyen and K. E. McCarthy, *J. Organomet. Chem.*, **285**, 437 (1985).
228. B. H. Lipshutz, D. A. Parker, S. L. Nguyen, K. E. McCarthy, J. C. Barton, S. E. Whitney and H. Kotsuki, *Tetrahedron*, **42**, 2873 (1986).
229. D. J. Ager and I. Fleming, *J. Chem. Soc., Chem. Commun.*, 177 (1978).
230. D. J. Ager, I. Fleming and S. K. Patel, *J. Chem. Soc., Perkin Trans. 1*, 2520 (1981).
231. I. Fleming and T. W. Newton, *J. Chem. Soc., Perkin Trans. 1*, 1805 (1984).
232. D. Seyferth and R. C. Hui, *J. Am. Chem. Soc.*, **107**, 4551 (1985).
233. D. Seyferth and R. C. Hui, *Tetrahedron Lett.*, **27**, 1473 (1986).
234. Y. Yamamoto and K. Maruyama, *J. Am. Chem. Soc.*, **100**, 3240 (1978).
235. Y. Yamamoto, H. Yatagai and K. Maruyama, *J. Org. Chem.*, **44**, 1744 (1979).
236. Y. Yamamoto, S. Yamamoto, H. Yatagai, Y. Ishihara and K. Maruyama, *J. Org. Chem.*, **47**, 119 (1982).
237. Y. Yamamoto, *Angew. Chem. Int. Ed. Engl.*, **25**, 947 (1986).

238. B. H. Lipshutz, D. A. Parker, J. A. Kozlowski and S. L. Nguyen, *Tetrahedron Lett.*, **25**, 5959 (1984).
239. T. Ibuka and E. Tabushi, *J. Chem. Soc., Chem. Commun.*, 703 (1982).
240. T. Ibuka, E. Tabushi and M. Yasuda, *Chem. Pharm. Bull. Jpn.*, **31**, 128 (1983).
241. T. Ibuka, H. Minakata, Y. Mitsui, K. Kinoshita and Y. Kawami, *J. Chem. Soc., Chem. Commun.*, 1193 (1980).
242. T. Ibuka, H. Minakata, Y. Mitsui, K. Kinoshita, Y. Kawami and N. Kimura, *Tetrahedron Lett.*, **21**, 4073 (1980).
243. E. J. Corey and N. W. Boaz, *Tetrahedron Lett.*, **26**, 6019 (1985).
244. A. Alexakis, J. Berlan and Y. Besace, *Tetrahedron Lett.*, **27**, 1047 (1986).
245. E. Nakamura, S. Matsuzawa, Y. Horiguchi and I. Kuwajima, *Tetrahedron Lett.*, **27**, 4029 (1986).
246. R. J. Linderman and A. Godfrey, *Tetrahedron Lett.*, **27**, 4553 (1986).
247. Y. Horiguchi, S. Matsuzawa, E. Nakamura and I. Kuwajima, *Tetrahedron Lett.*, **27**, 4025 (1986).
248. E. Nakamura and I. Kuwajima, *J. Am. Chem. Soc.*, **106**, 3368 (1984).
249. R. A. Kretchmer, *J. Org. Chem.*, **37**, 2744 (1972).
250. W. Langer and D. Seebach, *Helv. Chim. Acta*, **62**, 1710 (1979).
251. D. Seebach, G. Gras, E. M. Wilka, D. Hilvert and E. Brunner, *Helv. Chim. Acta*, **62**, 2695 (1979).
252. F. Leyendecker and D. Laucher, *Tetrahedron Lett.*, **24**, 3517 (1983).
253. H. Malmberg and M. Nilsson, *J. Organomet. Chem.*, **243**, 241 (1983).
254. B. Gustafsson, *Tetrahedron*, **34**, 3023 (1978).
255. H. Malmberg, M. Nilsson and C. Ullenius, *Acta Chem. Scand., Ser. B*, **35**, 625 (1981).
256. M. Huche, J. Berlan, G. Pourcelot and P. Cresson, *Tetrahedron Lett.*, **22**, 1329 (1981).
257. F. Ghozland, J. L. Luche and P. Crabbé, *Bull. Soc. Chim. Belg.*, **87**, 369 (1978).
258. B. Gustafsson, G. Hallnemo and C. Ullenius, *Acta Chem. Scand., Ser. B.*, **34**, 443 (1980).
259. J. S. Zweig, J. L. Luche, E. Barreiro and P. Crabbé, *Tetrahedron Lett.*, **28**, 2355 (1975).
260. T. Imamoto and T. Mukaiyama, *Chem. Lett.*, 45 (1980).
261. F. Leyendecker, F. Jesser and B. Ruhland, *Tetrahedron Lett.*, **22**, 3601 (1981).
262. F. Leyendecker, F. Jesser and D. Laucher, *Tetrahedron Lett.*, **24**, 3513 (1983).
263. R. K. Dieter and M. Tokles, *J. Am. Chem. Soc.*, **109**, 2040 (1987).
264. K. Yamamoto, M. Iijima and Y. Ogimura, *Tetrahedron Lett.*, **23**, 3711 (1982).
265. K. Yamamoto, M. Iijima, Y. Ogimura and J. Tsuji, *Tetrahedron Lett.*, **25**, 2813 (1984).
266. T. Takahashi, Y. Naito and J. Tsuji, *J. Am. Chem. Soc.*, **103**, 5261 (1981).
267. T. Takahashi, H. Okumoto and J. Tsuji, *Tetrahedron Lett.*, **25**, 1925 (1984).
268. H. Malmberg, M. Nilsson and C. Ullenius, *Tetrahedron Lett.*, **23**, 3823 (1982).
269. S. Andersson, S. Jagner, M. Nilsson and F. Urso, *J. Organomet. Chem.*, **301**, 257 (1986).
270. M. Nilsson, *Chem. Scr.*, **25**, 79 (1985).
271. G. H. Posner, J. P. Mallamo and K. Miura, *J. Am. Chem. Soc.*, **103**, 2886 (1981).
272. G. H. Posner, M. Hulce, J. P. Mallamo, S. A. Drexler and J. Clardy, *J. Org. Chem.*, **46**, 5244 (1981).
273. G. H. Posner, J. P. Mallamo, M. Hulce and L. L. Frye, *J. Am. Chem. Soc.*, **104**, 4180 (1982).
274. G. H. Posner and L. L. Frye, *Isr. J. Chem.*, **24**, 88 (1984).
275. G. H. Posner, T. P. Kogan and M. Hulce, *Tetrahedron Lett.*, **25**, 383 (1984).
276. G. H. Posner, L. L. Frye and M. Hulce, *Tetrahedron*, **40**, 1401 (1984).
277. E. C. Ashby and G. Heinsohn, *J. Org. Chem.*, **39**, 3297 (1974).
278. L. Bagnell, E. A. Jeffery, A. Meisters and T. Mole, *Aust. J. Chem.*, **28**, 801 (1975).
279. M. J. Loots and J. Schwartz, *J. Am. Chem. Soc.*, **99**, 8045 (1977).
280. J. Schwartz, M. J. Loots and H. Kosugi, *J. Am. Chem. Soc.*, **102**, 1333 (1980).
281. F. M. Dayrit, D. E. Gladkowski and J. Schwartz, *J. Am. Chem. Soc.*, **102**, 3976 (1980).
282. F. M. Dayrit and J. Schwartz, *J. Am. Chem. Soc.*, **103**, 4466 (1981).
283. J. L. Luche, C. Petrier, J. P. Lansard and A. E. Greene, *J. Org. Chem.*, **48**, 3837 (1983).
284. C. Petrier, J. L. Luche and C. Dupuy, *Tetrahedron Lett.*, **25**, 3463 (1984).
285. C. Petrier, J. C. De Souza Barbosa, C. Dupuy and J. L. Luche, *J. Org. Chem.*, **50**, 5761 (1985).
286. J. C. De Souza Barbosa, C. Petrier and J. L. Luche, *Tetrahedron Lett.*, **26**, 829 (1985).
287. A. E. Greene, J. P. Lansard, J. L. Luche and C. Petrier, *J. Org. Chem.*, **49**, 931 (1984).
288. A. Casares and L. A. Maldonado, *Synth. Commun.*, **6**, 11 (1976).
289. M. Isobe, S. Kondo, N. Nagasawa and T. Goto, *Chem. Lett.*, 679 (1977).
290. R. A. Watson and R. A. Kjonaas, *Tetrahedron Lett.*, **27**, 1437 (1986).
291. W. Tückmantel, K. Oshima and H. Nozaki, *Chem. Ber.*, **119**, 1581 (1986).

292. R. A. Kjonaas and E. J. Vawter, *J. Org. Chem.*, **51**, 3993 (1986).
293. S. Cacchi, F. La Torre and D. Misiti, *Tetrahedron Lett.*, **47**, 4591 (1979).
294. S. Cacchi, D. Misiti and G. Palmieri, *Tetrahedron*, **37**, 2941 (1981).
295. S. Cacchi and G. Palmieri, *Tetrahedron*, **39**, 3373 (1983).
296. S. Cacchi, D. Misiti and G. Palmieri, *J. Org. Chem.*, **47**, 2995 (1982).
297. S. Cacchi and G. Palmieri, *J. Organomet. Chem.*, **282**, C3–C6 (1985).
298. S. Cacchi and A. Arcadi, *J. Org. Chem.*, **48**, 4236 (1983).
299. S. Cacchi, F. La Torre and G. Palmieri, *J. Organomet. Chem.*, **268**, C48–C51 (1984).
300. A. Arcadi, F. Marinelli and S. Cacchi, *J. Organomet. Chem.*, **312**, C27–C32 (1986).
301. S. Cacchi and G. Palmieri, *Synthesis*, 575 (1984).
302. K. Yamamura, *J. Org. Chem.*, **43**, 724 (1978).
303. H. Schumann, W. Genthe, E. Hahn and J. Pickardt, *J. Organomet. Chem.*, **306**, 215 (1986).
304. K. Yokoo, Y. Yamanaka, T. Fukagawa, H. Taniguchi and Y. Fujiwara, *Chem. Lett.*, 1301 (1983).
305. A. B. Sigalov, L. F. Rybakova and I. P. Beletskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1690 (1983); *Chem. Abstr.*, **100**, 5946f (1984).
306. A. B. Sigalov, E. S. Petrov, L. F. Rybakova and I. P. Beletskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2615 (1983); *Chem. Abstr.*, **100**, 139255p (1984).
307. T. Imamoto, Y. Hatanaka, Y. Tawarayama and M. Yokoyama, *Tetrahedron Lett.*, **22**, 4987 (1981).
308. T. Imamoto, T. Kusumoto, Y. Tawarayama, Y. Sugiura, T. Mita, Y. Hatanaka and M. Yokoyama, *J. Org. Chem.*, **49**, 3904 (1984).
309. T. Imamoto, N. Takiyama and K. Nakamura, *Tetrahedron Lett.*, **26**, 4763 (1985).
310. T. Imamoto and Y. Sugiura, *J. Organomet. Chem.*, **285**, C21–C23 (1985).
311. A. L. Gemal and J. L. Luche, *J. Am. Chem. Soc.*, **103**, 5454 (1981).
312. H. Schumann, J. Muller, N. Bruncks, H. Lauke, J. Pickardt, H. Schwarz and K. Eckart, *Organometallics*, **3**, 69 (1984).
313. R. A. Ellison, *Synthesis*, 397 (1973).
314. Y. Ito, T. Konoike, T. Harada and T. Saegura, *J. Am. Chem. Soc.*, **99**, 1487 (1977).
315. D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **8**, 639 (1969).
316. D. Seebach and M. Kolb, *Chem. Ind.*, 687 (1974).
317. O. W. Lever, Jr., *Tetrahedron*, **32**, 1943 (1976).
318. T. A. Hase and J. K. Koskimies, *Aldrichimica Acta*, **14**, 73 (1981); **15**, 35 (1982); *Chem. Abstr.*, **96**, 67893u (1982); **97**, 181260f (1982).
319. E. J. Corey and L. S. Hegedus, *J. Am. Chem. Soc.*, **91**, 4926 (1969).
320. D. Seyferth, R. M. Weinstein, W. L. Wang, R. C. Hui and C. M. Archer, *Isr. J. Chem.*, **24**, 167 (1984).
321. W. Nagata, S. Hirai, H. Itazaki and K. Takeda, *J. Org. Chem.*, **26**, 2413 (1961).
322. C. Agami, J. Levisalles and C. Puchot, *J. Org. Chem.*, **47**, 3561 (1982).
323. W. Nagata, M. Yoshioda and S. Hirai, *J. Am. Chem. Soc.*, **94**, 4635 (1972).
324. K. Utimoto, M. Obayashi, Y. Shishiyama, M. Inoue and H. Nozaki, *Tetrahedron Lett.*, **21**, 3389 (1980).
325. K. Utimoto, Y. Wakabayashi, T. Horüe, M. Inoue, Y. Shishiyama, M. Obayashi and H. Nozaki, *Tetrahedron*, **39**, 967 (1983).
326. G. Stork and R. Borch, *J. Am. Chem. Soc.*, **86**, 935 (1964).
327. R. Locher and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **20**, 569 (1981).
328. D. Seebach, M. Ertas, R. Locher and W. Schweizer, *Helv. Chim. Acta*, **68**, 264 (1985).
329. G. Palmisano and R. Pellegata, *J. Chem. Soc., Chem. Commun.*, 892 (1975).
330. E. J. Corey and R. H. Wollenberg, *J. Chem. Soc.*, **96**, 5581 (1974).
331. J. Hooz and R. B. Layton, *J. Am. Chem. Soc.*, **93**, 7320 (1971).
332. R. F. Newton, D. P. Reynolds, J. Greenwood and F. Scheimann, *J. Chem. Soc., Perkin Trans. 1*, 2346 (1980).
333. M. S. Bruhn, C. H. Brown, P. W. Collins, J. R. Palmer, E. Z. Dajani and R. Pappo, *Tetrahedron Lett.*, 235 (1976).
334. J. A. Sinclair, G. A. Molander and H. C. Brown, *J. Am. Chem. Soc.*, **99**, 954 (1977).
335. R. Pappo and P. W. Collins, *Tetrahedron Lett.*, 2627 (1972).
326. P. W. Collins, E. Z. Dajani, M. S. Bruhn, C. H. Brown, J. R. Palmer and R. Pappo, *Tetrahedron Lett.*, 4217 (1975).
337. R. T. Hansen, D. B. Carr and J. Schwartz, *J. Am. Chem. Soc.*, **100**, 2244 (1978).

338. J. Schwartz, D. B. Carr, R. T. Hansen and F. M. Dayrit, *J. Org. Chem.*, **45**, 3053 (1980).
339. E. McMurry and J. Melton, *J. Am. Chem. Soc.*, **93**, 5309 (1971).
340. D. Seebach, E. W. Colvin, F. Lehr and T. Weller, *Chimia*, **33**, 1 (1979).
341. M. Kocor and W. Kroszczynski, *J. Indian Chem. Soc.*, **55**, 1179 (1978).
342. C. Kimura, K. Murai, S. Susuki and R. Hayashi, *Yukagaku*, **31**, 104 (1982); *Chem. Abstr.*, **97**, 6044s (1982).
343. D. A. White and M. M. Baizer, *Tetrahedron Lett.*, 3597 (1973).
344. T. Miyakoshi and S. Saito, *Yukagaku*, **31**, 35 (1982); *Chem. Abstr.*, **96**, 142217g (1982).
345. T. Miyakoshi and S. Saito, *Yukagaku*, **31**, 231 (1982); *Chem. Abstr.*, **97**, 38526s (1982).
346. N. Ono, H. Miyake and A. Kaji, *J. Chem. Soc., Chem. Commun.*, 875 (1983).
347. T. Miyakoshi, *Synthesis*, 766 (1986).
348. T. Miyakoshi and S. Saito, *Yukagaku*, **34**, 115 (1985); *Chem. Abstr.*, **103**, 160424q (1985).
349. T. Miyakoshi, *Yukagaku*, **35**, 157 (1986); *Chem. Abstr.*, **103**, 119489p (1987).
350. A. Garcia-Raso, J. Garcia-Raso, B. Campaner, R. Mestres and J. V. Sinisterra, *Synthesis*, 1037 (1982).
351. J. H. Clark, *J. Chem. Soc., Chem. Commun.*, 789 (1978).
352. J. H. Clark and D. G. Cork, *J. Chem. Soc., Chem. Commun.*, 635 (1982).
353. I. Belsky, *J. Chem. Soc., Chem. Commun.*, 237 (1977).
354. L. A. Carpino and A. C. Sau, *J. Chem. Soc., Chem. Commun.*, 514 (1979).
355. J. Boyer, R. J. P. Corriu, R. Perz and C. Reye, *Tetrahedron*, **39**, 117 (1983).
356. J. Clark, D. G. Cork and M. S. Robertson, *Chem. Lett.*, 1145 (1983).
357. J. Yamawaki, T. Kawate, T. Ando and T. Hanafusa, *Bull. Chem. Soc. Jpn.*, **56**, 1885 (1983).
358. S. Colonna, A. Re and H. Wynberg, *J. Chem. Soc., Perkin Trans. 1*, 547 (1981).
359. K. Matsumoto and T. Uchida, *Chem. Lett.*, 1673 (1981).
360. S. Hashimoto, K. Matsumoto and S. Otani, *J. Org. Chem.*, **49**, 4543 (1984).
361. S. F. Martin, *Synthesis*, 633 (1979).
362. H. Shechter and F. T. Williams, Jr., *J. Org. Chem.*, **27**, 3699 (1962).
363. A. H. Pagano and H. Shechter, *J. Org. Chem.*, **35**, 295 (1970).
364. J. E. McMurry, *Acc. Chem. Res.*, **7**, 281 (1974).
365. J. E. McMurry and J. Melton, *J. Org. Chem.*, **38**, 4367 (1973).
366. J. E. McMurry, J. Melton and H. Padgett, *J. Org. Chem.*, **39**, 259 (1974).
367. N. Kornblum and P. A. Wade, *J. Org. Chem.*, **38**, 1418 (1973).
368. R. M. Jacobson, *Tetrahedron Lett.*, 3215 (1974).
369. J. R. Williams, L. R. Unger and R. H. Moore, *J. Org. Chem.*, **43**, 1271 (1978).
370. D. Seebach, R. Henning and F. Lehr, *Angew. Chem., Int. Ed. Engl.*, **17**, 458 (1978).
371. W. E. Noland, *Chem. Rev.*, **55**, 137 (1955).
372. H. Stetter, *Angew. Chem., Int. Ed. Engl.*, **15**, 639 (1976).
373. H. Stetter and J. Krasselt, *J. Heterocycl. Chem.*, **14**, 573 (1977).
374. H. Stetter, W. Basse and K. Wiemann, *Chem. Ber.*, **111**, 431 (1978).
375. H. Stetter and J. Nienhaus, *Chem. Ber.*, **111**, 2825 (1978).
376. H. Stetter, G. Hilboll and H. Kuhlmann, *Chem. Ber.*, **112**, 84 (1979).
377. H. Stetter and A. Landscheidt, *Chem. Ber.*, **112**, 1410 (1979).
378. H. Stetter and J. Nienhaus, *Chem. Ber.*, **113**, 979 (1980).
379. H. Stetter and P. Lappe, *Chem. Ber.*, **113**, 1890 (1980).
380. H. Stetter and F. Jonas, *Chem. Ber.*, **114**, 564 (1981).
381. H. Stetter and K. H. Mohrmann, *Synthesis*, 129 (1981).
382. H. Stetter and W. Schlenker, *Tetrahedron Lett.*, **21**, 3479 (1980).
383. H. Stetter, K. H. Mohrmann and W. Schlenker, *Chem. Ber.*, **114**, 581 (1981).
384. H. Stetter and A. Mertens, *Liebigs Ann. Chem.*, 1550 (1981).
385. H. Stetter and F. Jonas, *Synthesis*, 626 (1981).
386. H. Stetter and A. Mertens, *Chem. Ber.*, **114**, 2479 (1981).
387. H. Stetter and H. T. Leinen, *Chem. Ber.*, **116**, 254 (1983).
388. H. Stetter and W. Haese, *Chem. Ber.*, **117**, 682 (1984).
389. H. Stetter and L. Simons, *Chem. Ber.*, **118**, 3172 (1985).
390. H. Stetter and G. Lorenz, *Chem. Ber.*, **118**, 1115 (1985).
391. B. H. Chang and Y. L. Chang, *J. Chinese Chem. Soc.*, **30**, 55 (1983); *Chem. Abstr.*, **98**, 214965r (1983).
392. G. Stork and L. Maldonado, *J. Am. Chem. Soc.*, **93**, 5286 (1971).

393. N. Seuron, L. Wartski and J. Seyden-Penne, *Tetrahedron Lett.*, **22**, 2175 (1981).
394. S. Huning and G. Wehner, *Chem. Ber.*, **112**, 2062 (1979).
395. M. C. Roux-Schmitt, N. Seuron and J. Seyden-Penne, *Synthesis*, 494 (1983).
396. E. Hatzigrigoriou, M. C. Roux-Schmitt, L. Wartski and J. Seyden-Penne, *J. Chem. Res.* (*S*), 344, (1985); (M), 3575 (1985).
397. M. C. Roux-Schmitt, L. Wartski, J. Seyden-Penne and C. Merienne, *Tetrahedron*, **39**, 3415 (1983).
398. E. Hatzigrigoriou and L. Wartski, *Bull. Soc. Chim. Fr.*, 313 (1983).
399. H. M. Taylor and C. R. Hauser, *J. Am. Chem. Soc.*, **82**, 1790 (1960).
400. E. Leete, *J. Org. Chem.*, **41**, 3438 (1976).
401. G. Büchi, P. H. Liang and H. Wüest, *Tetrahedron Lett.*, 2763 (1978).
402. T. Wakamatsu, S. Hobara and Y. Ban, *Heterocycles*, **19**, 1395 (1982).
403. J. Chauffaille, E. Herbert and Z. Welvart, *J. Chem. Soc., Perkin Trans. 2*, 1645 (1982).
404. T. Takahashi, K. Shibasaki, K. Ogura and H. Iida, *Chem. Lett.*, 859 (1983).
405. M. Zervos and L. Wartski, *Tetrahedron Lett.*, **25**, 4641 (1984).
406. E. J. Corey and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **4**, 1075 (1965); **4**, 1077 (1965).
407. D. Seebach, *Synthesis*, 17 (1969).
408. E. J. Corey and D. Seebach, *J. Org. Chem.*, **31**, 4097 (1966).
409. D. Seebach and E.J. Corey, *J. Org. Chem.*, **40**, 231 (1975).
410. E. J. Corey and D. Crouse, *J. Org. Chem.*, **33**, 298 (1968).
411. B. T. Grobel and D. Seebach, *Synthesis*, 357 (1977).
412. W. Ried and M. Vogl, *Liebigs Ann. Chem.*, 360 (1982).
413. I. Kuwajima, K. Sugimoto and T. Murofushi, *Chem. Lett.*, 625 (1974).
414. T. Mukaiyama, K. Narasaka and M. Furusato, *J. Am. Chem. Soc.*, **94**, 8641 (1972).
415. R. J. Cregge, J. L. Herrmann, J. E. Richman, R. F. Romanet and R. H. Schlessinger, *Tetrahehedron Lett.*, 2595 (1973).
416. J. L. Herrmann, J. E. Richman and R. H. Schlessinger, *Tetrahedron Lett.*, 2599 (1973).
417. R. J. Cregge, J. L. Herrmann and R. H. Schlessinger, *Tetrahedron Lett.*, 2603 (1973).
418. H. Paulsen, W. Koebernick and H. Koebernick, *Tetrahedron Lett.*, 2297 (1976).
419. M. Kato, H. Saito and A. Yoshikoshi, *Chem. Lett.*, 213 (1984).
420. J. E. Richman, J. L. Herrmann and R. H. Schlessinger, *Tetrahedron Lett.*, 3267 (1973).
421. J. E. Richman, J. L. Herrmann and R. H. Schlessinger, *Tetrahedron Lett.*, 3271 (1973); 3275 (1973).
422. A. R. B. Manas and R. A. J. Smith, *J. Chem. Soc., Chem. Commun.*, 216 (1975).
423. R. A. J. Smith and A. R. Lal, *Aust. J. Chem.*, **32**, 353 (1979).
424. T. Cohen and S. M. Nolan, *Tetrahedron Lett.*, 3533 (1978).
425. T. Cohen and L. C. Yu, *J. Org. Chem.*, **50**, 3266 (1985).
426. D. Seebach and R. Bürstinghaus, *Angew. Chem., Int. Ed. Engl.*, **14**, 57 (1975).
427. R. Bürstinghaus and D. Seebach, *Chem. Ber.*, **110**, 841 (1977).
428. K. Ogura, N. Yahata, M. Minoguchi, K. Ohtsuki, K. Takahashi and H. Iida, *J. Org. Chem.*, **51**, 508 (1986).
429. M. J. Tachner and G. A. Kraus, *J. Org. Chem.*, **43**, 4235 (1978).
430. M. Braun and M. Esdar, *Chem. Ber.*, **114**, 2924 (1981).
431. S. Hackett and T. Livinghouse, *J. Org. Chem.*, **51**, 879 (1986).
432. D. Van Ende, W. Dumont and A. Krief, *J. Organomet. Chem.*, **149**, C10-C12 (1978).
433. J. Lucchetti and A. Krief, *Tetrahedron Lett.*, **22**, 1623 (1981).
434. A. Krief and L. Hevesi, *Janssen Chim. Acta*, **2**, 3 (1984).
435. M. Clarembeau, A. Cravador, W. Dumont, L. Hevesi, A. Krief, J. Lucchetti and D. Van Ende, *Tetrahedron*, **41**, 4812 (1985).
436. S. Raucher and G. A. Koolpe, *J. Org. Chem.*, **43**, 3794 (1978).
437. J. Lucchetti and A. Krief, *Synth. Commun.*, **13**, 1153 (1983).
438. R. A. Benkeser, *Synthesis*, 347 (1971).
439. G. Courtois and L. Miginiac, *J. Organomet. Chem.*, **69**, 1 (1974).
440. W. A. De Meester and R. C. Fuson, *J. Org. Chem.*, **30**, 4332 (1965).
441. H. O. House and W. F. Fischer, Jr., *J. Org. Chem.*, **34**, 3615 (1969).
442. H. O. House, T. S. B. Sayer and C. C. Yau, *J. Org. Chem.*, **43**, 2153 (1978).
443. Y. Yamamoto, H. Yatagai and K. Maruyama, *J. Am. Chem. Soc.*, **103**, 1969 (1981).
444. Y. Yamamoto, H. Yatagai, Y. Saito and K. Maruyama, *J. Org. Chem.*, **49**, 1096 (1984).

445. Y. Yamamoto, N. Maeda and K. Maruyama, *J. Chem. Soc., Chem. Commun.*, 742 (1983).
446. Y. Yamamoto, H. Yatagai, Y. Ishihara, N. Maeda and K. Maruyama, *Tetrahedron*, **40**, 2239 (1984).
447. J. A. Marshall and B. S. DeHoff, *J. Org. Chem.*, **51**, 863 (1986).
448. Y. Naruta, *J. Am. Chem. Soc.*, **102**, 3774 (1980).
449. A. Pratt and E. J. Thomas, *J. Chem. Soc., Chem. Commun.*, 1115 (1982).
450. Y. Yamamoto, K. Maruyama and K. Matsumoto, *J. Chem. Soc., Chem. Commun.*, 489 (1983).
451. T. Hiyama, M. Sawahata and M. Obayashi, *Nippon Kagaku Kaishi*, 1022 (1984); *Chem. Abstr.*, **101**, 129789x (1984).
452. Y. Okude, S. Hirano, T. Hiyama and H. Nozaki, *J. Am. Chem. Soc.*, **99**, 3179 (1977).
453. T. Hiyama, K. Kimura and H. Nozaki, *Tetrahedron Lett.*, **22**, 1037 (1981).
454. G. W. Kramer and H. C. Brown, *J. Org. Chem.*, **42**, 2292 (1977).
455. C. Liu and K. K. Wang, *J. Org. Chem.*, **51**, 4733 (1986).
456. Y. Yamamoto, H. Yatagai and K. Maruyama, *J. Am. Chem. Soc.*, **103**, 3229 (1981).
457. A. Boaretto, D. Marton, G. Tagliavini and A. Gambaro, *Inorganica Chim. Acta Lett.*, **77**, L196 (1983); *Chem. Abstr.*, **100**, 155947w (1984).
458. A. Boaretto, D. Marton, R. Silvestri and G. Tagliavini, *Gazz. Chim. Ital.*, **115**, 391 (1985).
459. A. Boaretto, D. Marton, G. Tagliavini and A. Gambaro, *J. Organomet. Chem.*, **286**, 9 (1985).
460. A. Boaretto, D. Marton, G. Tagliavini and P. Ganis, *J. Organomet. Chem.*, **321**, 199 (1987).
461. G. Tagliavini, *Rev. Silicon, Germanium, Tin, Lead Compd.*, **8**, 237 (1985); *Chem. Abstr.*, **104**, 168528t (1986).
462. G. E. Keck, D. E. Abbott, E. P. Boden and E. J. Enholm, *Tetrahedron Lett.*, **25**, 3927 (1984).
463. Y. Yamamoto and K. Maruyama, *J. Org. Chem.*, **48**, 1564 (1983).
464. B. B. Snider, *Acc. Chem. Res.*, **13**, 426 (1980).
465. B. B. Snider, D. J. Rodini and J. Van Straten, *J. Am. Chem. Soc.*, **102**, 5872 (1980).
466. B. B. Snider and E. A. Deutsch, *J. Org. Chem.*, **47**, 745 (1982).
467. B. B. Snider and E. A. Deutsch, *J. Org. Chem.*, **48**, 1822 (1983).
468. B. B. Snider and B. E. Goldman, *Tetrahedron*, **42**, 2951 (1986).
469. J. K. Rasmussen, *Synthesis*, 91 (1977).
470. E. W. Colvin, *Chem. Soc. Rev.*, **7**, 15 (1978).
471. I. Fleming, *Comprehensive Organic Chemistry*, Vol. 3 (Ed. D. N. Jones), Pergamon, Oxford, 1979, pp. 541–686.
472. I. Fleming, *Chem. Soc. Rev.*, **10**, 83 (1981).
473. E. W. Colvin, *Silicon in Organic Synthesis*, Butterworths, London, 1981.
474. W. P. Weber, *Silicon Reagents for Organic Synthesis*, Springer-Verlag, New York, 1983.
475. P. Brownbridge, *Synthesis*, 1 (1983).
476. P. Brownbridge, *Synthesis*, 85 (1983).
477. D. Liotta, U. Sunay and S. Ginsberg, *J. Org. Chem.*, **47**, 2227 (1982).
478. T. Mukaiyama, *Angew. Chem., Int. Ed. Engl.*, **16**, 817 (1977).
479. I. Fleming, *Chimia*, 265 (1980).
480. H. Sakurai, *Pure Appl. Chem.*, **54**, 1 (1982).
481. H. Sakurai, A. Hosomi and J. Hayashi, *Org. Synth.*, **62**, 86 (1984).
482. E. D. Bergmann, D. Ginsburg and R. Pappo, *Org. React.*, **10**, 179 (1959).
483. K. Narasaka, K. Soai and T. Mukaiyama, *Chem. Lett.*, 1223 (1974).
484. K. Saigo, M. Osaki and T. Mukaiyama, *Chem. Lett.*, 163 (1976).
485. K. Narasaka, K. Soai, Y. Aikawa and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **49**, 779 (1976).
486. C. Goasdoue, N. Goasdoue and M. Gaudemar, *Tetrahedron Lett.*, **25**, 537 (1984).
487. J. Boyer, R. J. P. Corriu, R. Perz and C. Reye, *J. Organomet. Chem.*, **184**, 157 (1980).
488. J. Boyer, R. J. P. Corriu, R. Perz and C. Reye, *J. Chem. Soc., Chem. Commun.*, 122 (1981).
489. R. J. P. Corriu, R. Perz and C. Reye, *Tetrahedron*, **39**, 999 (1983).
490. C. Chuit, R. J. P. Corriu and C. Reye, *Synthesis*, 294 (1983).
491. T. H. Chan and P. Brownbridge, *J. Chem. Soc., Chem. Commun.*, 578 (1979).
492. M. Kikuchi and A. Yoshikoshi, *Bull. Chem. Soc. Jpn.*, **54**, 3420 (1981).
493. S. Danishefsky, K. Vaughan, R. Gadwood and K. Tsuzuki, *J. Am. Chem. Soc.*, **103**, 4136 (1981).
494. P. Brownbridge and T. H. Chan, *Tetrahedron Lett.*, **21**, 3431 (1980).
495. T. Yanani, M. Miyashita and A. Yoshikoshi, *J. Org. Chem.*, **45**, 607 (1980).
496. J. W. Huffman, S. M. Potnis and A. V. Satish, *J. Org. Chem.*, **50**, 4266 (1985).
497. H. Hagiwara, A. Okano and H. Uda, *J. Chem. Soc., Chem. Commun.*, 1047 (1985).

498. T. H. Chan and C. V. C. Prasad, *J. Org. Chem.*, **51**, 3012 (1986).
499. S. Danishefsky and M. Kahn, *Tetrahedron Lett.*, **22**, 485 (1981).
500. R. Noyori, K. Yokoyama, J. Sakata, I. Kuwajima, E. Nakamura and M. Shimizu, *J. Am. Chem. Soc.*, **99**, 1265 (1977).
501. E. Nakamura, M. Shimizu, I. Kuwajima, J. Sakata, K. Yokoyama and R. Noyori, *J. Org. Chem.*, **48**, 932 (1983).
502. H. Gerlach and P. Künzler, *Helv. Chim. Acta*, **61**, 2503 (1978).
503. T. V. Rajanbabu, *J. Org. Chem.*, **49**, 2083 (1984).
504. Y. Kita, J. Segawa, J. Haruta, T. Fujii and Y. Tamura, *Tetrahedron Lett.*, **21**, 3779 (1980).
505. Y. Kita, J. Segawa, J. Haruta, H. Yasuda and Y. Tamura, *J. Chem. Soc., Perkin Trans. 1*, 1099 (1982).
506. R. A. Bunce, M. F. Schlecht, W. G. Dauben and C. H. Heathcock, *Tetrahedron Lett.*, **24**, 4943 (1983).
507. C. H. Heathcock, C. Mahaim, M. F. Schlecht and T. Utawanit., *J. Org. Chem.*, **49**, 3264 (1984).
508. Y. Yamamoto, K. Maruyama and K. Matsumoto, *Tetrahedron Lett.*, **25**, 1075 (1984).
509. S. Kobayashi, M. Murakami and T. Mukaiyama, *Chem. Lett.*, 953 (1985).
510. T. Mukaiyama, T. Tamura and S. Kobayashi, *Chem. Lett.*, 1817 (1986).
511. T. Mukaiyama, Y. Sagawa and S. Kobayashi, *Chem. Lett.*, 1821 (1986).
512. S. Kobayashi and T. Mukaiyama, *Chem. Lett.*, 221 (1986).
513. S. Kobayashi and T. Mukaiyama, *Chem. Lett.*, 1805 (1986).
514. C. H. Heathcock, M. H. Norman and D. E. Uehling, *J. Am. Chem. Soc.*, **107**, 2797 (1985).
515. C. H. Heathcock and D. E. Uehling, *J. Org. Chem.*, **51**, 279 (1986).
516. T. Mukaiyama, M. Tamura and S. Kobayashi, *Chem. Lett.*, 1017 (1986).
517. R. Calas, J. Dunogues, G. Deleris and F. Psiciotti, *J. Organomet. Chem.*, **69**, C15 (1974).
518. G. Deleris, J. Dunogues and R. Calas, *J. Organomet. Chem.*, **93**, 43 (1975).
519. A. Hosomi and H. Sakurai, *Tetrahedron Lett.*, 1295 (1976).
520. A. Hosomi and H. Sakurai, *J. Am. Chem. Soc.*, **99**, 1673 (1977).
521. T. A. Blumenkopf and C. H. Heathcock, *J. Am. Chem. Soc.*, **105**, 2354 (1983).
522. C. H. Heathcock, S. Kiyooka and T. A. Blumenkopf, *J. Org. Chem.*, **49**, 4214 (1984).
523. T. Yanani, M. Miyashita and A. Yoshikoshi, *J. Chem. Soc., Chem. Commun.*, 525 (1979).
524. S. Knapp, U. O'Connor and D. Mobilio, *Tetrahedron Lett.*, **21**, 4557 (1980).
525. R. L. Danheiser, D. J. Carini and A. Basak, *J. Am. Chem. Soc.*, **103**, 1604 (1981).
526. S. R. Wilson and M. F. Price, *J. Am. Chem. Soc.*, **104**, 1124 (1982).
527. D. Schinzer, *Angew. Chem., Int. Ed. Engl.*, **23**, 308 (1984).
528. T. Tokoroyama, M. Tsukamoto and H. Iio, *Tetrahedron Lett.*, **25**, 5067 (1984).
529. D. Schinzer, S. Solyom and M. Becker, *Tetrahedron Lett.*, **26**, 1831 (1985).
530. G. Majetich, M. Behnke and K. Hull, *J. Org. Chem.*, **50**, 3615 (1985).
531. G. Majetich and C. Ringold, *Heterocycles*, **25**, 271 (1987).
532. M. Hayashi and T. Mukaiyama, *Chem. Lett.*, 289 (1987).
533. G. Majetich, A. Casares, D. Chapman and M. Behnke, *Tetrahedron Lett.*, **24**, 1909 (1983).
534. G. Majetich, A. Casares, D. Chapman and M. Behnke, *J. Org. Chem.*, **51**, 1745 (1986).
535. A. Hosomi and H. Sakurai, *Tetrahedron Lett.*, 4041 (1977).
536. A. Hosomi, A. Shirahata and H. Sakurai, *Tetrahedron Lett.*, 3043 (1978).
537. G. Majetich, R. N. Desmond and J. J. Soria, *J. Org. Chem.*, **51**, 1753 (1986).
538. A. Ricci, M. Forenza, M. A. Grifagni, G. Bartolini and G. Seconi, *Tetrahedron Lett.*, **23**, 5079 (1982).
539. G. Majetich, R. Desmond and A. M. Casares, *Tetrahedron Lett.*, **24**, 1913 (1983).
540. G. Majetich, K. Hull, J. Defauw and R. Desmond, *Tetrahedron Lett.*, **26**, 2747 (1985).
541. G. Majetich, K. Hull and R. Desmond, *Tetrahedron Lett.*, **26**, 2751 (1985).
542. G. Majetich, K. Hull, J. Defauw and T. Shawe, *Tetrahedron Lett.*, **26**, 2755 (1985).
543. G. Majetich, J. Defauw, K. Hull and T. Shawe, *Tetrahedron Lett.*, **26**, 4711 (1985).
544. G. Jones, *Org. React.*, **15**, 204 (1967).
545. F. Texier-Boullet and A. Foucaud, *Tetrahedron Lett.*, **23**, 4927 (1982).
546. D. J. Peterson, *J. Org. Chem.*, **33**, 789 (1968).
547. D. Seebach, M. Kolb and B. Th. Grobel, *Chem. Ber.*, **106**, 2277 (1973).
548. B. Th. Grobel and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **13**, 83 (1974).
549. J. I. G. Cadogan, *Organophosphorus Reagents in Organic Synthesis*, Academic Press, New York, 1979.

550. A. W. Johnson, *Ylid Chemistry*, Academic Press, New York, 1966.
551. W. S. Wadsworth, *Org. React.*, **25**, 73 (1978).
552. J. Boutagy and R. Thomas, *Chem. Rev.*, **74**, 87 (1974).
553. H. J. Bestmann, *Pure Appl. Chem.*, **52**, 771 (1980).
554. R. O. Larsen and G. Aksnes, *Phosphorus and Sulfur*, **15**, 229 (1983).
555. E. Widmer, *Pure Appl. Chem.*, **57**, 741 (1985).
556. M. Bernard and W. T. Ford, *J. Org. Chem.*, **48**, 326 (1983).
557. S. D. Clarke, C. R. Harrison and P. Hodge, *Tetrahedron Lett.*, **21**, 1375 (1980).
558. M. Moreno-Manas and A. Truis, *Bull. Chem. Soc. Jpn.*, **56**, 2154 (1983).
559. F. Texier-Boullet, D. Villemin, M. Ricard, H. Moison and A. Foucaud, *Tetrahedron*, **41**, 1259 (1985).
560. D. J. Burton and Y. Inouye, *Tetrahedron Lett.*, 3397 (1979).
561. M. Matsumoto and K. Kuroda, *Tetrahedron Lett.*, **21**, 4021 (1980).
562. Z. Arnold, V. Kral and D. Dvorak, *Tetrahedron Lett.*, **23**, 1725 (1982).
563. L. A. Yanovskaya, G. V. Kryshtal, D. Dvorak, V. Kral and Z. Arnold, *Coll. Czech. Chem. Commun.*, **50**, 1300 (1985).
564. Z. Arnold, V. Kral, G. V. Kryshtal and L. A. Yanovskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 457 (1984).
565. H. J. Bestmann, M. Schmidt and R. Schobert, *Angew. Chem.*, **97**, 418 (1985).
566. Y. Ishikawa, *Bull. Chem. Soc. Jpn.*, **36**, 1527 (1963).
567. W. Stilzand and H. Pommer, *Ger. Pat.*, 1.108.208 (1959); *Chem. Abstr.*, **56**, 11422e (1962).
568. U. Ramamurthy, G. Tustin, C. C. Yau and R. S. H. Liu, *Tetrahedron*, **31**, 193 (1975).
569. L. A. Yanovskaya and V. F. Kucherov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1341 (1964); *Chem. Abstr.*, **61**, 11887d (1964).
570. J. Camps, J. Font and P. De March, *Tetrahedron*, **37**, 2493 (1981).
571. J. P. Freeman, *J. Org. Chem.*, **31**, 538 (1966).
572. A. N. Pudovik and N. M. Lebedova, *Zh. Obshch. Khim.*, **22**, 2128 (1952); *Chem. Abstr.*, **48**, 564h (1954).
573. A. N. Pudovik and N. M. Lebedova, *Dokl. Akad. Nauk SSSR*, **90**, 799 (1953); *Chem. Abstr.*, **50**, 2429d (1956).
574. B. Fiszer and J. Michalski, *Roczniki Chem.*, **28**, 185 (1954), *Chem. Abstr.*, **49**, 9493e (1955).
575. B. Fiszer and J. Michalski, *Roczniki Chem.*, **34**, 1461 (1960), *Chem. Abstr.*, **55**, 15331g (1961).
576. E. D. Bergmann and A. Solomonovici, *Tetrahedron*, **27**, 2675 (1971).
577. K. F. Fujiwara, *J. Chem. Soc. Jpn., Pure Chem. Sect.*, **84**, 659 (1963).
578. J. Castells, J. Font, T. Ibarra, A. Llitjos and M. Moreno-Manas, *An. Quim.*, **74**, 773 (1978).
579. J. Khazarian, S. Geribaldi, F. Ferrero, M. Rouillard and M. Azzaro, *J. Org. Chem.*, **43**, 1817 (1978).
580. M. Rouillard, S. Geribaldi and M. Azzaro, *Org. Magn. Reson.*, **13**, 323 (1980).
581. M. W. Rathke and M. Nowak, *J. Org. Chem.*, **50**, 2624 (1985).
582. G. Cainelli, M. Contento, F. Manescalchi and R. Regnoli, *J. Chem. Soc., Perkin Trans. 1*, 2516 (1980).
583. M. Franck-Neumann, D. Martina and M. P. Heitz, *Tetrahedron Lett.*, **23**, 3493 (1982).
584. S. F. Martin, G. W. Phillips, T. A. Puckette and J. A. Colapret, *J. Am. Chem. Soc.*, **102**, 5866 (1980).
585. B. E. De Jong, H. De Koning and H. O. Huisman, *Recl. Trav. Chim. Pays-Bas*, **100**, 410 (1981).
586. Y. Vo-Quang, D. Carniato, L. Vo-Quang and F. Le Goffic, *J. Chem. Soc., Chem. Commun.*, 1505 (1983).
587. T. A. M. Van Schaik, A. V. Henzen and A. Van der Gen, *Tetrahedron Lett.*, **24**, 1303 (1983).
588. M. Nakano and Y. Okamoto, *Synthesis*, 917 (1983).
589. M. Nakata, T. Sakai, K. Tatsuta and M. Kinoshita, *Bull. Chem. Soc. Jpn.*, **54**, 1743 (1981).
590. D. B. Tulshian and B. Fraser-Reid, *J. Am. Chem. Soc.*, **103**, 474 (1981).
591. H. Marschall, J. Penninger and P. Weyerstahl, *Liebigs Ann. Chem.*, 49 (1982).
592. T. H. Kinstel and B. Y. Mandanas, *J. Chem. Soc., Chem. Commun.*, 1699 (1968).
593. G. Lefebvre and J. Seyden-Penne, *J. Chem. Soc., Chem. Commun.*, 1308 (1970).
594. J. Seyden-Penne and G. Lefebvre, *C. R. Acad. Sci. Paris, Ser. C*, **269**, 48 (1969).
595. B. Deschamps, G. Lefebvre and J. Seyden-Penne, *Tetrahedron*, **28**, 4209 (1972).
596. B. Deschamps, G. Lefebvre, A. Redjal and J. Seyden-Penne, *Tetrahedron*, **29**, 2437 (1973).
597. A. Redjal and J. Seyden-Penne, *Tetrahedron Lett.*, 1733 (1974).

598. B. Deschamps, J. P. Lampin, F. Mathey and J. Seyden-Penne, *Tetrahedron Lett.*, 1137 (1977).
599. E. Breuer and D. M. Bannet, *Tetrahedron Lett.*, 1141 (1977).
600. A. Loupy, K. Sogadji and J. Seyden-Penne, *Synthesis*, 126 (1977).
601. T. Bottin-Strzalko and J. Seyden-Penne, *Bull. Soc. Chim. Fr.*, 161 (1984).
602. W. C. Still and C. Gennari, *Tetrahedron Lett.*, **24**, 4405 (1983).
603. H. Nagaoka, W. Rutsch, G. Schmid, H. Iio, M. R. Johnson and Y. Kishi, *J. Am. Chem. Soc.*, **102**, 7965 (1980).
604. L. A. Yanovskaya and V. F. Kucherov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1504 (1965); *Chem. Abstr.*, **63**, 16387d (1965).
605. R. W. Dugger and C. H. Heathcock, *Synth. Commun.*, **10**, 509 (1980).
606. G. Etemad-Moghadam and J. Seyden-Penne, *Synth. Commun.*, **14**, 565 (1984).
607. G. Etemad-Moghadam and J. Seyden-Penne, *Tetrahedron*, **40**, 5153 (1984).
608. G. Etemad-Moghadam and J. Seyden-Penne, *Bull. Soc. Chim. Fr.*, 448 (1985).
609. G. Berti, in *Topics in Stereochemistry* (Eds. N. L. Allinger and E. L. Eliel), Wiley, Chichester, 1973, pp. 93–251.
610. N. C. Yang and R. A. Finnegan, *J. Am. Chem. Soc.*, **80**, 5845 (1958).
611. G. B. Payne, *J. Org. Chem.*, **25**, 275 (1960).
612. H. L. Holland, E. Riemland and U. Daum, *Can. J. Chem.*, **60**, 1919 (1982).
613. K. C. Joshi, R. Jain and S. Garg, *J. Heterocycl. Chem.*, **21**, 977 (1984).
614. M. Miyashita, T. Suzuki and A. Yoshikoshi, *Chem. Lett.*, 285 (1987).
615. C. A. Bunton and C. J. Minkoff, *J. Chem. Soc.*, 665 (1949).
616. H. O. House and R. S. Ro, *J. Am. Chem. Soc.*, **80**, 2428 (1958).
617. E. Weitz and A. Scheffer, *Chem. Ber.*, **54**, 2327 (1921).
618. D. H. Rosenblatt and G. Broome, *J. Org. Chem.*, **28**, 1290 (1963).
619. D. S. R. Rao, *Indian J. Chem.*, **20B**, 786 (1981).
620. D. S. R. Rao, *J. Indian Chem. Soc.*, **60**, 300 (1983).
621. H. E. Zimmerman, L. Singer and B. S. Thyagarajan, *J. Am. Chem. Soc.*, **81**, 108 (1959).
622. V. R. Valente and J. L. Wolfhagen, *J. Org. Chem.*, **31**, 2509 (1966).
623. R. Curci, F. Di Furia and M. Meneghin, *Gazz. Chim. Ital.*, **108**, 123 (1978).
624. J. R. Doherty, D. D. Keane, K. G. Marathe, W. I. O'Sullivan, E. M. Philbin, R. M. Simons and P. C. Teague, *Tetrahedron Lett.*, 441 (1968).
625. Y. Apeloig, M. Karni and Z. Rappoport, *J. Am. Chem. Soc.*, **105**, 2784 (1983).
626. E. Klein and G. Ohloff, *Tetrahedron*, **19**, 1091 (1963).
627. J. Katsuhara, *Bull. Chem. Soc. Jpn.*, **42**, 2391 (1969).
628. B. A. Brady, M. M. Healey, J. A. Kennedy, W. I. O'Sullivan and E. M. Philbin, *J. Chem. Soc., Chem. Commun.*, 1434 (1970).
629. D. D. Keane, W. I. O'Sullivan, E. M. Philbin, R. M. Simons and P. C. Teague, *Tetrahedron*, **26**, 2533 (1970).
630. J. Katsuhara, H. Yamasaki and N. Yamamoto, *Bull. Chem. Soc. Jpn.*, **43**, 1584 (1970).
631. R. T. Gray and H. E. Smith, *Tetrahedron*, **23**, 4229 (1967).
632. Z. G. Isaeva, V. V. Karlin, G. A. Bakaleinik and A. N. Karaseva, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1889 (1979); *Chem. Abstr.*, **92**, 58990p (1980).
633. C. G. Chavdarian, S. L. Woo, R. D. Clark, and C. H. Heathcock, *Tetrahedron Lett.*, 1769 (1976).
634. G. G. Haraldsson, L. A. Paquette and J. P. Springer, *J. Chem. Soc., Chem. Commun.*, 1035 (1985).
635. H. B. Henbest and W. R. Jackson, *J. Chem. Soc.* (*C*), 2459 (1967).
636. R. Helder, J. C. Hummelen, R. W. P. M. Laane, J. S. Wiering and H. Wynberg, *Tetrahedron Lett.*, 1831 (1976).
637. H. Wynberg, *Chimia*, **30**, 445 (1976).
638. S. Colonna, H. Molinari, S. Banfi, S. Julia, J. Masana and A. Alvarez, *Tetrahedron*, **39**, 1635 (1983).
639. S. Colonna, A. Manfredi and M. Spadoni, in *Organic Synthesis: Modern Trends* (Ed. O. Chizhov), Blackwell, Oxford, 1987, pp. 275–284.
640. J. P. Mazaleyrat, *Tetrahedron Lett.*, **24**, 1243 (1983).
641. S. Julia, J. Masana and J. C. Vega, *Angew. Chem., Int. Ed. Engl.*, **19**, 929 (1980).
642. N. Kobayashi and K. Iwai, *Makromol. Chem. Rapid Commun.*, **2**, 105 (1981).
643. S. Banfi, S. Colonna and S. Julia, *Synth. Commun.*, **13**, 1049 (1983).
644. S. Colonna, S. Banfi and A. Papagni, *Gazz. Chim. Ital.*, **115**, 81 (1985).
645. S. Colonna and A. Manfredi, *Tetrahedron Lett.*, **27**, 387 (1986).

646. J. C. Hummelen and H. Wynberg, *Tetrahedron Lett.*, 1089 (1978).
647. S. Julia, J. Guixer, J. Masana, J. Rocas, S. Colonna, R. Annuziata and H. Molinari, *J. Chem. Soc., Perkin Trans. 1*, 1317 (1982).
648. B. Marsman and H. Wynberg, *J. Org. Chem.*, **44**, 2312 (1979).
649. H. Wynberg and B. Greijdanus, *J. Chem. Soc., Chem. Commun.*, 427 (1978).
650. H. Pluim and H. Wynberg, *J. Org. Chem.*, **45**, 2498 (1980).
651. Y. Harigaya, H. Yamaguchi and M. Onda, *Heterocycles*, **15**, 183 (1981).
652. Y. Harigaya, H. Yamaguchi and M. Onda, *Chem. Pharm. Bull.*, **29**, 1321 (1981).
653. H. Wynberg and B. Marsman, *J. Org. Chem.*, **45**, 158 (1980).
654. M. Sugawara and M. M. Baizer, *J. Org. Chem.*, **48**, 4931 (1983).
655. E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1353 (1965).
656. B. Maurer, A. Hauser, W. Thommen, K. H. Schulte-Elte and G. Ohloff, *Helv. Chim. Acta*, **63**, 293 (1980).
657. M. Rosenberger, W. Jackson and G. Saucy, *Helv. Chim. Acta*, **63**, 1665 (1980).
658. C. R. Johnson, C. W. Schroeck and J. R. Shanklin, *J. Am. Chem. Soc.*, **95**, 7424 (1973).
659. G. B. Payne, *J. Org. Chem.*, **32**, 3351 (1967).
660. W. C. Still and V. J. Novack, *J. Am. Chem. Soc.*, **103**, 1283 (1981).
661. S. P. Tanis, M. C. McMills and P. M. Herrinton, *J. Org. Chem.*, **50**, 5887 (1985).
662. N. A. Milas, S. W. Lee, E. Sakal, H. C. Wohlers, N. S. McDonald, F. X. Grossi and H. F. Wright, *J. Am. Chem. Soc.*, **70**, 1584 (1948).
663. Z. Arnold, V. Kral, G. V. Kryshtal and L. A. Yanovskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2162 (1983); *Chem. Abstr.*, **100**, 34350n (1984).
664. Y. Maroni-Barnaud, M. C. Roux-Schmitt and J. Seyden-Penne, *Tetrahedron Lett.*, 3129 (1974).
665. C. Burford, F. Cooke, E. Ehlinger and P. Magnus, *J. Am. Chem. Soc.*, **99**, 4536 (1977).
666. C. Burford, F. Cooke, G. Roy and P. Magnus, *Tetrahedron*, **39**, 867 (1983).
667. E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **84**, 867 (1962).
668. C. R. Johnson, M. Haake and C. W. Schroeck, *J. Am. Chem. Soc.*, **92**, 6594 (1970).
669. B. M. Trost, *J. Am. Chem. Soc.*, **89**, 138 (1967).
670. H. Nozaki, M. Takaku and K. Kondo, *Tetrahedron*, **22**, 2145 (1966).
671. R. W. Curley, Jr. and H. F. De Luca, *J. Org. Chem.*, **49**, 1944 (1984).
672. R. W. La Rochelle, B. M. Trost and L. Krepski, *J. Org. Chem.*, **36**, 1126 (1971).
673. B. M. Trost and M. J. Bogdanowicz, *J. Am. Chem. Soc.*, **93**, 3773 (1971)
674. P. D. Kennewell and J. B. Taylor, *Chem. Soc. Rev.*, **9**, 477 (1980).
675. C. R. Johnson, G. F. Katekar, R. F. Huxol and E. R. Janiga, *J. Am. Chem. Soc.*, **93**, 3771 (1971).
676. C. R. Johnson and E. R. Janiga, *J. Am. Chem. Soc.*, **95**, 7692 (1973).
677. C. R. Johnson and C. W. Schroeck, *J. Am. Chem. Soc.*, **90**, 6852 (1968).
678. C. R. Johnson and L. J. Pepoy, *J. Org. Chem.*, **37**, 671 (1972).
679. S. S. Bhattacharjee, H. Ila and H. Junjappa, *Synthesis*, 301 (1982).
680. Y. Yamashita, Y. Miyauchi and M. Masumura, *Chem. Lett.*, 489 (1983).
681. D. T. Warner, *J. Org. Chem.*, **24**, 1536 (1959).
682. L. L. McCoy, *J. Am. Chem. Soc.*, **82**, 6416 (1960).
683. G. Bonavent, M. Causse, M. Guitard and R. Fraisse-Jullien, *Bull. Soc. Chim. Fr.*, 2462 (1964).
684. M. Causse-Zoller and R. Fraisse-Jullien, *Bull. Soc. Chim. Fr.*, 430 (1966).
685. C. R. Johnson, E. R. Janiga and M. Haake, *J. Am. Chem. Soc.*, **90**, 3890 (1968).
686. C. R. Johnson and P. E. Rogers, *J. Org. Chem.*, **38**, 1793 (1973).
687. E. J. Corey and M. Jautelat, *J. Am. Chem. Soc.*, **89**, 3912 (1967).
688. C. R. Johnson, and C. W. Schroeck, *J. Am. Chem. Soc.*, **93**, 5303 (1971).

The Chemistry of Enones
Edited by S. Patai and Z. Rappoport

CHAPTER 11

Addition of electrons or radicals to α,β-unsaturated ketones

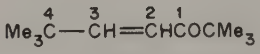
GLEN A. RUSSELL
Department of Chemistry, Iowa State University, Ames, Iowa 50011, USA

I. RADICAL IONS OF α, β-UNSATURATED KETONES

A. Electron Spin Resonance Studies

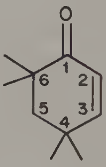
1. General comments

The original reports of the formation and observation by electron spin resonance of radical ions by alkali metal reductions of saturated[1] and α, β-unsaturated[2] cycloalkanones were flawed by reactions with molecular oxygen to yield 1, 2-semidiones (radical ions of 1, 2-diketones). Substitution of alkyl groups for the ionizable α-hydrogen atoms in α, β-unsaturated ketones, e.g. **1**[3] and **2**[4], allowed reasonably persistent radical anions to be observed at ambient temperatures by electrochemical or alkali metal reductions. The radical ions have high spin density at C(1) and C(3), consistent with the resonance hybrid **3** and with a species of high reactivity and low persistency in the absence of steric constraints. Protonation of these ions to give the hydroxyallyl radical **4** has but a minor perturbation on the electron spin densities and observed hyperfine splitting constants (hfsc)[†]. The hydroxyallyl radical **4** can be formed by protonation of **3** or by rearrangement of allyloxy radicals (reaction 1). Reaction of Ti(III)/H_2O_2 (a source of HO·) with 2-cyclopenten-1-ol in an ESR continuous-flow experiment yields the 1-hydroxycyclopentenyl radical by a process believed to involve initial formation of the cyclopentenyloxy radical[5]. On the other hand, $O\cdot^-$ generated by ionizing radiation at pH 14 is believed to directly abstract allylic hydrogen atoms (reaction 2)[6].

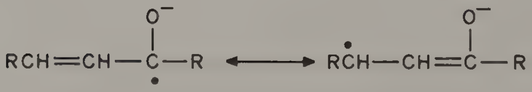


$\mathrm{Me_3}\overset{4}{\mathrm{C}}—\overset{3}{\mathrm{C}}\mathrm{H}=\overset{2}{\mathrm{C}}\mathrm{H}\overset{1}{\mathrm{C}}\mathrm{OCMe_3}$

(1)



(2)



(3)

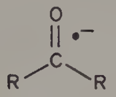
(4)

[†] In ESR spectroscopy the coupling of the electron spin with nuclear spins is measured by the splitting constant (*a*) which is usually reported in terms of magnetic field (1 gauss = 2.8 × 10^6 Hz). The coupling constant is a measure of electron density in the s-orbital of the nucleus in question. For protons attached to a planar radical, electron correlation effects (spin polarization) yields a negative value of a^H. Electron correlation effects also introduce negative spin densities at atoms in π-systems, e.g., at C-2 in allyl and at the meta-carbons in benzylic systems. Protons attached to atoms adjacent to a radical center undergo spin delocalization by hyperconjugation to yield a positive value of a^H. Weaker long range interactions may be observed, particularly in rigid systems, which may have either positive or negative values of a^H depending on the interplay between delocalization and electron correlation effects.

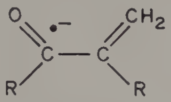
(1)

$$\begin{aligned}\mathrm{CH_2{=}CH{-}CH_2OH} + \mathrm{O}^{\cdot -} &\rightarrow \mathrm{CH_2{=}CH{-}\dot{C}H{-}OH} + \mathrm{OH}^- \\ &\rightarrow \mathrm{CH_2{=}CH{-}\dot{C}H{-}O^-} + \mathrm{H_2O}\end{aligned} \tag{2}$$

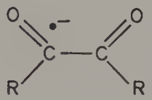
The persistency and ease of preparation of ketyls from α,β-unsaturated ketones is intermediate between saturated ketones (**5**) and 1,2-diketones (**7**). Both **6** and **7** can exist as (*E*) and (*Z*) isomers because of the partial double-bond character between the sp^2 hydridized carbon atoms in the radical ions. These isomers can also be considered to be the *s-cis* and *s-trans* conformations of 1,3-butadiene analogs.



(5)



(6)

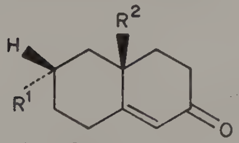


(7)

α,β-Unsaturated ketones have a low reduction potential (– 1.5 to – 2.5 V relative to SCE) and the ketyls are formed readily by electrochemical or alkali metal reductions. Table 1 lists some reported values for $E_{1/2}$ for the first reduction wave for α,β-unsaturated ketones[3].

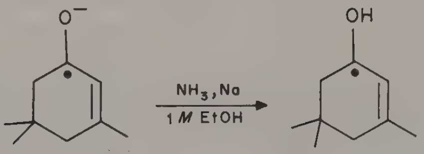
Radical anions of α,β-unsaturated ketones are readily protonated. Although little or no protonation is observed in liquid ammonia, the presence of 1 M ethanol leads to complete protonation of the ketyl ($\sim 10^{-3}$ M) in reaction 3 in a continuous-flow ESR experiment[2]; a pK_a of at least 17 is thus indicated. Only protonation on oxygen is observed by ESR. However, an enolate radical (from protonation at the β-carbon) would not be expected to

TABLE 1[a] Reduction potentials of enenones

Unsaturated ketone	$E_{1/2}$(vs. SCE)[b]
(*E*)-*t*-BuCH=CHCOBu-*t*	– 2.2
(*Z*)-*t*-BuCH=CHCOBu-*t*	– 2.2
(*E*)-PhCH=CHCOBu-*t*	– 1.7
(*Z*)-PhCH=CHCOBu-*t*	– 1.7
(*E*)-PhCH=CHCOMe	– 1.6
(*E*)-*t*-BuCH=CHCOPh	– 1.7
	
$R^1 = R^2 = H$	– 2.15
$R^1 = t\text{-Bu}; R^2 = H$	– 2.15
$R^1 = H; R^2 = Me$	– 2.10

[a] Reference 3.
[b] At 25–28 °C in DMF, 0.1–0.4 *M* *n*-Pr$_4$N$^+$ClO$_4^-$.

be persistent and would be readily reduced to the anion by sodium metal. Values of pK_a of 9.6, ~9.6 and 8.9 have been measured for $CH_2{=}CH\dot{C}HOH$, $CH_3CH{=}CHCH{=}CH\dot{C}HOH$ and $CH_2{=}CH\dot{C}(OH)CH{=}CH_2$, respectively, under conditions where both the protonated and unprotonated radicals can be simultaneously observed[6]. (For comparison, pK_a values of 12.2 and 11.6 have been measured for $Me_2\dot{C}OH$ and $Me\dot{C}HOH$, respectively[8].)



(3)

$a^H = 22.6$ (1H), C(4), axial; 14.3 (3H), C(3) methyl; 13.7 (1H), C(6) axial; 6.9 (1H), C(4), equat., 4.3 (1H), C(6), equat.; 1.2 (1H), C(2), in Gauss

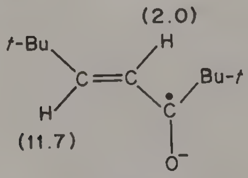
$a^H = 12.1$ (1H), C(4), axial; 9.2 (1H), C(6) axial; 8.8 (3H), C(3), methyl; 4.4 (1H), C(4), equat.; 3.0 (1H), C(6), equat.; 1.0 (1H), C(2), in Gauss

Radical anions of α,β-unsaturated ketones with ionizable hydrogen atoms have been observed in alkali metal reductions by the use of flow techniques and/or low temperatures, particularly with sodium in liquid ammonia at 200–230 K[7,9]. α,β-Unsaturated aldehydes fail to yield persistent ESR signals under these conditions, although the ketyls can be observed in aqueous solution (pH ~ 14) by radiolytic generation[6]. The persistency of radical anions derived from 2-cyclohexen-1-ones with ionizable hydrogen atoms can be appreciable, because the conformational preference of the six-membered ring is often not conducive to ionization at C(4). The presence of ionizable hydrogen atoms at C(1) alkyl group is not usually a serious limitation to persistency.

2. *Acyclic α, β-unsaturated ketyls*

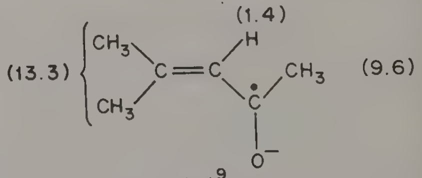
In 1970–71, ketyls **8**–**11** were reported[3,9,10]. All display a large hfsc (a^H) for the C(β) hydrogen atom because of the value of the electron spin density (ρ_c) at C(β) and the McConnell relationship, $a^H = -23\rho_c$.

Reduction of methyl vinyl ketone in liquid ammonia at 203 or 233 K gave a mixture of *s-cis* and *s-trans* conformations (**13** and **14**) which were not interconverted on the ESR time-scale [$k < (\Delta a^H)(2.8 \times 10^6)\,s^{-1}$] and with a **13**/**14** ratio of 1.7 at 203 K[7]. Similar mixtures of *s-cis* and *s-trans* isomers have been observed for $CH_2{=}CH\dot{C}HO^-$ (structures **15** and **16**)[6]. 3-Methyl-3-penten-2-one also yielded a mixture of *cis* and *trans* isomers for which the hfsc could be resolved for the *s-trans* form, **17**[7]. Only a single isomer was detected for the radical anion of mesityl oxide (**9**) which is itself known to exist mainly in the *s-cis* conformation.



(**8**)[3]

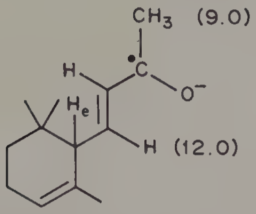
$a^H = 0.35$ (9H); 0.27 (9H), in Gauss



(**9**)[9]

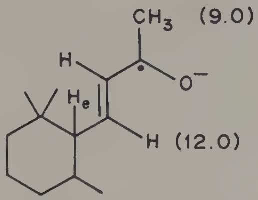
a^H in Gauss

The conformations of **10–12** have been assigned on the assumption that a^H for the methyl at C(1) will be 6–7 Gauss in the *s-trans* and ~9 Gauss in the *s-cis* conformation[7].



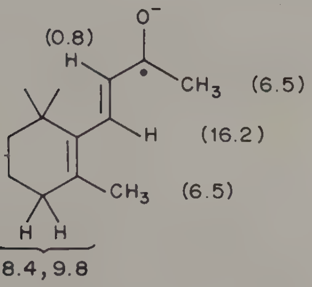
(10), α-ionone[10]

a^H for H_e = 3.2 Gauss



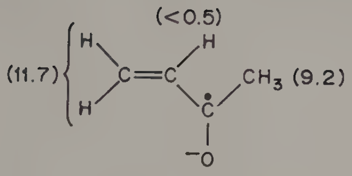
(11)[10]

a^H for H_e = 3.2 Gauss



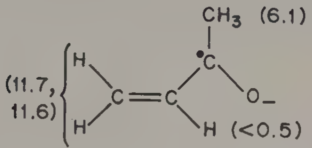
(12), β-ionone[7,10]

a^H in Gauss



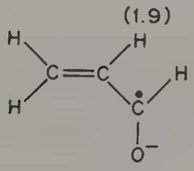
(13), *s-cis*

a^H in Gauss

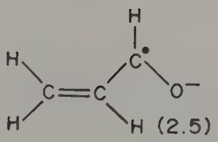


(14), *s-trans*

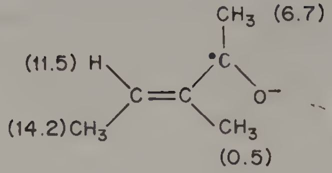
a^H in Gauss



15[6]
a^H = 12.85 (1H), 12.4 (1H), 12.0 (1H), in Gauss



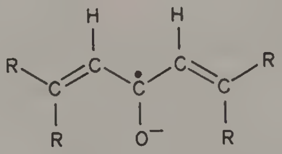
16[6]
a^H = 13.2 (1H), 12.4 (1H), 11.1 (1H), in Gauss



(17)[7]

a^H in Gauss

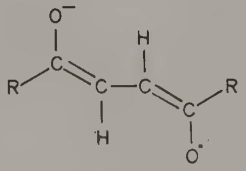
Radical anions of bis(1-alkenyl) ketones are known and they also display a high spin density at the β-carbon atom (**18**).



(18)

(**a**) $R = H$; $a^H = 8.8$ (2H), 8.4 (2H), 2.0 (2H), in Gauss[6]
(**b**) $R = CH_3$ (phorone), $a^H = 8.0$ (12H), 1.65 (2H), in Gauss[7]

β-Substitution of a second acyl group greatly stabilizes the ketyl of an α,β-unsaturated ketone since the resulting radical anion is a 1,4-semidione (**19**)[11]. However, substitution of a second carbonyl group for the alkyl substituent at C(1) yields an α,β-unsaturated 1,2-semidione (**20**) which has a low persistency because of the high spin density at C(β)[12]. For **19** and **20** a variety of stereoisomers are possible (*cis–trans–cis*, etc.) and most of the well studied examples have been in cyclic systems where only one stereoisomer is possible.

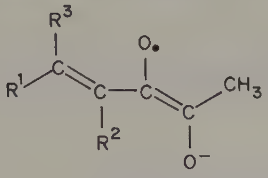


(19)[11]

$R = t$-Bu, $a^H = 5.5$ (2H), 0.2(18H), in Gauss

The unsaturated 1,2-semidione **20** can be observed in Me_2SO/Me_3COK only under flow conditions, because of the tendency for β-protonation followed by electron transfer to lead to the corresponding and more persistent saturated 1,2-semidione (reaction 4).

$$CH_2{=}CHC(O\cdot){=}C(O^-)CH_3 \xrightarrow[Me_2SO]{Me_3COK/Me_3COH} CH_3CH_2C(O)C(O)CH_3$$
$$\rightarrow CH_3CH_2C(O\cdot){=}C(O^-)CH_3 \qquad (4)$$



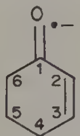
(20)[12]

(**a**) $R^1 - R^3 = H$; $a^H = 5.0\,(1H), 4.9\,(1H), 2.9\,(1H), 1.25\,(1H)$
(**b**) $R^1 = R^3 = H$, $R^2 = CH_3$; $a^H = 4.1\,(1H), 3.9\,(1H), 3.4\,(3H), 1.2\,(3H)$
(**c**) $R^2 = R^3 = H, R^1 = CH_3$; $a^H = 4.9\,(3H), 4.6\,(1H), 3.4\,(3H), 1.5\,(1H)$
(**d**) $R^1 = R^2 = H$, $R^3 = CH_3$; $a^H = 5.1\,(3H), 4.8\,(1H), 3.3\,(3H), 1.8\,(1H)$
(**e**) $R^1 = R^3 = CH_3$, $R^2 = H$; $a^H = 4.6\,(3H), 4.3\,(3H), 3.6\,(3H), 2.0\,(1H)$
(**f**) $R^1 = R^2 = CH_3$· $R^3 = H$; $a^H = 4.1\,(3H), 3.5\,(1H), 3.3\,(3H), 1.2\,(3H)$
(**g**) $R^1, R^2 = -(CH_2)_4-$, $R^3 = H$; $a^H = 5.5\,(2H), 4.1\,(3H), 3.4\,(1H), 1.4\,(2H)$

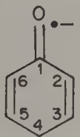
all in Gauss

3. *Radical anions of 2-cyclohexenones*

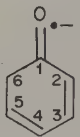
Electrolytic reduction of 4,4-dimethyl, 6,6-dimethyl or unsubstituted 2-cyclohexenone in DMF at 25 °C fails to yield a detectable ESR signal of the expected ketyl[4]. However, 4,4,6,6-tetramethyl-2-cyclohexenone ketyl could be readily observed under these conditions[4]. Reduction by sodium in liquid ammonia with continuous flow yielded the expected spectra for a series of 2-cyclohexenone ketyls. The ketyls exist in a half-chair conformation having magnetically non-equivalent axial and equatorial hydrogen atoms which at 208 K are not time-averaged by conformational motion[7,9]. Table 2 lists the observed hfsc for a series of 2-cyclohexenones (**21**). Included in Table 2 are the radical anions from 2,5-cyclohexadienones (**22**) and 2,4-cyclohexadienones (**23**). The 4,4-disubstituted-2,5-cyclohexadienones or the 6,6-disubstituted-2,4-cyclohexadienones can be easily prepared and observed by electrolytic or alkali metal reduction of the ketones in DMF at 25 °C[13–15] while the unsubstituted analogs (actually the radical anions of the keto forms of phenol) are obtained in matrices (e.g. argon, water) at low temperatures by photochemical electron transfer from sodium metal[16], or by X-irradiation[17]. The large hfsc for the methylene hydrogen atoms in **22** and **23** demonstrate that these species are essentially substituted cyclohexadienyl radicals, e.g. compare **23a,b** with **24** and **25**. The large hfsc for cyclohexadienyl methylene hydrogen atoms at C(4) results from the hyperconjugative delocalization mechanism which takes the form $a_4^H \cong 28\cos^2\theta(c_3 + c_5)^2$ where θ is the dihedral angle between the C(4)—H bond at the *p* orbitals at C(3) and C(5) and c_3, c_5 are the SOMO coefficients at C(3) and C(5); hyperconjugative interaction does



(21)



(22)



(23)

TABLE 2. Hyperfine splitting constants (in Gauss) for ketyls **21–23**

Ketyl	a_2^H	a_3^H	a_{4e}^H	a_{4a}^H	a_{6e}^H	a_{6a}^H	Ref.
21, Unsubstituted	0.8	13.3	6.1	23.5	4.35	12.9	9
21, 3,5-Dimethyl	1.25	14.8^a	7.5	23.2	4.6	13.8	9
21, 4,4-Dimethyl	< 1	~ 13	$< 1^a$	$< 1^a$	4.8	13.0	9
21, 5,5-Dimethyl	0.7	13.2	5.8	23.7	4.4	12.9	9
21, 4,4,6-Trimethyl	< 1	~ 13	$< 1^a$	$< 1^a$	$< 1^a$	~ 13	9
21, 3,5,5-Trimethyl	1.2	14.3^a	6.9	22.6	4.35	13.7	9
21, 4,4,6,6-Tetramethyl	0.8	11.8	0.8^a	0.8^a	0.3^a	0.3^a	4
21, 3-MeO-4,4-dimethyl	2.0	0.9^b	7.6	22.6	4.5	14.1	7
21, 3-Ethoxy	2.1	0.93^c	7.8	23.1	4.6	14.4	7
21, 3-Methyl-4-MeO_2C	—	$\sim 13^a$	7.0	—	7.0	13.0	7

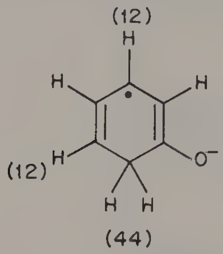
	a_2^H	a_3^H	a_4^H	a_5^H	a_6^H	Ref.
22, 4,4-Dimethyl	1.1	7.1	—	7.1	1.1	4
22, 2,4,4-Trimethyl	1.4^a	7.3	—	6.7	1.1	4
22, 4,4-Diphenyl	1.0	7.0	—	7.0	1.0	4
21, 4,4-Tetramethylene	0.9	7.5	1.25 (2H), 0.7 (2H)	7.1	0.9	13

22, 4-Oxa (γ-pyrone)	1.7	8.1	—	8.1	1.7	7
22, 4-Aza (4(1H)-pyridone)	—	9.0	not obs.	9.0	—	16
22, 2,6-Di-*t*-Bu-4-Me-4-Me, Et, *i*-Pr or *t*-Bu or 4,4-diethyl	—	6.5 6.9	—	6.5 6.9	—	14, 15
	1.3	7.6	1.44(2H), 0.9 (2H)	7.6	1.3	13
23, Unsubstituted	~0	12	~0	12	44(2H)	16, 17
23, 6,6-Dimethyl	1.3	8.1	1.3	9.4	44(2H)	4
23, 2-Hydroxy	~0	11	~0	11	44(2H)	16
23, 3-Hydroxy	~0	—	~0	12	38(2H)	16
23, 4-Hydroxy	~0	10	~0	10	38(2H)	16
23, 2-Aza (2(3*H*)-pyridone)	~0	12	~0	12	33(2H)	16
23, 4-Aza (4(5*H*)-pyridone)	~0	11	~0	11	41(2H)	16
23, 6-Aza (2(1*H*)-pyridone)	~0	11	~0	11	not obs.	16
23, 6-Methyl-2,4,6-tri-*t*-butyl	—	6.5	—	9.1	—	14

---

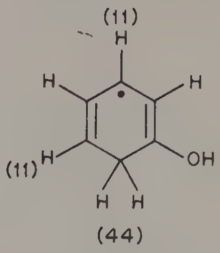
[a] a^H of CH_3 group.
[b] a^H of CH_3O group.
[c] a^H for CH_2 of CH_3CH_2O group.

not depend on the sum of the spin densities (i.e. c_2^3 and c_5^3) but upon the square of the sum of the molecular orbital coefficients[20].



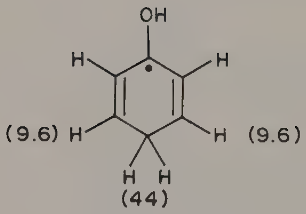
a^H in Gauss

(23a)



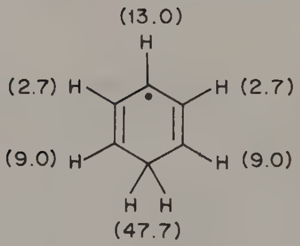
a^H in Gauss

(23b)



a^H in Gauss

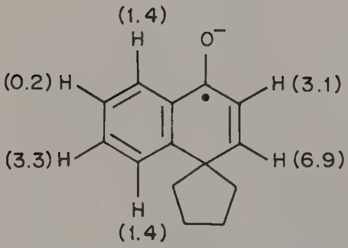
(24)



a^H in Gauss

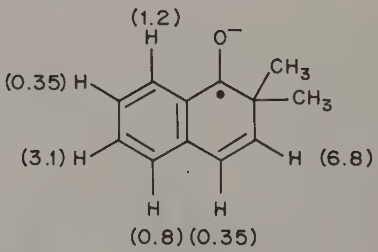
(25)

Various benzo derivatives of the α, β-unsaturated ketyls are known, such as $CH_3\dot{C}(O^-)C_6H_5$, $C_6H_5\dot{C}(O^-)C_6H_5$ (benzo derivatives of **13** and **18a**). Ketyls **26** and **27** are examples of benzo derivatives of **22** and **23**, respectively.



$a^H = 0.6$ (2H), 0.2 (2H), in Gauss

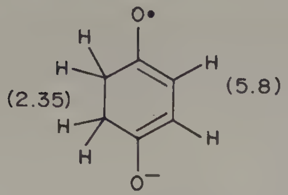
(26)[4]



a^H in Gauss

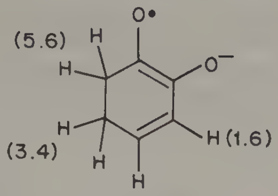
(27)[4]

The introduction of a second carbonyl group into **21** yields the persistent 1,4-semidione **28**[11] or the less persistent 1,2-semidione, such as **29** and **30**[11,21].



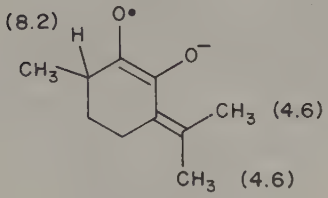
a^H in Gauss

(28)



a^H in Gauss

(29)

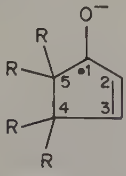


$a^H = 1.6, 0.9, 0.8, 0.3$, in Gauss

(30)

4. Other cyclic systems

The conjugated cyclopentenone ketyl can be easily prepared by electrolytic reduction when the α-hydrogen atoms have been substituted by alkyl groups (**31b**, $R = CH_3$)[4]. The parent system (**31a**, R = H) has been prepared by continuous-flow ESR using sodium in liquid ammonia as the reducing agent[7].

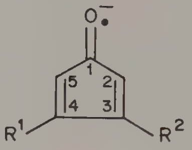


(31)

(**a**) R = H, $a^H = < 0.3$, C(2); 12.65, C(3); 17.2, C(4); 11.3, C(5), in Gauss
(**b**) $R = CH_3$, $a^H = 0.45$, C(2); 11.0, C(3); 0.6(6H), C(4) methyls, in Gauss

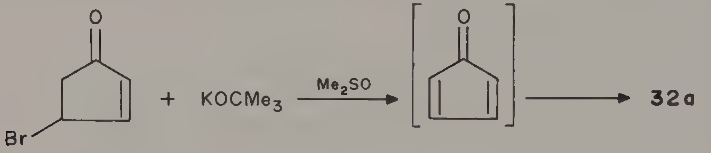
Tetraarylcyclopentadienones readily form a persistent ketyl. For the tetraphenyl derivative the ketyl has hfs by 12 *ortho* and *para* hydrogen atoms (0.56 Gauss) and two sets of *meta* hydrogen atoms [0.28 (4H) and 0.14 (4H) Gauss][22]. The unsubstituted ketyl **32** ($R^1 = R^2 = H$) has a relatively low spin density at the C(3), C(4) positions compared with **22** or with tropone ketyl (**33**)[23]. The ketyl **32a** has a lifetime of several minutes in Me_2SO/Me_3COK and is conveniently prepared and observed in a continuous-flow apparatus (reaction 5) by E2 elimination of HBr from 4-bromo-2-cyclopentenone[23]. Ketyls **32b,c** were prepared in a continuous-flow system starting from the

5-acetoxy ketones[21]. The total spin density at C(2)–C(5) in **32** is approximately 0.6 $[\sum a^{\mathrm{H}}/Q^{\mathrm{H}}_{\mathrm{CH}} = 16.4/(23\text{–}28)]$ while for **33** the spin density at C(2)–C(7) approaches 1 $(\sum a^{\mathrm{H}} = 27.6$ Gauss). Ketyl **33** is thus a 7π system (**33a**) while **32** has a large contribution from the 6π resonance hybrid (**32d**).

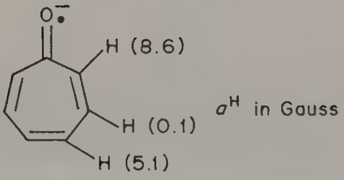


(32)

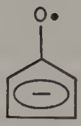
(**a**) $R^1 = R^2 = H$: $a^{\mathrm{H}} = 2.9$(2H), C(2, 5); 5.3(2H), C(3.4), in Gauss
(**b**) $R^1 = H$, $R^2 = CH_3$: $a^{\mathrm{H}} = 2.4$(1H), C(2 or 5); 3.5 (1H), C(5 or 2); 5.3(1H), C(4); 6.3(3H), C(3) methyl, in Gauss
(**c**) $R^1 = R^2 = CH_3$: $a^{\mathrm{H}} = 2.5$(2H), C(2, 5); 5.9(6H), C(3, 4) methyls, in Gauss;



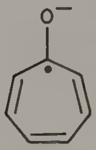
(5)



(33)[4,24]

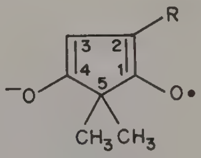


(32d)



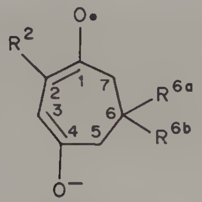
(33a)

1, 4-Semidiones are known for both the C_5 and C_7 rings (**34** and **35**)[11]. The α, β-unsaturated 1, 2-semidione in the C_5 ring (**36**) has a low persistency but can be prepared by the reaction of Me_3COK/Me_2SO with α-hydroxy ketones[21]. In the absence of gem dialkyl substituents the 1, 2-semidione **36** readily forms a radical dianion with the cyclopentadienoid aromatic sextet (reaction 6)[21].



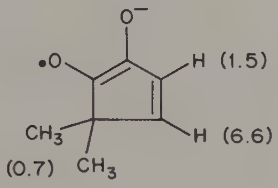
(34)

(**a**) $R = H$: $a^{\mathrm{H}} = 6.4$ (2H), in Gauss
(**b**) $R = CH_3$: $a^{\mathrm{H}} = 6.5$ (3H), C(2); 5.8 (1H), C(3), in Gauss



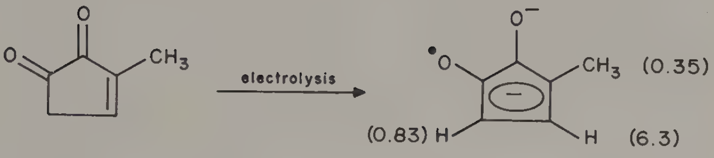
(35)

(a) $R^{6a} = R^{6b} = R^2 = H$: $a^H = 4.9\,(2H)$, C(2, 3); 2.6 (4H), C(5, 7), in Gauss
(b) $R^{6a} = R^2 = H$, $R^{6b} = CH_3$: $a^H = 4.9\,(2H)$, C(2, 3); 3.4 (2H), 1.8 (2H), C(5, 7), in Gauss
(c) $R^{6a} = R^{6a} = CH_3$, $R^2 = H$: $a^H = 4.7\,(2H)$, C(2, 3); 2.3 (4H), C(5, 7), in Gauss
(d) $R^{6a} = R^{6b} = R^2 = CH_3$: $a^H = 5.0\,(3H)$, C(2) methyl; 2.8 (1H), C(3); 2.0 (4H), C(5, 7), in Gauss



(36)

a^H in Gauss

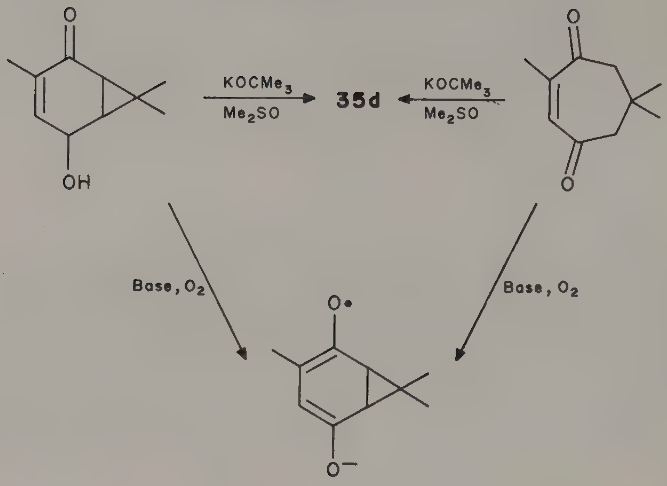


a^H in Gauss (6)

Semidione **35d** is formed in basic solution from either the cyclohept-2-ene-1, 4-dione or the 3, 7, 7-trimethyl-5-hydroxy-2-ketobicyclo[4.1.0]hept-2-ene (Scheme 1)[11]. In the presence of oxygen both the monocyclic dione and the bicyclic hydroxy ketone are converted to the bicyclic 1, 4-semidione, **37**, a product also obtained upon oxidation of eucarvone (2, 6, 6-trimethylcyclohepta-2, 4-dienone) in basic solution[11].

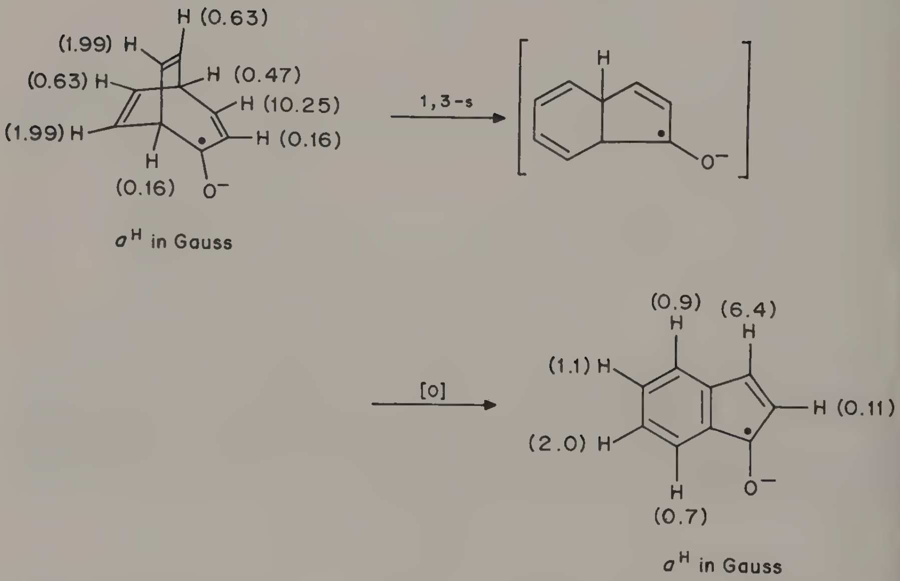
5. Molecular rearrangement of a bicyclic ketyl of an α,β-unsaturated ketone

Electrolytic reduction of bicyclo[3.2.2]nona-3, 6, 8-triene-2-one in DMF or CH_3CN at − 60 °C or below yields the expected ketyl[25]. However, above − 60 °C the spectrum appears to be that of the rearranged and dehydrogenated radical anion[23,25]. The reaction 6a apparently involves a 1, 3-sigmatropic rearrangement followed by aromatization of the aromatic ring. Other examples of 1, 3-sigmatropic rearrangements of unsaturated 1, 2-semidiones are known[26,27].



(37)

SCHEME 1



B. Reactions of α, β-Unsaturated Ketones Involving Electron Transfer

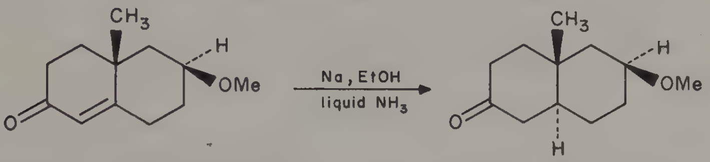
1. Dissolving metal reductions

α, β-Unsaturated ketones can be reduced by Zn or Zn(Hg) in acetic or aqueous acid (Clemmensen conditions). However, a more widely applied process involves an alkali metal, usually lithium or sodium, in liquid ammonia in the presence of a proton donor[28]. The pK_a of $R_2C{=}CH{-}\dot{C}(OH)R$ is too low for $R_2C{=}CH{-}\dot{C}(O^-)R$ to abstract a proton from NH_3; see Section I.A.1. The reactions involve the formation of the enolate anion which can be trapped by MeI to give the C-methylated product[29] (Scheme 2).

$$\begin{tikzcd}
R_2C{=}CH\dot{C}(O^-)R \arrow[r, "\text{Na or Li}", "\text{liquid } NH_3\text{,}R'OH"'] & R_2CH{-}CH{=}C(O^-)R \arrow[d, no head] & \\
R_2CHCH(CH_3)COR & \arrow[l, "MeI"'] \arrow[r, "H_2O"] & R_2CHCH_2COR
\end{tikzcd}$$

SCHEME 2

The formation of the enolate ion is controlled by stereoelectronic considerations involved in the reaction of the planar *s-cis* or *s-trans* radical anions[30]. The final product is not necessarily the product of thermodynamic control as illustrated in the example of reaction 7[30,31].



(7)

Reactions of α, β-unsaturated ketones with sodium metal in inert solvents such as THF (heterogeneous) give an approximately 1:1 stoichiometry with hydrolytic work-up yielding the dihydro dimer (Scheme 3)[3]. In the presence of alcohols in THF, mixtures of the dihydro dimer and the saturated ketone are observed[3]. The suggestion that the saturated ketone arises by further reduction of *t*-BuCH=CHĊ(OH)Bu-*t* (**4a**) by sodium seems unreasonable. Disproportionation of **4a** seems more reasonable (Scheme 4).

$$t\text{-}BuCH{=}CHCOBu\text{-}t \xrightarrow{\text{Na, THF}} \underset{\mathbf{(8a)}}{t\text{-}BuCH{=}CH{-}\dot{C}(ONa)Bu\text{-}t}$$

$$2\,\mathbf{8a} \longrightarrow \begin{array}{c} t\text{-}BuCH{=}CH{-}C(ONa)Bu\text{-}t \\ | \\ t\text{-}BuCH{=}CH{-}C(ONa)Bu\text{-}t \end{array} \xrightarrow{H_2O} \begin{array}{c} t\text{-}BuCH{=}CH{-}C(OH)Bu\text{-}t \\ | \\ t\text{-}BuCH{=}CH{-}C(OH)Bu\text{-}t \end{array}$$

SCHEME 3

$$\mathbf{8a} + ROH \longrightarrow \underset{\mathbf{(4a)}}{t\text{-}BuCH{=}CH\dot{C}(OH)Bu\text{-}t}$$

$$2\,\mathbf{4a} \begin{array}{l} \rightarrow [t\text{-}BuCH{=}CH{-}C(OH)(t\text{-}Bu)\ ]_2 \\ \rightarrow t\text{-}BuCH_2CH{=}C(OH)Bu\text{-}t + t\text{-}BuCH{=}CHCOBu\text{-}t \end{array}$$

$$\mathbf{8a} + t\text{-}BuCH_2CH{=}C(OH)Bu\text{-}t \rightleftharpoons \mathbf{4a} + t\text{-}BuCH_2CH{=}C(O^-)Bu\text{-}t$$

SCHEME 4

Reduction by lithium or sodium in liquid ammonia in the presence of a proton donor leads to the saturated ketone with little of the dihydro dimer. A convenient rationale is shown in Scheme 5. However, ESR results clearly indicate that protonation at oxygen is highly preferred for the α,β-unsaturated ketyl. (Protonation at the β-carbon would yield a reactive enolate radical which would not be detected by solution ESR spectroscopy.) Rearrangement of the hydroxyallyl radical (**4b**) is a possibility (reaction 8), but this must be a slow process for the ESR results of Section A (see Section I.A.1). Another possibility is that the rapid reduction by Li or Na in liquid ammonia in the presence of small amounts of a weak proton donor, leads to appreciable concentrations of both $R_2C{=}CH{-}\dot{C}(O^-)R$ (**3b**) and $R_2C{=}CH{-}\dot{C}(OH)R$ (**4b**). Reaction between **3b** and **4b** could lead to the enolate anion (reaction 9), a process which could predominate over disproportionation or coupling reactions of **4b** (see Scheme 4). The formation of $R_2\bar{C}CH(OM)R\,M^+$ in the absence of a proton donor may also be a possibility with sodium in liquid amonia, although this process does not occur in the heterogeneous reduction in THF.

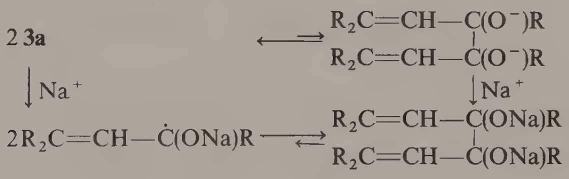
$$\begin{gathered} R_2C{=}CH{-}COR + M^0 \rightarrow R_2C{=}CH{-}\dot{C}(O^-)R\,M^+ \\ R_2C{=}CH{-}\dot{C}(O^-)R + H^+ \rightarrow R_2CH{-}CH{=}C(O^\cdot)R \\ R_2CH{-}CH{=}C(O^\cdot)R + M^0 \rightarrow R_2CH{-}CH{=}C(OM)R \end{gathered}$$

SCHEME 5

$$\underset{(\mathbf{4b})}{R_2C{=}CH{-}\dot{C}(OH)R} \rightleftarrows R_2CH{-}C{=}C(O^\cdot)R \qquad (8)$$

$$\mathbf{3b} + \mathbf{4b} \longrightarrow R_2CHCH{=}C(O^-)R + R_2C{=}CHCOR \qquad (9)$$

Ion pairing, and hence the dielectric constant of the solvent, will have a large effect upon the course of the reaction. In aprotic polar solvents there is no evidence for dimerization of the ketyl (Scheme 6). In liquid ammonia, ion pairing may not be important and dimerization of the ketyl either occurs slowly or has an unfavorable equilibrium. As the hydroxyallyl radical (**4b**) is formed by protonation, it will be readily consumed by reaction with the ketyl (reaction 9) which has a high spin density at the β-carbon atom.



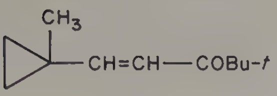
$$\begin{array}{ccc} 2\,\mathbf{3a} & \rightleftarrows & \begin{array}{l} R_2C{=}CH{-}C(O^-)R \\ \qquad\qquad\ \ | \\ R_2C{=}CH{-}C(O^-)R \end{array} \\ \downarrow Na^+ & & \downarrow Na^+ \\ 2R_2C{=}CH{-}\dot{C}(ONa)R & \rightleftarrows & \begin{array}{l} R_2C{=}CH{-}C(ONa)R \\ \qquad\qquad\ \ | \\ R_2C{=}CH{-}C(ONa)R \end{array} \end{array}$$

SCHEME 6

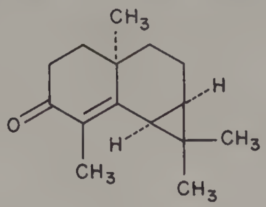
Indirect evidence for radical anions in enone reduction by alkali metals in liquid ammonia include the *cis* to *trans* isomerization observed for unreacted $RCH{=}CHCOBu\text{-}t$ ($R = Ph$ or t-Bu)[32]. However, although cyclopropylcarbinyl ring opening was observed upon alkali metal reduction of cyclopropyl methyl ketone or bicyclo[4.1.0]heptan-2-one[33], ring opening is not observed for the reduction of **38**[34] or **39**[35]. Ring closure of the 5-hexenyl type was also not observed in the reduction of **40**[34].

2. *Photochemical electron transfer to α, β-unsaturated ketones*

Electron transfer to the π,π^* triplet state[36] of an α,β-unsaturated ester[37], ketone[38] or the enone excimer[39,40] from an electron donor (D:) is possible (reaction 10). However, back



(38)



(39)

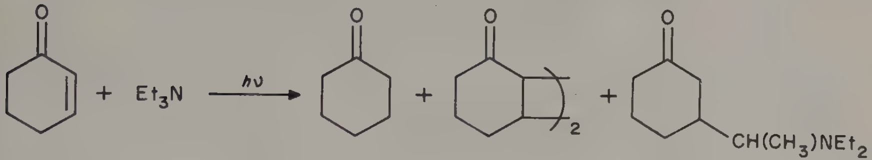
$$CH_2{=}CHCH_2CH_2C(CH_3)_2CH{=}CHCOBu\text{-}t$$

(40)

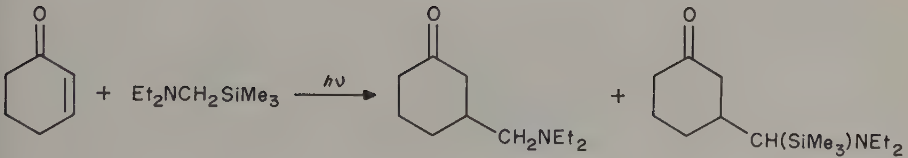
electron transfer will regenerate D: and $R_2C{=}CHCOR$, often with polarization of nuclear spins (CIDNP)[41] (reaction 11). Electron transfer occurs in competition with hydrogen atom abstraction from trialkylamines[38], from alcohols[42] or benzylic positions[43] (leading to the saturated ketone) and with the photochemical 2 + 2 dimerization of the enone. Electron transfer with an amine such as 1,4-diazabicyclo[2.2.2]octane (DABCO) does not form any reaction product, although the transient $DABCO^{\cdot +}$ can be detected by nanosecond spectroscopy[36]. However, if $D^{\cdot +}$ readily loses a proton to the enone radical anion, coupling products can be observed (reaction 12)[40]. In a modification of this process, α-silylamines can be employed (reaction 13)[44]. Table 3 summarizes some yields of coupling products observed upon UV irradiation of enones with Et_3N or $Et_2NCH_2SiMe_3$.

$$R_2C{=}CHCOR^* + D: \longrightarrow R_2C{=}CH\dot{C}(O^-)R + D^{\cdot +} \tag{10}$$

$$R_2C{=}CH\dot{C}(O^-)R + D^{\cdot +} \longrightarrow R_2C{=}CHCOR + D: \tag{11}$$



(12)



(13)

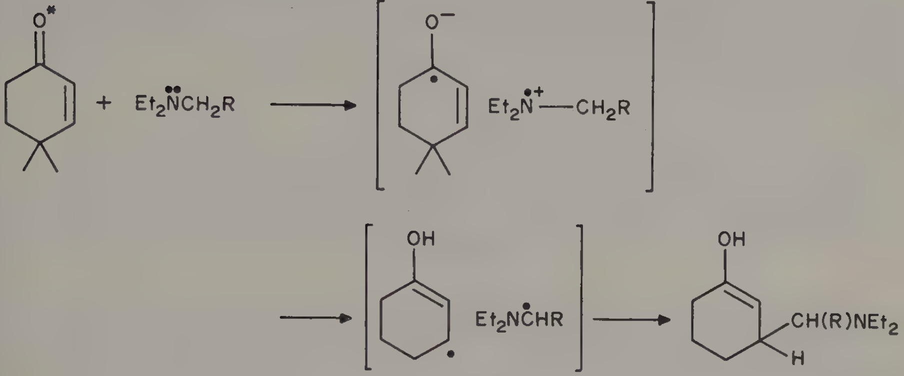
In solvents of low polarity the reaction proceeds via an ion pair in which the enone radical anion serves as the proton acceptor (Scheme 7). With $Et_2NCH_2SiMe_3$ in CH_3CN, or even better in CH_2Cl_2 or c-C_6H_{12}, the contact ion pairs reacts to form the substituted cyclohexanone with R = Me_3Si in Scheme 7[44]. In MeOH, or other solvents of high polarity, dissociation of the ion pair can occur. Now the reaction of $Et_2NCH_2SiMe_3^{\cdot +}$ with a nucleophile (Nu^-) leads mainly to $Et_2NCH_2^{\cdot} + NuSiMe_3$. The resulting aminomethyl radical can add to the starting α,β-unsaturated ketone (see Section II) to

TABLE 3. Photochemical reaction of 2-cyclohexenones with tertiary amines

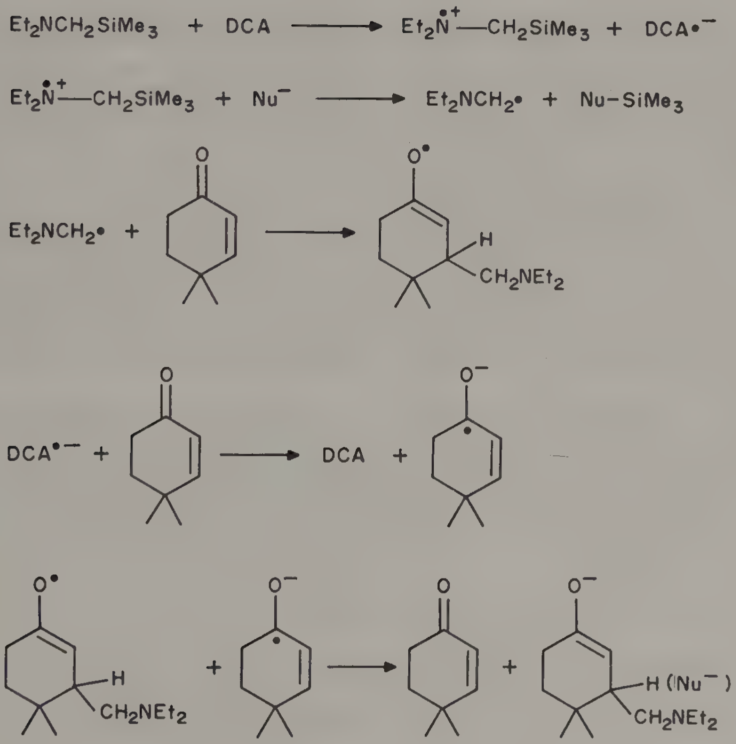
2-Cyclohexenone	Amine	Solvent	Substituted cyclohexenones (%)	Ref.
Unsubstituted	$Et_2NCH_2SiMe_3$	MeCN	3-$CH(NEt_2)SiMe_3$ (30%), 3-CH_2NEt_2 (0%)	44
Unsubstituted	$Et_2NCH_2SiMe_3$	MeOH	3-$CH(NEt_2)SiMe_3$(trace), 3-CH_2NEt_2 (30%)	44
Unsubstituted	Et_3N	Neat	3-$CH(CH_3)NEt_2$ (43%)[a]	40
4,4-Dimethyl	$Et_2NCH_2SiMe_3$	MeCN	4,4-Me_2-3-$CH(NEt_2)SiMe_3$ (70%), 4,4-Me_2-3-CH_2NEt_2 (5%)	44
4,4-Dimethyl	$Et_2NCH_2SiMe_3$	MeOH	4,4-Me_2-3-$CH(NEt_2)SiMe_3$ (30%), 4,4-Me_2-3-CH_2NEt_2 (60%)	44
2-Me-4-isopropenyl	$Et_2NCH_2SiMe_3$	MeOH	2-Me-4-isopropenyl-3-CH_2NEt_2 (86%)	44
2-Me-4-isopropenyl	Et_3N	Neat	2-Me-4-isopropenyl-3-$CH(CH_3)NEt_2$ (28%)	38
3,5,5-Trimethyl	$Et_2NCH_2SiMe_3$	MeOH	3,5,5-Trimethyl-3-CH_2NEt_2 (40%)	44
Pugelone	Et_3N	Neat	2-Me-5-$Et_2NCH(CH_3)CMe_2$ (44%)	38
17β-Hydroxyandrost-4-en-3-one	Et_3N	Neat	17-β-Hydroxy-5-$Et_2NCH(CH_3)$-androst-3-one (39%)	38
$Me_2C{=}CHCOCH_3$	Et_3N	Neat	$Et_2NCH(Me)CMe_2CH_2COMe$ (25%), $CH_2{=}C(Me)CMe_2C(OH)(Me)CH(Me)NEt_2$ (6%)	38
1-Acetylcyclohexene	Et_3N	Neat	1-CH_3CO-2-$Et_2NCH(CH_3)$-c-C_6H_{10} (28%)	38

[a] 12% of cyclohexanone and 28% of enone dimer.

give (after hydrolysis) the saturated ketone with a β-CH_2NEt_2 substituent. This product is also the major one in the reaction photosensitized by an electron acceptor such as 9,10-dicyanoanthracene (DCA) (Scheme 8)[44].



SCHEME 7



SCHEME 8

3. *Electron transfer with organocuprate reagents*

Ketones without ionizable hydrogen atoms react with organomagnesium or lithium reagents to give ketyl radical anions, which can be detected by ESR spectroscopy[45–47]. In the case of fluorenone, the ketyl can be the major reaction product[45]. It is not unreasonable that α,β-unsaturated ketones should behave in a similar fashion. Indirect evidence has been presented that certain conjugate additions of organocuprates, $(\mathrm{R_2CuLi})_2$, can occur by the process of Scheme 9[48].

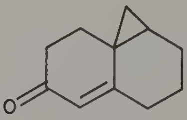
$$\begin{aligned}(\mathrm{R'_2CuLi})_2 + \mathrm{RCH{=}CH{-}COR} &\longrightarrow (\mathrm{R'_2CuLi})_2^{+}\cdot + \mathrm{RCH{=}CH{-}\dot{C}(O^-)R}\\ &\longrightarrow (\mathrm{R'_2CuLi})_2^{+}\mathrm{{-}C(H)R{-}CH{=}C(O^-)R}\\ &\longrightarrow \mathrm{R'CH(R){-}CH{=}C(O^-)R} + \mathrm{Li^+} + \mathrm{RCu} + \mathrm{R_2CuLi}\end{aligned}$$

SCHEME 9

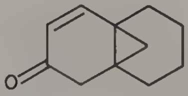
Evidence for the general process of Scheme 9 is based on a consideration of the oxidation and reduction potentials required for conjugate addition[48], the observation of *cis*-to-*trans* isomerization of certain enones[32] and the observation of rearrangement or fragmentation products consistent with a radical anion intermediate[49–51]. It is argued that the electron transfer mechanism of Scheme 9 would be expected only when $E_{\mathrm{red}} - E_{\mathrm{ox}}$ is more positive than -0.4 V[48]. [E_{red} is the reduction potential of the α,β-unsaturated ketone; a more easily reduced system has a more positive, i.e. less negative, value of E_{red}. E_{ox} is the oxidation potential of the organometallic reagent; the more easily oxidized molecules (better reducing reagents) have a more negative value of E_{ox}.] Thus, with $((\mathrm{CH_3})_2\mathrm{CuLi})_n$ in $\mathrm{Et_2O}$, conjugate addition is observed for $(\mathrm{CH_3})_2\mathrm{C{=}C(CH_3)COCH_3}$ [E_{red} (vs. SCE) $= -2.35$] but not for 5,5-dimethyl-3-butoxy-2-cyclohexen-1-one ($E_{\mathrm{red}} = -2.43$), cyclopropyl methyl ketone ($E_{\mathrm{red}} = -2.88$) or bicyclo[4.1.0]heptan-2-one ($E_{\mathrm{red}} = -2.81$)[39].

Reaction of $\mathrm{Ph_3CLi}$ in DME ($E_{\mathrm{ox}} = -1.3$ V) with (E)-PhCH=CHCOPh ($E_{\mathrm{red}} = -1.41$ V) occurs rapidly to form $\mathrm{Ph_3CCH(Ph)CH_2COPh}$. On the other hand, reaction with (E)-*t*-BuCH=CHCOBu-*t* ($E_{\mathrm{red}} = -2.22$ V) occurs slowly[52]. The recovered enone from the reaction of either (Z)-PhCH=CHCOBu-*t* ($E_{\mathrm{red}} = -1.71$ V) or (Z)-*t*-BuCH=CHCOBu-*t* ($E_{\mathrm{red}} = -2.21$ V) with $(\mathrm{Me_2CuLi})_2$ in $\mathrm{Et_2O}$ was almost completely the (E) isomer, highly suggestive of a radical anion intermediate[32]. This isomerization would be catalytic because of electron transfer between ketyl and ketone molecules, but does not require that the ketyl is an intermediate in the conjugate addition accompanying isomerization.

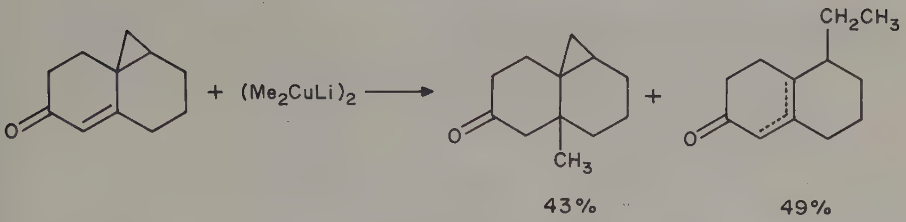
Ketyls derived from enones **38** and **40** do not readily undergo the cyclopropylcarbinyl ring opening or the 5-hexenyl ring closure reactions characteristic of radical species[53]. With $(\mathrm{Me_2CuLi})_2$ or $\mathrm{Li/NH_3}$—*t*-BuOH no rearrangement was observed upon conjugate addition or reduction[32]. On the other hand, the cyclopropyl derivatives **41** and **42** give rearranged products upon reaction with $(\mathrm{Me_2CuLi})_2$, e.g. reaction 14[51], which could occur by cyclopropylcarbinyl radical ring opening or from nucleophilic attack at a cyclopropyl carbon atom.



(41)

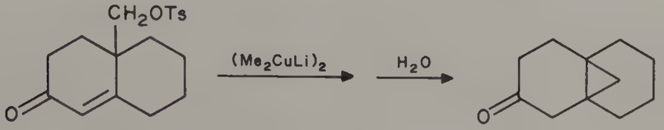


(42)



(14)

Fragmentations are observed in reactions of some enones with $(Me_2CuLi)_2$ which can be interpreted in terms of a radical anion intermediate. Thus, 4,4-dimethoxycyclohexadienone yields 4-methoxyphenol[49] and the octalone **43** yields the decalone **44** (reaction 15)[50]. (See Note Added in Proof on page 512.)

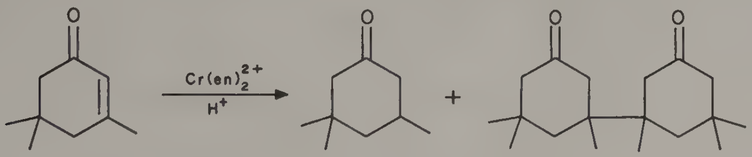


(43) **(44)**

(15)

4. One-electron reduction of α, β-unsaturated ketones by Cr(II)

α, β-Unsaturated ketones can be reduced by $Cr(en)_2(OAc)_2$ in MeOH; often higher yields are obtained by having both a proton donor (HOAc) and a hydrogen atom donor (RSH) present[54]. With 2-cyclohexenones, the presence of a thiol completely eliminates the formation of the dihydro dimer, e.g. in reaction 16 of isophorone. The reaction appears to follow Scheme 10 although the timing of the proton transfer is uncertain. *Cis*-to-*trans* isomerization is observed when the enones $RCH{=}CHCOBu$-*t*, R = Ph or *t*-Bu, are treated with a deficiency of the chromous complex[32], suggesting that $R\dot{C}H{-}CH{=}C[OCr(en)_2^{2+}]Bu$-*t* is formed reversibly or can dissociate into $RCH{=}CH{-}\dot{C}(O^-)Bu$-*t* and a Cr(III) species. Isophorone with a $E_{1/2}$ of -2.24 V (DMF) or -1.65 V (MeOH) is reduced by Cr(II) but 3-isobutoxy-4, 4-dimethyl-2-cyclohexenone with $E_{1/2} = -2.43$ V (DMF) or -1.92 V (MeOH) is not reduced. Table 4 summarizes some results of reduction of ketones by a mixture of Cr(II), ethylenediamine, RSH and HOAc in MeOH.



(16)

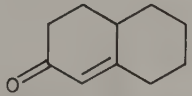
$$\mathrm{RCH{=}CH{-}COR} + \mathrm{Cr(en)_2^{2+}} \longrightarrow \mathrm{R\dot{C}H{-}CH{=}C(OCr(en)_2^{2+})R}$$

$$\xrightarrow[(-\mathrm{RS\cdot})]{\mathrm{RSH}} \mathrm{RCH_2CH{=}C(OCr(en)_2^{2+})R} \xrightarrow{\mathrm{H^+}} \mathrm{RCH_2CH_2COR} + \mathrm{Cr(en)_2^{3+}}$$

$$2\mathrm{RS\cdot} \longrightarrow \mathrm{RSSR}$$

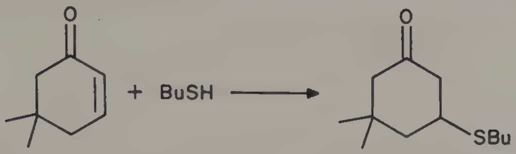
SCHEME 10

TABLE 4. Cr(II) reduction of α, β-unsaturated ketones in MeOH

Ketone (mmol); chromium(II) salt (mmol)	Additives (mmol)[a]; conditions	%Yield of products
Isophorone (51); $Cr(OAc)_2$ (175)	en (405), BuSH (150) HOAc (250); 24 h, 25 °C	3, 3, 5-trimethylcyclohexanone (79%)
 (6, 7); $Cr(OAc)_2$ (23)	en (54), PrSH (20) HOAc (33); 2 h, 28–35 °C	*trans*-2-decalone (57%) *cis*-2-decalone (11%)
t-BuCH=CHCOBu-*t* (1.1); $Cr(ClO_4)_2$ (2.6)	en (8); DMF–H_2O (75%:25%) 18 min, 25 °C	*t*-$BuCH_2CH_2COPh$ (72%)
5, 5-Dimethyl-2-cyclohexenone (24); $Cr(OAc)_2$ (84)	en (194), BuSH (72), HOAc (120); 23 h, 25 °C	5, 5-dimethylcyclohexanone (18%)
4, 4-Dimethyl-2-cyclohexenone (32); $Cr(OAc)_2$ (113)	en (261), BuSH (97), HOAc (160); 23 h, 25 °C	4, 4-dimethylcyclohexanone (47%)

[a] en = ethylenediamine

A side-reaction observed when a 2-cyclohexenone is reacted with Cr(II) in the presence of RSH is the free radical addition of the thiol to the enone (reaction 17). Further examples of regioselective free radical addition to enones will be given in Section II.



(17)

II. FREE RADICAL ADDITION TO α, β-UNSATURATED KETONES

A. Additions Involving Hydrogen Atom Transfer

1. *Additions involving a single addend*

The carbonyl group is less effective in stabilizing a radical center than a carbanion. For example, the spin density for **45** is estimated from ESR data to be 77% at C(α) and 23% at oxygen[55]. However, the carbonyl group is effective in controlling the regiochemistry of attack of both nucleophilic and electrophilic radicals upon α, β-unsaturated ketones, since the free radical addition of the reagents Z—H yield almost exclusively the β-substituted ketone or aldehyde with Z = R_3Ge, RCO, RS or PhC(O)S. The acetyl group is slightly more effective than two methyl groups in stabilizing a radical center at which it is substituted. Values of σ^r which can be used as a measure of relative reactivity in processes forming $RCH_2\cdot$ ($\log k_R/\log k_H = \sigma^r\rho^r + \sigma^*\rho^*$) vary from 0 for R = H to 0.32 for R = CH_3, 0.66 for R = PhO and 0.72 for R = CH_3CO[56].

(45)

α, β-Unsaturated ketones or aldehydes do not usually form telomers in free radical reactions with Z—H molecules[57]. Table 5 presents some examples of the formation of 1:1 adducts according to reaction 18.

$$R_2C{=}CHCOR + H{-}Z \xrightarrow[\text{or } h\nu]{\text{peroxides}} ZCR_2CH_2COR \qquad (18)$$

2. *Reactions involving alkyl halides and metal hydrides*

Alkyl radicals are generated from alkyl halides by attack of $R_3Sn\cdot$ or $R_3Ge\cdot$ radicals. The resulting alkyl radicals react readily with R_3SnH and less readily with R_3GeH to form the alkane and the organometallic radical[65,66]. In the presence of a reactive radicaphile the alkyl radical can be trapped to give an adduct radical, which can either enter into a telomerization reaction with the radicaphile or abstract a hydrogen atom from the metal hydride (Scheme 11).

TABLE 5. Free radical addition of H—Z to α, β-unsaturated ketones and aldehydes

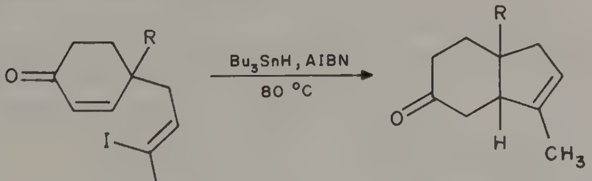
Substrate	Z—H	Product (% yield)	Ref.
$PhCH{=}CHCOPh$	$PhCH_2S{-}H$	$PhCH(CH_2SPh)CH_2COPh$	58
$MeCH{=}CHCHO$	$MeC(O)S{-}H$	$MeCH(SCOMe)CH_2CHO$ (100)	59
$Me_2C{=}CHCOMe$	$MeC(O)S{-}H$	$Me_2C(SCOMe)CH_2COMe$ (92)	59
$PhCH{=}CHCOCH_3$	$MeC(O)S{-}H$	$PhCH(SCOMe)CH_2COMe$ (90)	59
$PhCH{=}CHCHO$	$MeC(O)S{-}H$	$PhCH(SCOMe)CH_2CHO$ (90)	59
$HC{\equiv}CCHO$	$PhC(O)S{-}H$	$PhC(O)SCH{=}CHCHO$ (16)	60
$Me_2C{=}CHCOMe$	$MeC(O){-}H$	$MeCOCMe_2CH_2COMe$ (31)	61
$MeCH{=}CHCOMe$	$PrC(O){-}H$	$PrCOCH(Me)CH_2COMe$ (64)	61
$CH_2{=}C(CH_3)COMe$	$PrC(O){-}H$	$PrCOCH_2CH(Me)COMe$	62
$Me_2C{=}CHCOMe$	$PrC(O){-}H$	$PrCOCMe_2CH_2COMe$ (88); $PrCOCH(i\text{-}Pr)COMe$ (9)	62
$Me_2C{=}CHCOCH{=}CMe_2$	$PrC(O){-}H$	$PrCOCMe_2CH_2COCH{=}CMe_2$ (80); $PrCOCMe_2CH_2COCH_2CMe_2COPr$ (10)	61
$n\text{-}C_6H_{13}CH{=}CHCOMe$	$PrC(O){-}H$	$PrCOCH(n\text{-}C_6H_{13})CH_2COMe$ (42)	62
$MeCH{=}CHCOPh$	$PrC(O){-}H$	$PrCOCH(Me)CH_2COPh$ (24)	62
$Me_2C{=}CHCOMe$	$n\text{-}C_6H_{13}C(O){-}H$	$n\text{-}C_6H_{13}COCMe_2CH_2COMe$ (61)	62
$CH_2{=}CHCHO$	$Et_3Ge{-}H$	$Et_3GeCH_2CH_2CHO$	63
$CH_2{=}CHCHO$	$Bu_3Ge{-}H$	$Bu_3GeCH_2CH_2CHO$	63
$CH_2{=}CHCOMe$	$Ph_3Ge{-}H$	$Ph_3GeCH_2CH_2COMe$ (53)	64

$$\mathrm{R\cdot + CH_2{=}CHZ \longrightarrow RCH_2\dot{C}HZ}$$
$$\mathrm{RCH_2\dot{C}HZ + CH_2{=}CHZ \longrightarrow RCH_2CH(Z)CH_2\dot{C}HZ}$$
$$\mathrm{RCH_2\dot{C}HZ + R'_3MH \longrightarrow RCH_2CH_2Z + R'_3M\cdot}$$
$$\mathrm{R'_3M\cdot + RX \longrightarrow R'_3MX + R\cdot}$$
$$\mathrm{R\cdot + R'_3MH \longrightarrow RH + R'_3M\cdot}$$

SCHEME 11

In general, R'_3SnH and R'_3GeH are too reactive towards the alkyl radical (generated from the alkyl halide) to allow a significant fraction of the alkyl radicals to be trapped by an α, β-unsaturated ketone or aldehyde when stoichiometric amounts of RX, R'_3MH and the unsaturated derivative are employed. For satisfactory yields of the adduct (RCH_2CH_2Z) in Scheme 11, either a large excess of $CH_2{=}CHZ$ or a 'catalytic' amount of R'_3MH must be employed. One technique is to use only 0.2 equivalents of Bu_3SnH and to allow the Bu_3SnX generated in Scheme 11 to be recycled to Bu_3SnH by reaction with $NaBH_4$[67,68]. Using 0.2 equivalent of Bu_3SnH and 5–10 equivalents of $CH_2{=}CHCHO$ or $CH_2{=}CHCOCH_3$, yields of c-$C_6H_{11}CH_2CH_2CHO$ of 90% and c-$C_6H_{11}CH_2CH_2COCH_3$ of 85% have been reported from c-$C_6H_{11}I$[68,69]. Table 6 summarizes the yields of adducts and alkanes observed in reactions of alkyl iodides with 2-cyclohexenone with Bu_3SnH and Bu_3GeH as the hydrogen atom transfer reagents[70].

Intramolecular addition of an alkyl or vinyl radical to a suitably located double bond will not suffer from competition with external Bu_3SnH at normal concentrations. Thus, reaction 19 occurs at 80 °C with azobisisobutyronitrile (AIBN) initiation[71]. The cyclization of reaction 20 occurs in a yield increasing from X = Cl to Br to I[71]. Excellent yields of the tricyclic product are obtained in reaction 21[71] while in reaction 22 the first-formed enolyl radical undergoes a second cyclization of the 5-hexenyl type[72]. Macrocyclic ketones have been synthesized by the reaction of 3–5 mM solutions of ω-iodo-3-keto-1-alkenes with 10% excess of Bu_3SnH in refluxing benzene containing 0.1 equiv of AIBN. Some representative yields are given in Figure 1[73].



R=H, 85%

R=CH$_3$, 83%

(19)

TABLE 6. Reaction of alkyl iodides, 2-cyclohexenone and Bu_3SnH or Bu_3GeH[a]

RI	2-Cyclohexenone (equiv)	M in Bu_3MH (equiv)	Product (% yield) 3-R-cyclohexanone	RH
$C_{11}H_{23}I$	1.25	Ge (1.0)	21	60
$C_{11}H_{23}I$	1.25	Sn (1.0)	3	95
$C_{11}H_{23}I$	10	Ge (1.0)	68	—
c-$C_6H_{11}I$	1.25	Ge (1.0)	31	—
c-$C_6H_{11}I$	1.25	Sn (1.0)	7	—

[a] Reference 70.

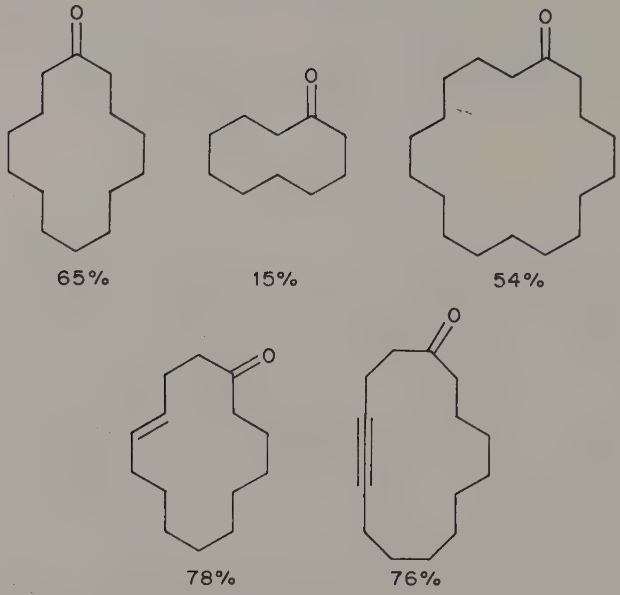
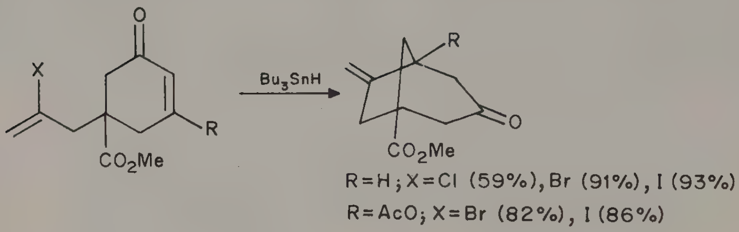
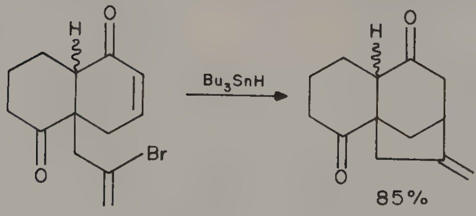


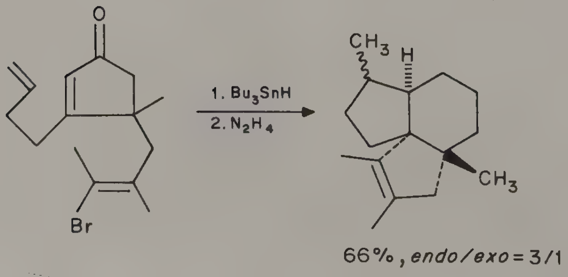
FIGURE 1. Yields of macrocyclic ketones. The 18-membered ring ketone was synthesized under high dilution conditions (after Reference 73)



(20)



(21)



(22)

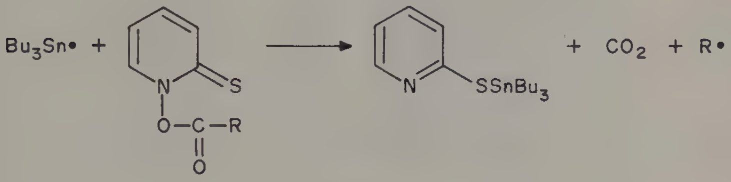
Trialkylstannyl radicals will also generate alkyl radicals by S_H2 displacement on alkyl phenyl selenides (reaction 23)[74], by electron transfer with alkyl mercury halides[75] or *tert*-alkyl nitro compounds (reactions 24 and 25)[76], or by attack at a C=S bond of xanthate esters, thiourethanes (reaction 26)[77] or *O*-acylthiohydroxamates (reaction 27)[78]. All of these processes should be applicable to the addition of an alkyl group and a hydrogen atom in a regioselective manner to an α, β-unsaturated ketone[68].

$$\mathrm{Bu_3Sn\cdot + RSePh \longrightarrow Bu_3SnSePh + R\cdot} \quad (23)$$

$$\mathrm{RHgCl + Bu_3Sn\cdot \longrightarrow Bu_3Sn^+Cl^- + Hg^0 + R\cdot} \quad (24)$$

$$\mathrm{RNO_2 + Bu_3Sn\cdot \longrightarrow Bu_3Sn^+RNO_2^-\cdot \longrightarrow R\cdot + Bu_3SnNO_2} \quad (25)$$

$$\mathrm{Bu_3Sn\cdot + RO{-}C({=}S)X \longrightarrow Bu_3SnSC({=}O)X + R\cdot} \quad (26)$$



(27)

3. *Reactions involving alkylmercury salts and metal hydrides*

The Giese process (reaction 28) has been applied to numerous electron-deficient alkenes including α, β-unsaturated ketones (e.g., $Z = COCH_3$ in reaction 28)[79]. The reaction with $NaBH_4$ involves the formation of RHgH from RHgX (X = halogen, carboxylate), followed by the chain sequence of Scheme 12. When Bu_3SnH is employed, the current evidence[80] favors a chain sequence not involving RHgH but proceeding through reaction 24 (Scheme 13). Table 7 summarizes some reactions of α, β-unsaturated ketones with the $RHgX/NaBH_4$ system.

$$\mathrm{RHgX + CH_2{=}CHZ + NaBH_4 \xrightarrow[CH_2Cl_2]{OH^-} RCH_2CH_2Z + Hg^\circ} \quad (28)$$

$$\begin{gathered}\mathrm{R\cdot + CH_2{=}CHZ \longrightarrow RCH_2\dot{C}HZ}\\ \mathrm{RCH_2\dot{C}HZ + RHgH \longrightarrow RCH_2CH_2Z + RHg\cdot}\\ \mathrm{RHg\cdot \longrightarrow R\cdot + Hg^0}\end{gathered}$$

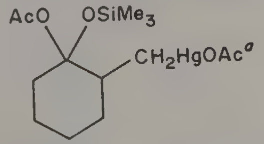
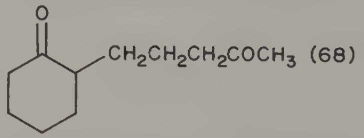
SCHEME 12

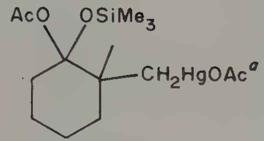
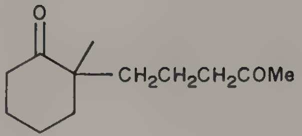
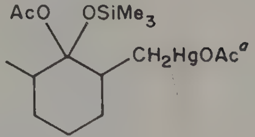
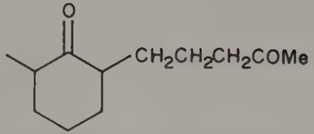
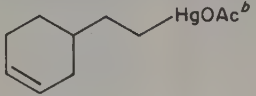
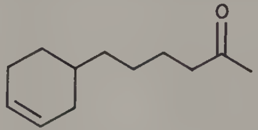
$$\begin{gathered}\mathrm{R\cdot + CH_2{=}CHZ \longrightarrow RCH_2\dot{C}HZ}\\ \mathrm{RCH_2\dot{C}HZ + Bu_3SnH \longrightarrow RCH_2CH_2Z + Bu_3Sn\cdot}\\ \mathrm{Bu_3Sn\cdot + RHgX \longrightarrow Bu_3SnX + Hg^0 + R\cdot}\end{gathered}$$

SCHEME 13

Organomercurials formed by solvomecuration will undergo intramolecular ring closure reactions with appropriate double bonds when treated by $NaBH(OMe)_3$. Thus, reaction 29–31 have been reported[85]. Similar cyclizations have been achieved with N(*o*-allylphenyl)α-methyl acrylamide in which the acrylanilide reacts with $Hg(OAc)_2$ to give the amidomercuration product[86].

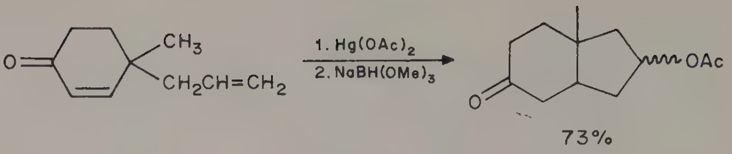
TABLE 7. Reaction of RHgX and $NaBH_4$ with α, β-unsaturated ketones and aldehydes

RHgX	α, β-Unsaturated compound (equiv)	Product (% yield)	Ref.
c-$C_6H_{11}HgOAc$	$CH_2{=}CHCOCH_3$ (3)	c-$C_6H_{11}CH_2CH_2COCH_3$ (70)	81
$C_6H_{13}HgCl$	$CH_2{=}CHCOCH_3$ (3)	$C_8H_{17}COCH_3$ (51)	81
t-BuHgCl	$CH_2{=}CHCOCH_3$ (3)	t-$BuCH_2CH_2COCH_3$ (69)	81
c-$C_6H_{11}HgOAc$	$CH_2{=}CHCHO$ (3)	c-$C_6H_{11}CH_2CH_2CHO$ (27)	81
1-AcO-c-$C_6H_{10}HgCl$	$CH_2{=}CHCOCH_3$ (~ 10)	1-AcO-c-C_6H_{10}—$CH_2CH_2COCH_3$ (43)	82
2-AcO-2-norbornyl HgCl	$CH_2{=}CHCOCH_3$ (~ 10)	2-AcO-2-norbornyl-$CH_2CH_2COCH_3$ (68)	82
	$CH_2{=}CHCOCH_3$		69
$EtC(OAc)(OSiMe_3)CH(Bu)CH_2HgOAc^a$	$CH_2{=}CHCOCH_3$	$EtCOCH(Bu)CH_2CH_2CH_2COMe$ (65)	83
$BuCH_2C(OAc)(OSiMe_3)CH_2CH_2HgOAc^a$	$CH_2{=}CHCOCH_3$	$BuCH_2COCH_2CH_2CH_2CH_2COMe$ (66)	83
$EtC(OAc)(OSiMe_3)CMe_2CH_2HgOAc^a$	$CH_2{=}CHCOCH_3$	$EtCOCMe_2CH_2CH_2CH_2COMe$ (51)	83
$Me_2CHC(OAc)(OSiMe_3)CH_2CH_2HgOAc^a$	$CH_2{=}CHCOCH_3$	$Me_2CHCOCH_2CH_2CH_2CH_2COMe$ (73)	83

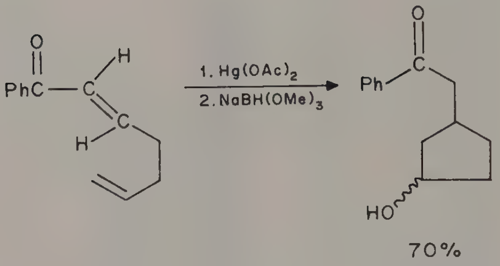
	$CH_2{=}CHCOMe$	 (30)	83
	$CH_2{=}CHCOMe$	 (65)	83
$AcOC(OSiMe_3)_2CH_2CH_2HgOAc^a$	$CH_2{=}CHCOMe$	$MeO_2CCH_2CH_2CH_2CH_2COMe$ (72)	83
$Me_3SiOCH(OAc)CH(Bu)CH_2HgOAc^a$	$CH_2{=}CHCOMe$	$OCHCH(Bu)CH_2CH_2CH_2COMe$ (62)	83
$Me_3SiOCH(OAc)CMe_2CH_2HgOAc^a$	$CH_2{=}CHCOMe$	$OCHCMe_2CH_2CH_2CH_2COMe$ (55)	83
	$CH_2{=}CHCOMe$	 (44)	84

---

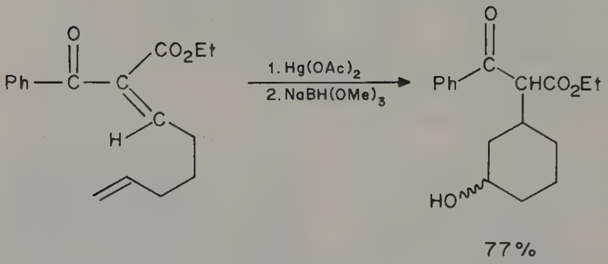
[a] Mercurials formed *in situ* by cleavage of cyclopropyl trimethylsilyl ethers with $Hg(OAc)_2$.
[b] Mercurial formed by reaction of diene with $(c\text{-}C_6H_{11})_3BH$ followed by $Hg(OAc)_2$ cleavage.



(29)



(30)



(31)

B. Alkylation of α,β-Unsaturated Ketones by Free Radical Chain Processes Involving Organometallic Reagents

1. Organoboranes

Alkoxy or peroxy radicals readily displace an alkyl radical from R_3B (reaction 32)[87,88]. A modification of reaction 32 is a key step in the free radical reaction of trialkylboranes with α,β-unsaturated ketones[89] or aldehydes[90] in a reaction stimulated by the presence of traces of oxygen[91,92], acyl peroxides[93] or by photolysis[94] (Scheme 14). Table 8 summarizes alkylation products observed from the hydroboration products of a variety of alkenes (reaction 33). The reaction occurs readily with substituted acroleins including 2-bromoacrolein[94], with α-methylene cycloalkanones[95] and with acetylacetylene[96,97]. Reactions of organoboranes with quinones follow a mechanism similar to Scheme 14[98,99]. A limitation to reaction 33 is that only one alkyl group of R'_3B can be utilized and the reactions are poor for enones such as $Me_2C{=}CHCOMe$ or $CH_2{=}CHCOPh$[97].

$$R'O\cdot(R'OO\cdot) + R_3B \longrightarrow R'OBR_2(R'OOBR_2) + R\cdot \tag{32}$$

$$\begin{gathered}
R\cdot + CH_2{=}CHCOCH_3 \longrightarrow RCH_2CH{=}C(O\cdot)CH_3 \\
RCH_2CH{=}C(O\cdot)CH_3 + R_3B \longrightarrow RCH_2CH{=}C(OBR_2)CH_3 + R\cdot \\
RCH_2CH{=}C(OBR_2)CH_3 + H_2O \longrightarrow RCH_2CH_2COCH_3 + R_2BOH
\end{gathered}$$

SCHEME 14

$$\mathrm{RCH{=}CH_2 + B_2H_6 \longrightarrow R'_3B \xrightarrow[h\nu\ \mathrm{or}\ O_2]{CH_2{=}CHCOCH_3} \xrightarrow{H_2O} R'CH_2CH_2COCH_3} \tag{33}$$

2. *Trialkylaluminum compounds*

Reaction of Pr_3Al with α, β-unsaturated ketones occurs at −78 °C in the presence of traces of oxygen or upon UV irradiation[100]. No reaction is observed in the absence of these initiation processes and the photochemically initiated reaction is completely inhibited by 5 mol% of galvinoxyl. The reaction follows the mechanism of Scheme 14 with R_3Al in place of R_3B. Reaction of equal molar amounts of Pr_3Al with unsaturated ketones at −78 °C with UV irradiation produced 3-propylcyclohexanone (75% in 7 h from 2-cyclohexenone), 4-methyl-2-heptanone (60% in 1 h from 3-penten-2-one) and 2-heptanone (30% in 1 min from methyl vinyl ketone).

3. *Organomercurials*

Carbon or heteroatom-centered acceptor radicals ($R_A\cdot$) readily attack alkyl mercurials (reaction 34)[101]. Electron-deficient alkenes ($CH_2{=}CHZ$) will trap R· and generate an adduct radical ($RCH_2\dot{C}HZ$) which can serve as the acceptor radical in reaction 34[75]. The

$$\mathrm{R_A\cdot + RHgX(or\ R) \rightarrow R_AHgX(or\ R) + R\cdot} \tag{34}$$

overall reaction described in Scheme 15 results. The new mercurial can be reduced by $NaBH_4$ to yield RCH_2CH_2Z or cleaved by iodine to yield $RCH_2CH(I)Z$. Excellent yields of these products are observed with electron-withdrawing substituents (Z) such as $PhSO_2$, $(EtO)_2PO$ or p-$O_2NC_6H_4$. However, the reactions give only poor yields when Z = is COR or CO_2R with RHgCl (R = 1°, 2°, 3°-alkyl). Acetylenic ketones or esters are more reactive and excellent yields of t-BuCH=C(HgCl)COMe or t-BuC(CO_2Et)=C(HgCl)CO_2Et are obtained in photostimulated chain reactions between HC≡CCOMe or $EtO_2CC{\equiv}CCO_2Et$ and t-BuHgCl[75].

$$\mathrm{R\cdot + CH_2{=}CHZ \longrightarrow RCH_2\dot{C}HZ}$$
$$\mathrm{RCH_2\dot{C}HZ + RHgCl \longrightarrow RCH_2CH(Z)HgCl + R\cdot}$$

SCHEME 15

In Me_2SO, the substitution of RHgI for RHgCl in Scheme 15 results in a much more rapid reaction with $CH_2{=}CHZ$ and high yields of alkylation products are observed from α, β-unsaturated ketones[80]. A convenient technique is to employ RHgCl and 1–3 equiv of NaI in Me_2SO. The resulting mercurials [$RCH_2CH(HgX)Z$] are readily hydrolyzed upon work-up to yield RCH_2CH_2Z. Table 9 summarizes the yields of the hydrolysis product observed for three α, β-unsaturated systems in reaction 35.

$$t\text{-}\mathrm{BuHgX + CH_2{=}CHZ \xrightarrow{h\nu} \xrightarrow{H_3O^+}}\ t\text{-}\mathrm{BuCH_2CH_2Z} \tag{35}$$

The excellent yields of the alkylation products observed in the mercury iodide systems may indicate that RHgX is more reactive in reaction 34 when X is iodide than when X is chloride. On the other hand, the iodide ion may be more intimately involved in the reaction. One possibility, involving electron transfer, is shown in Scheme 16. Consistent with Scheme 16, the presence of methanol as a proton donor is observed to increase the yield of the alkylation products of α, β-unsaturated ketones in the iodide systems.

TABLE 8. Reaction of alkene hydroboration products with α,β-unsaturated ketones and aldehydes

Carbonyl compound	Alkene	Product (% yield)	Ref.
$CH_2{=}CHCOMe$	$CH_2{=}CH_2$	BuCOMe (99)	89
$CH_2{=}CHCOMe$	$MeCH{=}CH_2$	n-$C_5H_{11}COMe$ (100)	89
$CH_2{=}CHCOMe$	$EtCH{=}CH_2$	n-$C_6H_{13}COMe$ (85), $EtCH(Me)CH_2CH_2COMe$ (15)	89
$CH_2{=}CHCOMe$	$MeCH{=}CHMe$	$EtCH(Me)CH_2CH_2COMe$ (80)	89
$CH_2{=}CHCOMe$	$Me_2C{=}CH_2$	$Me_2CHCH_2CH_2CH_2COMe$ (65)	89
$CH_2{=}CHCOMe$	$C_6H_{13}CH{=}CH_2$	n-$C_{10}H_{21}COMe$ (85), n-$C_6H_{13}CH(Me)CH_2CH_2COMe$ (15)	89
$CH_2{=}CHCOMe$	$PhCH{=}CH_2$	$PhCH_2CH_2CH_2CH_2COMe$ (55), $PhCH(Me)CH_2CH_2COMe$ (42)	89
$CH_2{=}CHCOMe$	c-C_5H_8	c-$C_5H_9CH_2CH_2COMe$ (99)	89
$CH_2{=}CHCOMe$	c-C_6H_{10}	c-$C_6H_{11}CH_2CH_2COMe$ (100)	89
$CH_2{=}CHCOMe$	norbornene	4-(*exo*-2-norbonyl)-2-butanone (99)	89
$CH_2{=}CHCHO$	$EtCH{=}CH_2$	n-$C_6H_{13}CHO$ (47), $EtCH(Me)CH_2CH_2CHO$ (8)	90
$CH_2{=}CHCHO$	$Me_2C{=}CH_2$	$Me_2CHCH_2CH_2CH_2CHO$ (87)	90
$CH_2{=}CHCHO$	$BuCH{=}CH_2$	n-$C_8H_{17}CHO$ (71), $BuCH(CH_3)CH_2CH_2CHO$ (12)	90
$CH_2{=}CHCHO$	c-C_5H_8	c-$C_5H_9CH_2CH_2CHO$ (88)	90
$CH_2{=}CHCHO$	c-C_6H_{10}	c-$C_6H_{11}CH_2CH_2CHO$ (77)	90
$CH_2{=}CHCHO$	norbornene	3-(*exo*-2-norbornyl)propanal (80)	90
$CH_2{=}C(Me)COMe$	$PrCH{=}CH_2$	n-$C_6H_{13}CH(Me)COMe$ (70), $PrCH(Me)OCH_2C(Me)COMe$ (26)	91
$CH_2{=}C(Me)COMe$	$BuCH{=}CH_2$	n-$C_7H_{16}CH(Me)COMe$ (65), $BuCH(CH_3)CH_2CH(Me)COMe$ (13)	91
$CH_2{=}C(Me)COMe$	$C_6H_{13}CH{=}CH_2$	n-$C_9H_{19}CH(Me)COMe$ (68), n-$C_6H_{13}CH(Me)CH_2CH(Me)COMe$ (9)	91
$CH_2{=}C(Me)COMe$	c-C_5H_8	c-$C_5H_9CH_2CH(Me)COMe$ (88)	91
$CH_2{=}C(Me)COMe$	c-C_6H_{10}	c-$C_6H_{11}CH(Me)COMe$ (100)	92
$MeCH{=}CHCOMe$	$CH_2{=}CH_2$	$EtCH(Me)CH_2COMe_2$ (88)	92, 93
$MeCH{=}CHCOMe$	$EtCH{=}CH_2$	$BuCH(Me)CH_2COMe$ (56), $EtCH(Me)CH(Me)CH_2COMe$ (7)	92

$\mathrm{MeCH{=}CHCOMe}$	$c\text{-}\mathrm{C_6H_{10}}$	$c\text{-}\mathrm{C_6H_{11}CH(Me)CH_2COMe}$ (96)	92, 93
$\mathrm{MeCH{=}CHCOMe}$	$c\text{-}\mathrm{C_5H_8}$	$c\text{-}\mathrm{C_5H_9CH(Me)CH_2COMe}$ (98)	92
$\mathrm{MeCH{=}CHCHO}$	$\mathrm{CH_2{=}CH_2}$	$\mathrm{EtCH(Me)CH_2CHO}$ (60)	92, 93
$\mathrm{MeCH{=}CHCHO}$	$c\text{-}\mathrm{C_6H_{10}}$	$c\text{-}\mathrm{C_6H_{11}CH(Me)CH_2CHO}$ (100)	92, 93
2-cyclohexenone	$\mathrm{CH_2{=}CH_2}$	3-ethylcyclohexanone (95)	92, 93
2-cyclohexenone	$c\text{-}\mathrm{C_6H_{10}}$	3-cyclohexylcyclohexanone (100)	92, 93
2-cyclohexenone	$c\text{-}\mathrm{C_5H_8}$	3-cyclopentylcyclohexanone (96)	92, 93
2-cyclopentenone	$\mathrm{CH_2{=}CH_2}$	3-ethylcyclopentanone (68)	92
2-cyclopentenone	$c\text{-}\mathrm{C_5H_8}$	3-cyclopentylcyclopentanone (85)	92
$\mathrm{MeCH{=}CHCHO}$	$\mathrm{EtCH{=}CH_2}$	$\mathrm{BuCH(Me)CH_2CHO}$ (54), $\mathrm{PrCH(Me)CH(Me)CH_2CHO}$ (6)	92
$\mathrm{MeCH{=}CHCHO}$	$\mathrm{MeCH{=}CHMe}$	$\mathrm{EtCH(Me)CH(Me)CH_2CHO}$ (90)	92
$\mathrm{MeCH{=}CHCHO}$	$\mathrm{Me_2C{=}CH_2}$	$\mathrm{Me_2CHCH_2CH(Me)CH_2CHO}$ (50)	92
$\mathrm{CH_2{=}C(Br)CHO}$	$\mathrm{EtCH{=}CH_2}$	$\mathrm{C_5H_{11}CH(Br)CHO}$ (85)	94
$\mathrm{CH_2{=}C(Br)CHO}$	$\mathrm{MeCH{=}CHMe}$	$\mathrm{EtCH(Me)CH_2CH(Br)CHO}$ (81)	94
$\mathrm{CH_2{=}C(Br)CHO}$	$\mathrm{Me_2C{=}CH_2}$	$\mathrm{Me_2CHCH_2CH_2CH(Br)CHO}$ (80)	94
$\mathrm{CH_2{=}C(Br)CHO}$	$c\text{-}\mathrm{C_6H_{10}}$	$c\text{-}\mathrm{C_6H_{11}CH_2CH(Br)CHO}$ (65)	94
$\mathrm{CH_2{=}C(Me)CHO}$	$\mathrm{MeCH{=}CHMe}$	$\mathrm{EtCH(Me)CH_2CH(Me)CHO}$ (95)	94
$\mathrm{CH_2{=}C(Me)CHO}$	$\mathrm{Me_2C{=}CH_2}$	$\mathrm{Me_2CHCH_2CH_2CH(Me)CHO}$ (95)	94
$\mathrm{CH_2{=}C(Me)CHO}$	$c\text{-}\mathrm{C_6H_{10}}$	$c\text{-}\mathrm{C_6H_{11}CH_2CH(Me)CHO}$ (92)	94
$\mathrm{CH_2{=}C(Me)CHO}$	norbornene	2-methyl-3-(*exo*-2-norbornyl)propanal (97)	94
2-methylenecyclopentanone	$\mathrm{CH_2{=}CH_2}$	2-propylcyclopentanone (90)	95
2-methylenecyclohexanone[a]	$\mathrm{CH_2{=}CH_2}$	2-propylcyclohexanone (85)	95
2-methylenecyclohexanone[a]	$\mathrm{MeCH{=}CHMe}$	2-(2-methylbutyl)cyclohexanone (61)	95
	$c\text{-}\mathrm{C_5H_8}$	2-(cyclopentylmethyl)cyclohexanone (90)	95
3-methylenenorbornane-2-one[a]	$\mathrm{CH_2{=}CH_2}$	3-*n*-propylnorbornan-2-one (94)	95
$\mathrm{HC{\equiv}CCOCH_3}$	$\mathrm{CH_2{=}CH_2}$	$\mathrm{EtCH{=}CHCOCH_3}$ (77)	96
$\mathrm{HC{\equiv}CCOCH_3}$	$\mathrm{EtCH{=}CH_2}$	$\mathrm{BuCH{=}CHCOCH_3}$ (72)	96
$\mathrm{HC{\equiv}CCOCH_3}$	$\mathrm{MeCH{=}CHMe}$	$\mathrm{EtCH(Me)CH{=}CHCOCH_3}$ (47)	96
$\mathrm{HC{\equiv}CCOCH_3}$	$\mathrm{Me_2C{=}CH_2}$	$\mathrm{Me_2CHCH_2CH{=}CHCOCH_3}$ (34)	96
$\mathrm{HC{\equiv}CCOCH_3}$	$c\text{-}\mathrm{C_5H_8}$	$c\text{-}\mathrm{C_5H_9CH{=}CHCOCH_3}$ (65)	96
$\mathrm{HC{\equiv}CCOCH_3}$	$c\text{-}\mathrm{C_6H_{10}}$	$c\text{-}\mathrm{C_6H_{11}CH{=}CHCOCH_3}$ (65)	96
$\mathrm{HC{\equiv}CCOCH_3}$	norbornene	4-(*exo*-2-norbornyl)-3-buten-2-one (67)	96

[a] Formed *in situ* by reaction of MeI and $\mathrm{K_2CO_3}$ with the Mannich bases of the cycloalkanones.

TABLE 9. Effect of the anion X in reaction 35

t-BuHgX (equiv; equiv NaI, time)	% Yield of β-*t*-butylation product[a]		
	$CH_2{=}CHCOMe$	2-Cyclohexenone	$CH_2{=}CHCO_2Et$
t-BuHgCl (2, 0, 10 h)	6.5	35	5.0
t-BuHgI (1, 0, 2 h)	70[b]	82[b]	88[b]
t-BuHgCl (2, 2, 6 h)	85	85	80[b]

[a] Reactions were irradiated by a 275W sunlamp in Me_2SO at 40 °C.
[b] Solvent was a mixture of Me_2SO and MeOH (60%:40%).

$$\begin{gathered} R\cdot + CH_2{=}CHCOCH_3 \longrightarrow RCH_2\dot{C}HCOCH_3 \\ RCH_2\dot{C}HCOCH_3 + I^- \longrightarrow RCH_2CH{=}C(O^-)CH_3 + I\cdot \\ I\cdot + RHgI \longrightarrow R\cdot + HgI_2 \end{gathered}$$

SCHEME 16. R = *t*-Bu·

C. Acylation and Alkylation of α,β-Unsaturated Ketones by Co(III) Species

1. *Acylation*

The simultaneous irradiation (incandescent light) and electrolytic reduction in DMF of a mixture of a carboxylic anhydride and an α,β-unsaturated ketone in the presence of catalytic amounts of vitamin B_{12}, or a similar Co(III) complex, results in acylation (reaction 36)[102]. The reduction potential of the system is much lower with irradiation and reaction occurs at potentials where none of the reactants is reduced. The reaction appears to form acyl Co(III) intermediates, which can be photolyzed to acyl radicals and an easily reduced Co(II) species (Scheme 17). Addition of $R\dot{C}{=}O$ to the α,β-unsaturated ketone or aldehyde in a regioselective manner produces an enolyl radical which would be readily reduced to the enolate anion (reaction 37). Yields of the observed 1,4-dicarbonyl compounds are summarized in Table 10[102].

$$(R^1CO)_2O + R^3HC{=}CR^2COZ \xrightarrow[\text{DMF}, B_{12}]{e^-,\, h\nu} R^1C(O)CHR^3CHR^2COZ + R^1CO_2 \qquad (36)$$

$$\begin{aligned} R^1\dot{C}{=}O + R^3CH{=}CR^2C(O)Z &\longrightarrow R^1C({=}O)CHR^3{-}CR^2{=}C(O\cdot)Z \\ &\xrightarrow{e^-} R^1C({=}O)CHR^3{-}CR^2{=}C(O^-)Z \end{aligned} \qquad (37)$$

$$\begin{gathered} RC({=}O){-}Co(III) \xrightarrow{h\nu} R\dot{C}{=}O + \cdot Co(II) \\ \cdot Co(II) + e^- \longrightarrow :Co(I)^- \\ :Co(I)^- + (RCO)_2O \longrightarrow RC({=}O){-}Co(III) + RCO_2{}^- \end{gathered}$$

SCHEME 17

TABLE 10. Formation of 1,4-dicarbonyl compounds by acylation of α,β-unsaturated ketones and aldehydes (reaction 36)[a]

	α,β-Unsaturated Compound			
Anhydride, R^1	R^2	R^3	Z	Product (% yield)[b]
CH_3	H	H	CH_3	$CH_3COCH_2CH_2COCH_3$ (63)
n-C_6H_{13}	H	H	CH_3	n-$C_6H_{13}COCH_2CH_2COCH_3$ (55)
CH_3	2-cyclopentenone			3-acetylcyclopentanone (42)
CH_3	2-cyclohexenone			3-acetylcyclohexanone (40)
CH_3	H	H	H	$CH_3COCH_2CH_2CHO$ (47)
n-C_6H_{13}	H	H	H	n-$C_6H_{13}COCH_2CH_2CHO$ (71)
CH_3	H	CH_3	H	$CH_3COCH(CH_3)CH_2CHO$ (50)
n-C_6H_{13}	H	CH_3	H	n-$C_6H_{13}COCH(CH_3)CH_2CHO$ (80)
CH_3	CH_3	H	H	$CH_3COCH_2CH(CH_3)CHO$ (34)
CH_3	CH_3	CH_3	H	$CH_3COCH(CH_3)CH(CH_3)CHO$ (30)
$CH_3O_2C(CH_2)_7$	H	H	CH_3	$CH_3O_2C(CH_2)_7COCH_2CH_2COCH_3$ (> 65)[c]

[a] Reference 102.

[b] Ratio of anhydride: unsaturated compound: B_{12} = 0.5–2:1.0:0.02–0.10. Irradiation with two 500 W incandescent bulbs with electrolysis in DMF (0.3 N $LiClO_4$) at a constant potential of − 0.95 V (vs. SCF) at a Hg pool cathode in a divided H-cell.

[c] Reference 103.

2. Alkylation

Reactions of alkyl or 1-alkenyl bromides or iodides with α, β-unsaturated ketones in the presence of vitamin B_{12} or similar Co(III) compounds occurs upon electrolysis. In certain cases, photolysis increases the rate and improves the yield[103]. Intramolecular cyclizations are summarized in Figure 2 using vitamin B_{12a} or dibromo(1-hydroxy-8H-HDP)cobalt(III)[104].

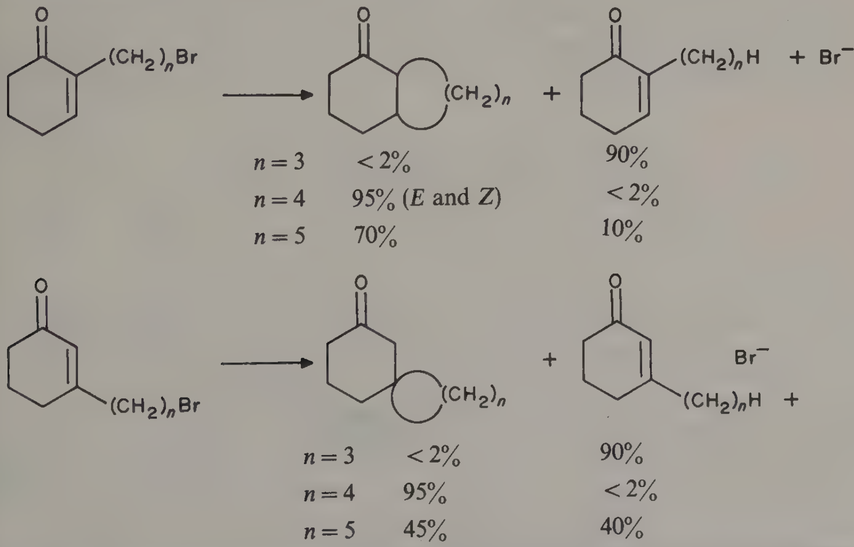
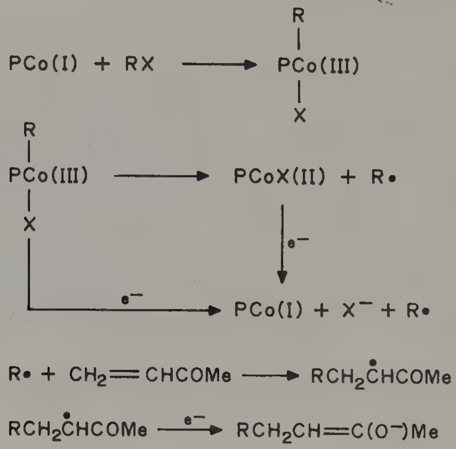


FIGURE 2. Yields of intramolecular cyclization products observed upon electrolysis (NH_4Br in DMF) in the presence of 5 mol% of vitamin B_{12a} (after Reference 104)

The reactions of Figure 2 occur at a reduction potential below that at which the α,β-unsaturated ketone is reduced. Scheme 18 gives a likely reaction pathway, where P is a univalent porphyrin ligand.



SCHEME 18

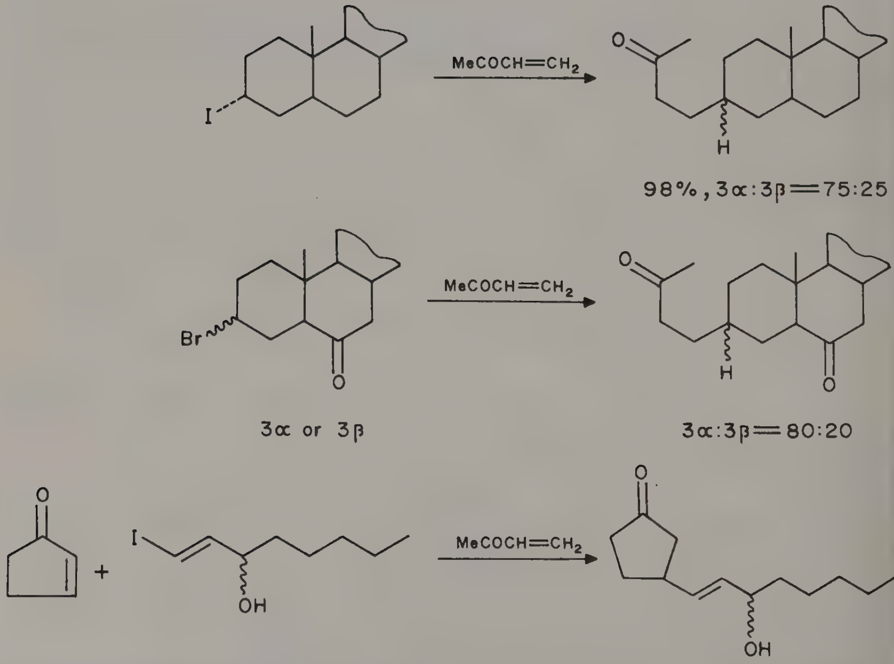
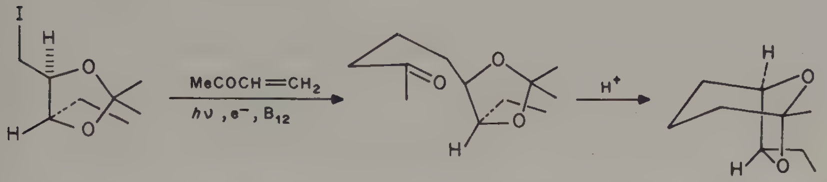


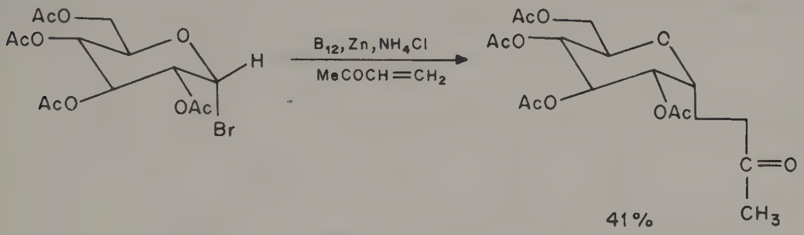
FIGURE 3. Intermolecular alkylation and alkenylation reactions observed upon electrolysis in the presence of vitamin B_{12} in DMF, NH_4Cl

Photochemical activation may be involved in the cleavage of PCo(R)(X) to give the alkyl radical. Combined electrolysis and photolysis have been used in the synthesis of 1*R*, 5*S*, 7*R*-exo-brevicomin (reaction 38)[103]. Some other intermolecular reactions are summarized in Figure 3[103,105].



(38)

Electrons can be supplied to the catalytic cycle of Scheme 18 by dissolving metals. Thus, in DMF in the presence of NH_4Cl, reaction 39 occurs[106]. This reaction is related to the catalytic effect of B_{12} in the electrochemical reduction of α, β-unsaturated ketones in the presence of zinc and acetic acid where alkyl cobalt intermediates are believed to be involved[107].



(39)

D. Substitutive Alkylations of Vinyl Ketones

Alkylation by a free radical chain process involving radical addition and elimination occurs readily with alkylmercury halides, where X in Scheme 19 can be HgCl, R_3Sn, halogen, $PhSO_2$[80]. The reaction occurs for both 1-alkenyl and 1-alkynyl derivatives[108,109].

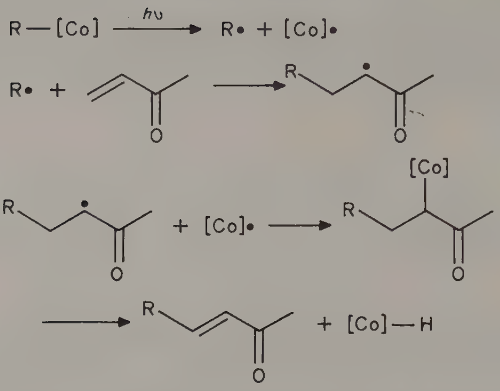
$$R\cdot + R'CH{=}CHX \longrightarrow R'\dot{C}H{-}CH(X)R$$

$$R'CH{-}CH(X)R \longrightarrow R'CH{=}CHR + X\cdot$$

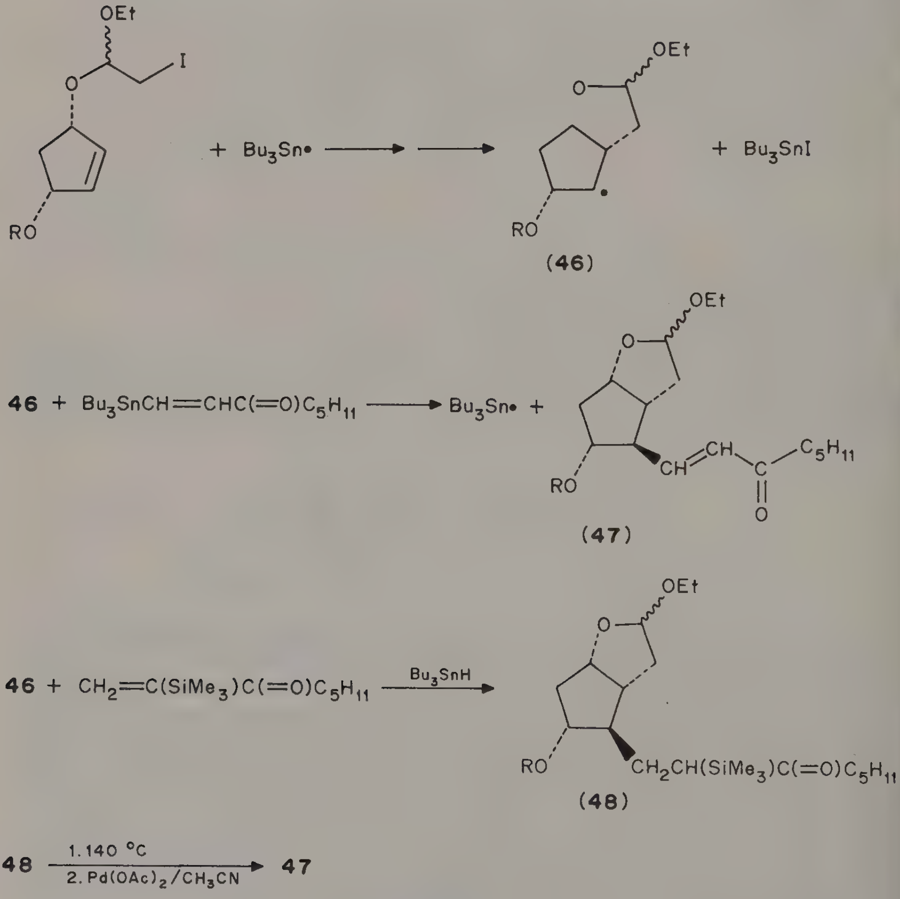
$$X\cdot + RHgCl \longrightarrow R\cdot + XHgCl$$

SCHEME 19 ($R' = Ph, PhCO, EtO_2C, Cl, PhSO_2$)

Reaction of (*E*)-PhCOCH=CHCl with *t*-BuHgCl (5 equiv) with sunlamp irradiation in Me_2SO at 35–40 °C gives a 68% yield of (*E*)-PhCOCH=CHBu-*t* in 2 h[110]. The yield is increased to 100% in the presence of 10 equiv of NaI for 1 h. The iodide may increase the efficiency of the reaction by electron transfer with the β-eliminated chlorine atom or by exchange with *t*-BuHgCl to form the more reactive *t*-BuHgI. In chain reactions involving attack of an acceptor radical [e.g. halogen atom, PhS·, PhSe·, $RCH_2\dot{C}HP(O)(OEt)_2$] upon RHgCl, a relative reactivity sequence of *tert*-butyl > isopropyl ≫ *n*-butyl is observed[75]. Thus, (*E*)-PhCOCH=CHCl and *i*-PrHgCl (5 equiv) yields < 10% of PhCOCH=CHPr-*i* upon irradiation for 18 h in Me_2SO. However, in the presence of 10 equiv of NaI the yield is increased in 2 h to 62% of PhCOCH=CHPr-*i* with a *E*/*Z* ratio of 32[110]. Substitutions following Scheme 19 are more apt to be stereospecific (with retention) when the β-elimination reaction occurs more readily, i.e. I > Br > Cl[108].



SCHEME 20 ([Co] = pyridine complex of cobalt 'salophen' reagent)



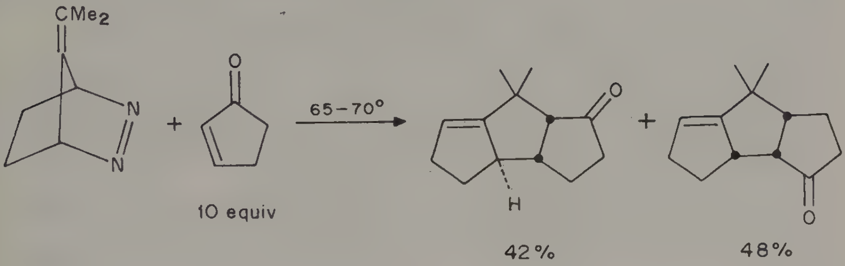
SCHEME 21

Photolysis of alkylcobaloximes in the presence of α,β-unsaturated ketones leads to substitution of a β-hydrogen atom[111]. The reaction is presumed to be the nonchain process described in Scheme 20.

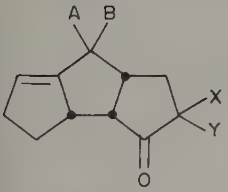
Radicals generated by stannyl radical attack upon alkyl iodides will undergo regioselective β-attack upon β-stannyl enones to form the β-alkylated enone and regenerate the stannyl radical[112]. This procedure has been used for the synthesis of a precursor to prostaglandin F_{2a}. In an alternate route to the prostaglandin, a cyclized cyclopentyl radical was added to $CH_2{=}CH(SiMe_3)C({=}O)C_5H_{11}$ in the presence of tributyltin hydride. Rearrangement of the resulting α-trimethylsilyl-β-cyclopentyl ketone to the enol silyl ether followed by oxidation to the α,β-unsaturated ketone also gave a precursor to the prostaglandin (Scheme 21)[113].

E. Diyl Trapping Reactions

Thermolysis of cyclic azo compounds produces diradicals, which can be trapped by α,β-unsaturated ketones but with low stereo- and regioselectivities. Reaction 40 illustrates the formation of tricyclopentanoids from an azo precursor of a trimethylenemethane diradical[114]. In a similar fashion, **49a** and **49b** were synthesized. Intramolecular ring closure of the trimethylenemethane diradical involving the carbonyl group of an acyl substituent has also been observed (reaction 41)[115].



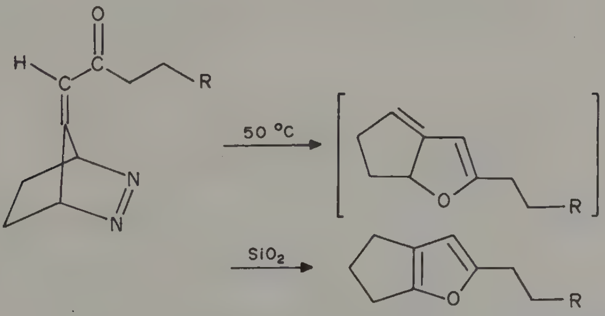
(40)



(**49**)

(**a**) A=B=X=Me; Y=EtO_2C; 50%

(**b**) A=X=Y=H; B=*p*-$MeOC_6H_4$; 24–30%



(41)

R=Et, 87% R=$CH_2{=}CH$, 70%

III. REFERENCES

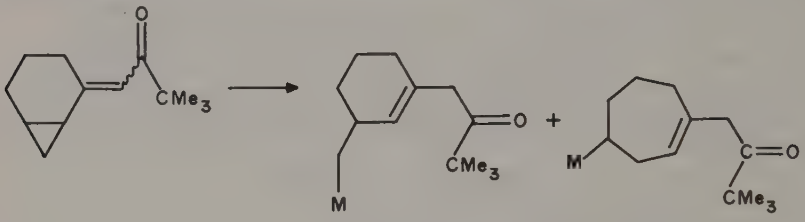
1. J. W. Lown, *Can. J. Chem.*, **43**, 2571, 3294 (1965); *J. Phys. Chem.*, **70**, 591 (1969).
2. H.-L. J. Chen and M. Bersohn, *Mol. Phys.*, **13**, 573 (1967).
3. K. W. Bowers, R. W. Giese, J. Grimshaw, H. O. House, N. H. Kolodny, K. Kronberger and D. R. Roe, *J. Am. Chem. Soc.*, **92**, 2783 (1970).
4. G. A. Russell and G. R. Stevenson, *J. Am. Chem. Soc.*, **93**, 7091 (1971).
5. B. C. Gilbert, R. G. G. Holmes and R. O. C. Norman, *J. Chem. Res.*, 1 (1977).
6. M. Simic, P. Neta and E. Haydon, *J. Phys. Chem.*, **77**, 2662 (1973).
7. I. H. Elson, T. J. Kemp, D. Greatorex and H. D. B. Jenkins, *Trans. Faraday Soc. II*, **69**, 665 (1973).
8. K. D. Asmus, A. Henglein, A. Wigger and G. Beak, *Ber. Bunsenges Phys. Chem.*, **70**, 756 (1966).
9. I. H. Elson, T. J. Kemp and T. J. Stone, *J. Chem. Soc.*, **93**, 7091 (1971).
10. J. Harbour and A. V. Guzzo, *Mol. Phys.*, **20**, 565 (1971).
11. G. A. Russell, R. L. Blankespoor, J. Mattox, P. R. Whittle, D. Symalla and J. R. Dodd, *J. Am. Chem. Soc.*, **96**, 7249 (1974).
12. G. A. Russell, M. Ballenegger and H. L. Malkus, *J. Am. Chem. Soc.*, **97**, 1900 (1975).
13. F. Gerson, R. Gleiter, G. Moshuk and A. S. Dreiding, *J. Am. Chem. Soc.*, **96**, 2342 (1974).
14. A. I. Prokof'ev, S. D. Solodovnikov, A. A. Volod'kin and V. V. Ershov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1712 (1968).
15. A. I. Prokof'ev, N. N. Bubnov, S. D. Solodovnikov, I. I. Prokof'eva, A. A. Volod'kin and V. V. Ershov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2337 (1975).
16. P. H. Kasai and D. McLeod, *J. Am. Chem. Soc.*, **96**, 2342 (1974).
17. J. Moan and O. Kaalhus, *J. Chem. Phys.*, **61**, 3556 (1974).
18. P. Devolder and P. Goudmand, *C.R. Acad. Sci. Paris, Ser. C*, **280**, 1281 (1975).
19. R. W. Fessenden and R. H. Schuler, *J. Chem. Phys.*, **38**, 773 (1963).
20. D. H. Whiffen, *Mol. Phys.*, **6**, 223 (1963).
21. G. A. Russell, R. L. Blankespoor, K. D. Trahanovsky, C. S. C. Chung, P. R. Whittle, J. Mattox, C. L. Myers, R. Penny, T. Ku, Y. Kosugi and R. S. Givens, *J. Am. Chem. Soc.*, **97**, 1906 (1975).
22. N. K. Ray, P. T. Narasimhav and R. K. Gupta, *Indian J. Pure Appl. Phys.*, **7**, 175 (1969).
23. G. A. Russell and R. L. Blankespoor, *Tetrahedron Lett.*, 4573 (1971).
24. Y. Ikegami and S. Seto, *Bull. Chem. Soc. Jpn.*, **41**, 2225 (1968).
25. F. Gerson, G. Moshuk, C. Wydler and M. J. Goldstein, *Org. Magn. Reson.*, **6**, 667 (1974).
26. G. A. Russell, K. D. Schmitt and J. Mattox, *J. Am. Chem. Soc.*, **97**, 1882 (1975).
27. G. A. Russell, in *Aspects of Mechanism and Organometallic Chemistry* (Ed. J. H. Brewster), Plenum Press, New York, 1978, p. 59.
28. A. J. Birch, H. Smith and R. E. Thornton, *J. Chem. Soc.*, 1339 (1957).
29. G. Stork, P. Rosen and N. L. Goldman, *J. Am. Chem. Soc.*, **83**, 2965 (1961).
30. G. Stork and S. D. Darling, *J. Am. Chem. Soc.*, **82**, 1512 (1960).
31. D. Caine, *Org. React.*, **23**, 1 (1976).
32. H. O. House and P. D. Weeks, *J. Am. Chem. Soc.*, **97**, 2770 (1975).
33. S. W. Staley, *Sel. Org. Transform.*, **2**, 309 (1972).
34. H. O. House and P. D. Weeks, *J. Am. Chem. Soc.*, **97**, 2778 (1975).
35. R. B. Bates, G. Büchi, T. Matsuura and R. R. Shaffer, *J. Am. Chem. Soc.*, **82**, 2327 (1960).
36. D. A. Dunn, D. I. Schuster and R. Bonneau, *J. Am. Chem. Soc.*, **107**, 2802 (1985); D. I. Schuster, R. Bonneau, D. A. Dunn, J. M. Rao and J. M. Joussot-Dubien, *J. Am. Chem. Soc.*, **106**, 2706 (1984).
37. R. C. Cookson, J. Hudec and N. A. Mirza, *Chem. Commun.*, 824 (1967).
38. R. C. Cookson, J. Hudec and N. A. Mirza, *Chem. Commun.*, 180 (1968).
39. N. J. Pienta, *J. Am. Chem. Soc.*, **106**, 2704 (1984).
40. N. J. Pienta and S. E. McKimmey, *J. Am. Chem. Soc.*, **104**, 5501 (1982).
41. N. J. Pienta, *Tetrahedron Lett.*, **25**, 915 (1984).
42. D. I. Schuster, I. M. Numez and C. B. Char, *Tetrahedron Lett.*, **22**, 1187 (1981).
43. D. von Bellus, R. Kearns and K. Schaffner, *Helv. Chem. Acta*, **52**, 971 (1969).
44. U.-C. Yoon, J.-U. Kim, E. Hasegawa and P. S. Mariano, *J. Am. Chem. Soc.*, **109**, 4421 (1987).
45. G. A. Russell, E. G. Janzen and E. T. Strom, *J. Am. Chem. Soc.*, **86**, 1807 (1964).
46. E. C. Ashby, J. Laemule, and H. M. Neumann, *Acc. Chem. Res.*, **7**, 272 (1974).
47. K. Maruyama and T. Katagiri, *J. Am. Chem. Soc.*, **108**, 6263 (1986).

48. H. O. House, *Acc. Chem. Res.*, **9**, 59 (1976).
49. A. Nilsson and A. Ronlan, *Tetrahedron Lett.*, 1107 (1975).
50. D. J. Hannah and R. A. J. Smith, *Tetrahedron Lett.*, 187 (1975).
51. S. A. Marshall and R. A. Ruden, *J. Org. Chem.*, **37**, 659 (1972).
52. H. O. House and P. D. Weeks, *J. Am. Chem. Soc.*, **97**, 2785 (1975).
53. D. Griller and K. U. Ingold, *Acc. Chem. Res.*, **13**, 317 (1980).
54. H. O. House and E. F. Kinloch, *J. Org. Chem.*, **39**, 1173 (1974).
55. G. A. Russell and J. Lokensgard, *J. Am. Chem. Soc.*, **89**, 5059 (1967).
56. I. B. Anfanas'ev, *Russ. Chem. Res.*, **40**, 216 (1971).
57. C. M. Starks, *Free Radical Telomerization*, Academic Press, New York, 1974.
58. B. N. Nicolet, *J. Am. Chem. Soc.*, **57**, 1098 (1935).
59. R. Brown, W. E. Jones and A. R. Pinder, *J. Chem. Soc.*, 2123 (1951).
60. H. Behringer, *Liebigs Ann. Chem.*, **564**, 219 (1949).
61. T. M. Patrick, *J. Org. Chem.*, **17**, 1009 (1952).
62. E. C. Ladd, U. S. Patent 2,621,212 (1952); *Chem. Abstr.*, **47**, 9351e (1953).
63. M. Lesbre and Z. Satgé, *C.R. Acad. Sci. Paris, Ser. C*, **247**, 471 (1958).
64. M. C. Henry and M. E. Downey, *J. Org. Chem.*, **26**, 2299 (1961).
65. H. G. Kuivila, L. W. Menapace and C. R. Warner, *J. Am. Chem. Soc.*, **84**, 3584 (1962).
66. L. J. Johnston, J. Lusztyk, D. D. M. Wagner, A. N. Abeywickreyma, A. L. J. Beckwith, J. C. Scaiano and K. U. Ingold, *J. Am. Chem. Soc.*, **107**, 4594 (1985).
67. E. J. Corey and J. W. Suggs, *J. Org. Chem.*, **40**, 2554 (1975).
68. B. Giese, J. A. Gonzáles-Gómez and T. Witzel, *Angew. Chem., Int. Ed. Engl.*, **23**, 69 (1984).
69. B. Giese, *Angew. Chem., Int. Ed. Engl.*, **24**, 553 (1985).
70. P. Pike, S. Hershberger and J. Hershberger, *Tetrahedron Lett.*, **26**, 6289 (1985).
71. N. N. Marinovic and H. Ramanathan, *Tetrahedron Lett.*, **23**, 2575 (1982).
72. D. P. Curran and S. C. Kuo, *J. Am. Chem. Soc.*, **108**, 1106 (1986).
73. N. A. Porter, D. R. Magnin and B. T. Wright, Preprints of Papers, Div. of Petroleum Chem., Am. Chem. Soc., **31**, 875 (1986).
74. S. D. Burke, W. F. Fobare and D. M. Armistead, *J. Org. Chem.*, **47**, 3348 (1982).
75. G. A. Russell, W. Jiang, S. S. Hu and R. K. Khanna, *J. Org. Chem.*, **51**, 5498 (1986).
76. D. D. Tanner, E. V. Blackburn and G. E. Diaz, *J. Am. Chem. Soc.*, **103**, 1557 (1981).
77. D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1*, 1574 (1975).
78. D. H. R. Barton, D. Crich and W. B. Motherwell, *Chem. Commun.*, 939 (1983).
79. B. Giese, *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*, Pergamon Press, Oxford, 1986.
80. G. A. Russell and D. Guo *Tetrahedron Lett.*, **25**, 5239 (1984).
81. B. Giese and J. Meister, *Chem. Ber.*, **110**, 2588 (1977).
82. B. Giese and U. Erfort, *Chem. Ber.*, **116**, 1240 (1983).
83. B. Giese and H. Horler, *Tetrahedron*, **41**, 4025 (1985).
84. B. Giese and G. Kretzschmar, *Angew. Chem., Int. Ed. Engl.*, **20**, 965 (1981).
85. S. Danishefsky, S. Chackalamanni and B. J. Vang, *J. Org. Chem.*, **47**, 2231 (1982).
86. S. Danishefsky and E. Taniyama, *Tetrahedron Lett.*, **24**, 15 (1983).
87. A. G. Davies and B. P. Roberts, *Acc. Chem. Res.*, **5**, 387 (1972).
88. H. C. Brown, M. M. Midland and G. W. Kabalka, *J. Am. Chem. Soc.*, **93**, 1024 (1971).
89. A. Suzuki, A. Arase, H. Matsumoto, M. Itoh, H. C. Brown, M. M. Rogić and M. W. Rathke, *J. Am. Chem. Soc.*, **89**, 5708 (1967).
90. H. C. Brown, M. M. Rogić, M. W. Rathke and G. W. Kabalka, *J. Am. Chem. Soc.*, **89**, 5709 (1967).
91. G. W. Kabalka, H. C. Brown, A. Suzuki, S. Honma, A. Arase and M. Itoh, *J. Am. Chem. Soc.*, **92**, 710 (1970).
92. H. C. Brown and G. W. Kabalka, *J. Am. Chem. Soc.*, **92**, 714 (1970).
93. H. C. Brown and G. W. Kabalka, *J. Am. Chem. Soc.*, **92**, 712 (1970).
94. H. C. Brown, G. W. Kabalka, M. W. Rathke and M. M. Rogić, *J. Am. Chem. Soc.*, **90**, 4165 (1968).
95. H. C. Brown, M. W. Rathke, G. W. Kabalka and M. M. Rogić, *J. Am. Chem. Soc.*, **90**, 4166 (1968).
96. A. Suzuki, S. Nozawa, M. Itoh, H. C. Brown and G. W. Kabalka, *J. Am. Chem. Soc.*, **92**, 3503 (1970).

97. N. Sasaki, N. Miyaura, M. Itoh and A. Suzuki, *Synthesis*, 317 (1975).
98. G. W. Kabalka, *J. Organomet. Chem.*, **33**, C25 (1971).
99. G. W. Kabalka, *Intra-Sci. Chem. Rep.*, **7**, 57 (1973).
100. G. W. Kabalka and R. F. Daley, *J. Am. Chem. Soc.*, **95**, 4428 (1973).
101. G. A. Russell and H. Tashtoush, *J. Am. Chem. Soc.*, **105**, 1398 (1983).
102. R. Scheffold and R. Orlinski, *J. Am. Chem. Soc.*, **105**, 7200 (1983).
103. R. Scheffold, *Chimia*, **39**, 203 (1985).
104. R. Scheffold, M. Dike, S. Dike, T. Herold and L. Walder, *J. Am. Chem. Soc.*, **102**, 3642 (1980).
105. R. Scheffold, G. Rytz, L. Walder, R. Orlinski and Z. Chilmonczyk, *Pure Appl. Chem.*, **55**, 1791 (1983).
106. S. Albrecht and R. Scheffold, *Chimia*, 211 (1985).
107. A. Fischli and D. Süss, *Helv. Chim. Acta*, **62**, 48, 2361 (1979).
108. G. A. Russell and P. Ngoviwatchai, *Tetrahedron Lett.*, **26**, 4975 (1985).
109. G. A. Russell and P. Ngoviwatchai, *Tetrahedron Lett.*, **27**, 3479 (1986).
110. G. A. Russell, S. Hu, S. Herron, W. Baik, P. Ngoviwatchai, W. Jiang and M. Nebgen, *J. Phys. Org. Chem.*, **1**, 299 (1988).
111. V. F. Patel and G. Pattenden, *J. Chem. Soc., Chem. Commun.*, 871 (1987).
112. G. E. Keck and D. A. Burnett, *J. Org. Chem.*, **52**, 2960 (1987).
113. G. Stork, P. M. Sher and H.-L. Chen, *J. Am. Chem. Soc.*, **108**, 6384 (1986).
114. R. D. Little, A. Bukhari and M. G. Venegas, *Tetrahedron Lett.*, **20**, 304 (1979).
115. K. D. Moeller and R. D. Little, *Tetrahedron Lett.*, **26**, 3417 (1985).

Note Added in Proof (see page 491)

Conversion of **i** to **ii** (M = R) has been considered to involve electron transfer in the reaction with an alkyl cuprate (H. O. House and K. A. J. Snoble, *J. Org. Chem.*, **41**, 3076 (1976)) although other interpretations are possible (e.g. C. P. Casey and M. C. Cesa, *J. Am. Chem. Soc.*, **101**, 4236 (1979).



(I) (II) (III)

Although **i** with Li/HMPA/*t*-BuOH forms only **ii** (M = H), with Me_3SnLi or Me_3SiCl in THF or HMPA, **i** yields a mixture of **ii** and **iii** with M = Me_3Sn or Me_3Si (R. T. Taylor and J. G. Galloway, *Tetrahedron Lett.*, **23**, 3147 (1982)). It is suggested that the direction of ring opening for $\mathbf{i}^{-}$ is influenced by the size of the reducing agent (Li^0, $Me_3Si{:}^-$, $Me_3Sn{:}^-$). Both $Me_3Sn{:}^-$ and $Me_3Si{:}^-$ are known to undergo conjugate additions to α,β-unsaturated carbonyl systems (W. C. Still, *J. Org. Chem.*, **41**, 3063 (1976)), but it has been argued that $Me_3Si{:}^-$ reacts by electron transfer whereas $Me_3Sn{:}^-$ adds by nucleophilic attack because of a lower steric requirement for the stannyl system (W. C. Still, *J. Am. Chem. Soc.*, **99**, 4836 (1977)). With 2-cyclohexenones, Me_3SnLi in THF yields the conjugate addition product via the facile rearrangement of the kinetically preferred adduct to the carbonyl group (W. C. Still and A. Mitra, *Tetrahedron Lett.*, 2659 (1978)).

The Chemistry of Enones
Edited by S. Patai and Z. Rappoport

CHAPTER 12

The reaction of enones with electrophiles

KLAUS MÜLLEN and PETER WOLF

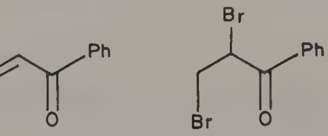
Department of Organic Chemistry, University of Mainz, J. J. Becher-Weg 18–20, D-6500 Mainz, FRG

I. INTRODUCTION

The carbonyl group of a conjugated enone is known to decrease the electron density in the $C_\alpha C_\beta$ double bond. Thus, while the carbonyl atom and the β-ethylenic carbon are activated for nucleophilic attack (see structure **1**), the olefinic unit should be less susceptible to direct electrophilic attack than simple olefins. A typical example is the epoxidation of olefins which proceeds smoothly upon reaction with electrophilic peracids[1], while that of enones requires more vigorous conditions[2] and is most commonly performed with the nucleophilic system H_2O_2/NaOH (see Section VI)[3].

(1)

It appears somewhat surprising in view of this situation that enones have been shown to react instantaneously with a number of rather mild electrophiles such as acetyl hypofluorite[4], that phenyl vinyl ketone (**2**) reacts almost explosively with bromine in methylene chloride[5] to yield **3** and that enones readily undergo hydration in aqueous acidic media[6].



(2) (3)

The fundamental questions for an understanding of the reactions between enones and electrophiles are the following: (1) What is the mechanistic difference between electrophilic attack on an enone and on an olefin? (2) How can the positively polarized partner of an agent $^{\delta+}X{-}Y^{\delta-}$ attack the enone and activate it for a subsequent attack of the nucleophile? (3) What is the role of acid catalysis?

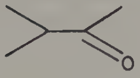
Clearly, the basicity of conjugated enones is of great interest in reactivity studies since, as in the case of saturated ketones and aldehydes, acid-catalyzed reactions of enones could in principle proceed via a preequilibrium protonation of the carbonyl group followed by some sort of nucleophilic attack. Consequently, the following Section II is concerned with the protonation of enones and the eventual quenching of the intermediate carbenium ions with various nucleophiles.

II. PROTONATION, HYDRATION, HYDROHALOGENATION AND RELATED REACTIONS

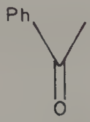
The protonation of unsaturated ketones, aromatic ketones and α,β-unsaturated keto steroids in concentrated sulfuric acid was studied spectrophotometrically[7–10]. It was concluded that these compounds follow the H_A acidity function for sulfuric acid solutions. This function is defined in the same way as the Hammett H_0 function, but based upon primary amides as indicators. Difficulties arising from the use of visible and/or UV absorptions of protonated and unprotonated species in the determination of basicity constants[11–13] led to the application of ^1H NMR methods[14] or to the definition of a basicity scale for carbonyl compounds based on heats of ionization[15]. From pK_a values of the protonated species the following conclusions could be drawn[8–16]:

(a) Conjugation with an olefin or with a cyclopropyl group increases the basicity of a ketone; thus, methyl cyclopropyl ketone (**4**) (pK_a, -5.9) is far more basic than methyl isopropyl ketone (**5**) (-7.4) and still significantly more basic than acetophenone (**6**) (-6.4). Olefinic conjugation is most effective in stabilizing protonated ketones, as is obvious from the pK_a values of 4-methyl-3-penten-2-one (mesityl oxide, 7) (-2.4) and 3-methylcyclohexenone (**9**) (-3.8).

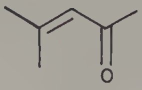
(4)



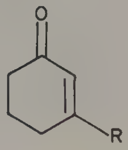
(5)



(6)



(7)



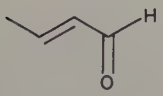
(8) R=H

(9) R=CH_3

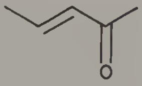
(b) The lower basicity of crotonaldehyde (**10**) relative to mesityl oxide (7) is an indication of the lower basicity of aldehydes relative to ketones.

(c) Substituent effects on the basicity of α,β-unsaturated ketones can be rationalized by simple inductive and resonance stabilization of the protonated form[16]. This holds for alkyl, amino or hydroxy substituents in both the α- or β-positions[9].

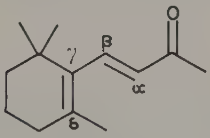
^{13}C NMR studies of a series of unsaturated ketones (7, **8** and **11**–**18**)[17] in fluorosulfonic acid/fluorosulfuryl chloride solutions showed that these ketones were quantitatively protonated on oxygen. The following results are significant for understanding the bonding in protonated enones and dienones:



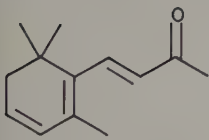
(10)



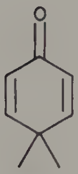
(11)



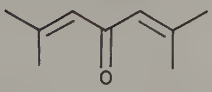
(12)



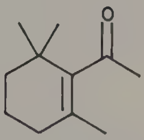
(13)



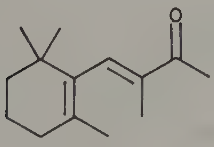
(14)



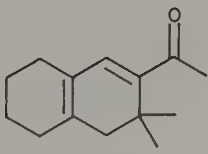
(15)



(16)



(17)

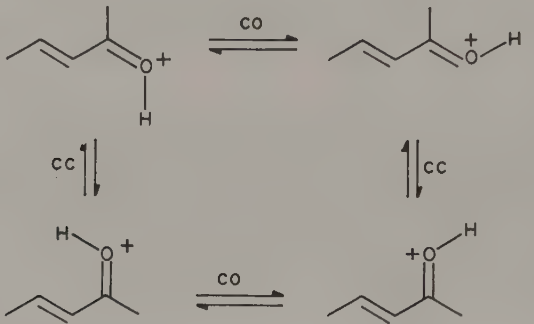


(18)

(a) Upon going from the neutral to the cationic species the ^{13}C NMR signals of the carbonyl carbon, of C_β and of C_δ undergo the most pronounced downfield shifts while those of C_α and C_γ may even experience an upfield shift. It is readily concluded that the positive charge is largely localized at C_β, C_δ and the carbonyl carbon, in accordance with the predictions from simple resonance theory[18].

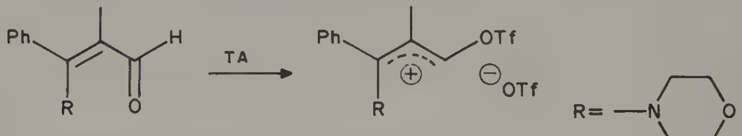
(b) Steric hindrance of the conjugation within a dienone induces a localization of the charge in the enone moiety.

(c) Low-temperature ^{13}C NMR spectra indicate that protonated enones and dienones, depending on the substitution patterns, can exhibit two different types of dynamic behavior[17,19,20]: rotation about the enone CC single bond and isomerization around the CO bond (see Scheme 1).

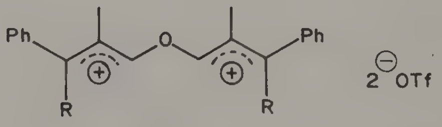


SCHEME 1

In the case of even more basic enones electrophiles other than proton can be introduced, e.g. via alkylation or acylation reactions[21,22]. An interesting example is provided by the reaction of enaminones such as **19** with one quivalent of trifluoromethanesulfonic acid anhydride (triflic anhydride, TA) which yields the 3-trifloxypropenium triflate **20** through sulfonylation on oxygen. Addition of two equivalents of triflic anhydride gives rise to the bistriflate of the dicationic ether **21**[23]. It should be noted that protonation of enaminones is observed to occur not only on oxygen, but also on N and C_α[21,22].



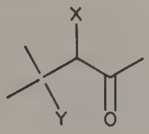
(19) **(20)**



(21)

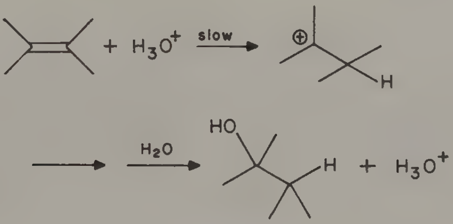
It should be emphasized that under the above reaction conditions the protonated bases do not undergo nucleophilic attack by the counterions (HSO_4^-, FSO_3^-). Therefore, a significant question within the present context is the hydration of enones in aqueous acidic media.

The first question concerning the addition of reagents of the general structure $^{\delta+}X—Y^{\delta-}$ to enones is one of regiochemistry. The reactions of mesityl oxide (7), not only with water but also with hydrohalic acids, mixed halogens and hypohalic acids (see also Section III), yield products of the type **22**[24]. The formation of **22** is in accord with Markownikow's rule, and the relative stability of alternative carbenium ion intermediates will, indeed, appear significant throughout the following considerations.



(22)

For the discussion of the mechanism of the addition reactions of enones, reference to the addition reactions of olefins and of other carbonyl compounds is a useful starting point. The hydration of olefins under acidic conditions[25–27] is known to involve a rate-determining proton transfer from a hydronium ion to the olefinic carbon and subsequent addition of water to the resulting carbenium ion according to Scheme 2. The hydration reactions are characterized by solvent isotope effects $k(H_2O)/k(D_2O)$ 1.4–5 and activation entropies of −5 to 0 eu.

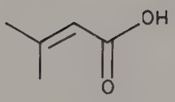


SCHEME 2

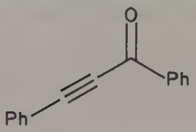
A rate-determining proton transfer was also established from measurements of the effect of pressure on the rate of the acid-catalyzed addition of water to mesityl oxide (7), but no conclusion was made as to the site of the original protonation or to the source of the proton[28].

Early kinetic studies of the hydration of mesityl oxide (7) and crotonaldehyde (**10**)[29] in aqueous acidic media had revealed that the rates increase more rapidly than the acid concentration, but less rapidly than the acidity function H_0. The studies also revealed that solutions of sulfuric and phosphoric acid give abnormally high rates, indicative of a general acid catalysis; that the hydration of mesityl oxide in D_2O is slower than in water by a factor of 3–4; and that the hydration of mesityl oxide (7)[29] occurs with greater ease than that of the structurally related dimethylacrylic acid (**23**)[30].

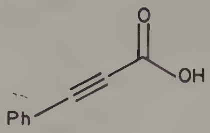
The last finding must be contrasted with the fact that the rate of hydration of ketone **24** is of the same magnitude as that of phenylpropiolic acid (**25**)[31]. This may suggest that the reaction of enones proceeds in a different manner than that of **24** and **25**, on the one hand, and that of α, β-unsaturated acids, on the other. While we shall return to the reactivity of conjugated acids later, the following pieces of evidence demonstrate the reactivity of enones.



(23)

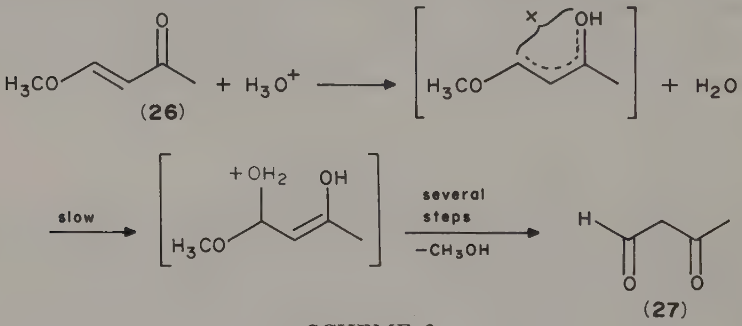


(24)



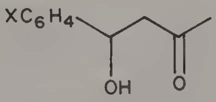
(25)

4-Methoxy-3-buten-2-one (**26**), an alkoxy-substituted α,β-unsaturated ketone, undergoes a vinyl ether hydrolysis to give 3-ketobutanal (**27**) (see Scheme 3)[32]. The reaction proceeds only via specific acid-catalysis and exhibits an inverse deuterium solvent kinetic isotope effect $k(D_2O)/k(H_2O) > 1$. This differs from observations made for the hydrolysis of alkyl vinyl ethers where general acids catalyze the hydrolysis and $k(H_2O)/k(D_2O) > 1$[33–37]. While in the latter case a rate-determining protonation of the olefinic bond, followed by rapid addition of water to give the hydrolytically labile hemiacetal was assumed, the hydrolysis of **26** was described as proceeding via a 1,4-addition of water to the conjugated system and subsequent loss of methanol according to Scheme 3[32,38].

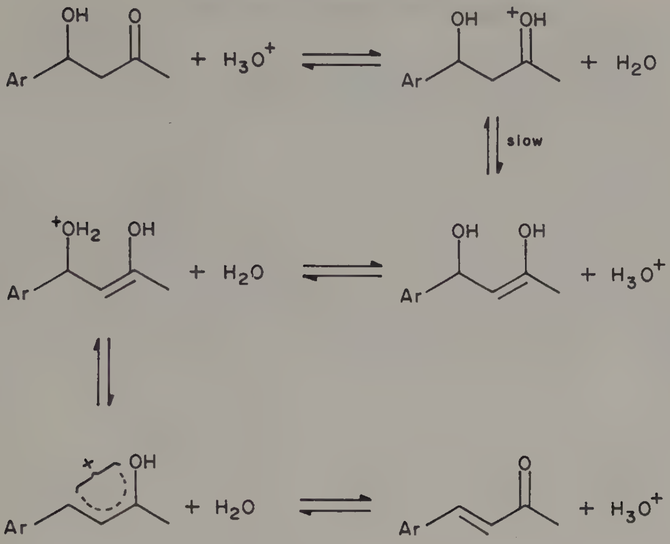


SCHEME 3

A β-phenyl substituent contributes to the stabilization of the carbenium ion formed during the dehydration of β-aryl-β-hydroxy ketones. Although the dehydration rates for 4-phenyl-4-hydroxy-2-butanone (**29**) and its *p*-methoxy- (**28**) and *p*-nitro-derivative (**30**)[39,40] are comparable in 1 M sulfuric acid, the reaction of **28** obeys a different mechanism to that of **29** and **30**. The latter compounds show a nonlinear dependence upon H_O, while **28** exhibits a linear correlation with H_O. Furthermore, the entropies of activation of **29** and **30** (*ca* − 20 eu) are more negative than that of **28**. It can be concluded that **29** and **30** undergo dehydration by rate-determining enolization according to Scheme 4. On the other hand, increasing carbenium ion stabilization as in **28** favors a reaction via the reverse of Scheme 2.

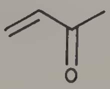


(28) $X=OCH_3$
(29) $X=H$
(30) $X=NO_2$

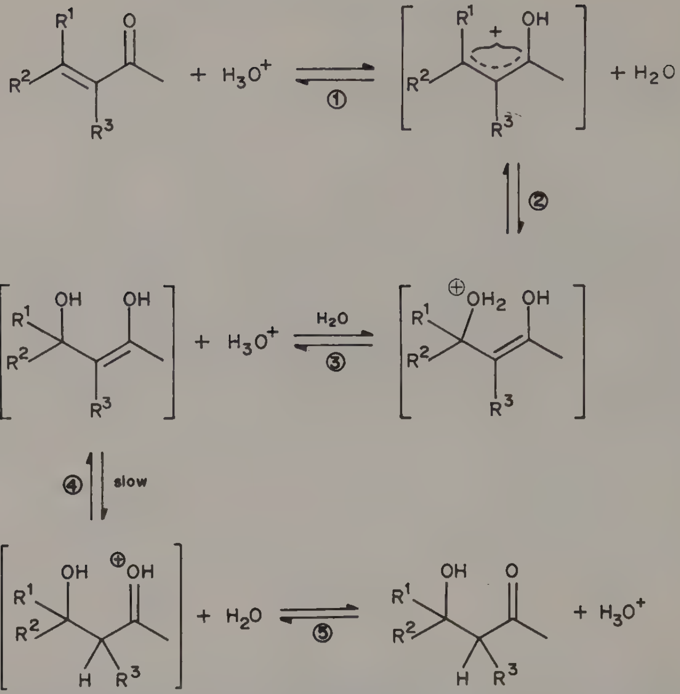


SCHEME 4

In view of these results the two crucial questions in the hydration of enones are whether the reaction proceeds via a 1,2- or 1,4-addition of water, and whether attack by water or proton transfer from hydronium ion to carbon (see step 4 of Scheme 5) is rate controlling. These questions have been investigated in detail for homologues of 3-buten-2-one[6]. Kinetic studies of the hydration of 3-buten-2-one (**31**), 3-penten-2-one (**11**) and 4-methyl-3-penten-2-one (**7**) in 1–10 M perchloric acid show a very large solvent isotope effect $k(H_2O)/k(D_2O)$ (up to 3.5), a very large negative entropy of activation (up to −25 eu) and that **31** is hydrated three times faster than **7**. The mechanism by which hydration of simple aliphatic α, β-unsaturated ketones proceeds is described in Scheme 5. At concentrations of perchloric acid below 6 M, the first equilibrium is shifted far to the left and the proton transfer in the fourth step is rate controlling. Thereby, the primary solvent isotope effect reveals that this step implies proton transfer to carbon. The large negative entropy indicates that not only a hydronium ion, but also a water molecule must be incorporated into the transition state, and the greater reactivity of **31** over **7** demonstrates that the reaction cannot occur via Scheme 2 (note, for example, that isobutene is hydrated significantly faster than propene)[41]. As the acidity of the medium increases beyond *ca* 6M $HClO_4$, the ketone exists increasingly as a protonated species and the first equilibrium is thus shifted to the right. The rate of hydration will decrease with increasing acidity and the equilibrium constant will decrease, thus favoring the α,β-unsaturated ketone over the β-hydroxy ketone.

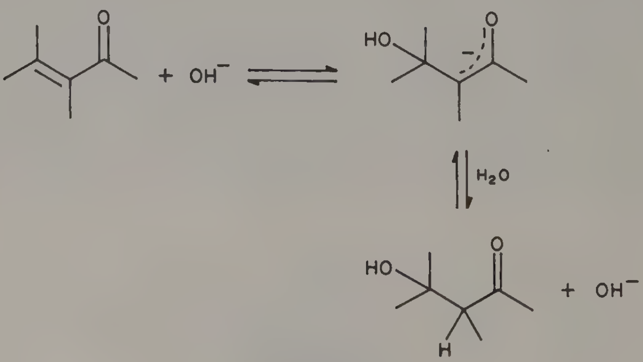


(31)



SCHEME 5

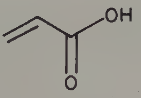
It should be mentioned that, although this reaction type is beyond the scope of the present text, α,β-unsaturated carbonyl compounds can also undergo base-catalyzed hydration. The reaction, kinetically studied for β-oxy-α,β-unsaturated ketones[38], propenals[42] and homologues of 3-buten-2-one[43], proceeds as a two-step process (see Scheme 6) formally resembling a Michael addition. The formation of such aldols via hydration of enones in dilute aqueous base is important, since in some cases the products may undergo retro-aldol condensation. The mechanisms of nucleophilic addition to



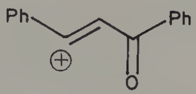
SCHEME 6

activated olefins have recently been studied in great detail[44,45]. The acid-catalyzed addition of methanol to 7[46,47] appears to be mechanistically similar to that for the addition of water. The values of the activation volume determined for both the forward and reverse reaction[28] (elimination) indicate a transition state containing two methoxy units.

With the possible exception of the hydration of acrylic acid (**32**)[48] the acid-catalyzed hydration of unsaturated acids bearing an aryl group at C_β was described as following[31,49] a route different from that of enones but similar to that of *p*-substituted styrenes[26]: hydration involves a rate-limiting addition of a proton to the olefinic carbon to afford a carbenium ion, which is rapidly transformed into a β-hydroxy acid. A related case is found in the hydration of phenylbenzoylacetylene (**24**), the rate-determining step of which is believed to be the protonation at carbon to yield the vinylic carbenium ion **33**[31]. In **24** the regioselective product formation can be explained by the stability of the alternative carbenium ions.



(32)

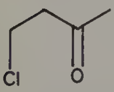


(33)

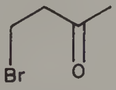
A variety of phosphorus- and/or sulfur-containing acids such as dialkyl phosphites, dialkyl dithiophosphates or ethyl alkylphosphonites add to **7** in high yields[24]. Both the uncatalyzed, base-catalyzed and free-radical catalyzed reactions have been reported, but there are no detailed mechanistic studies.

The addition of hydrohalic acids to **7** affords the expected Markownikow product with the halide at the β-position[50,51]. It should be emphasized that in spite of the weak nucleophilicity of the α,β-bond, methyl vinyl ketone (**31**) has been reported to react 'instantly' with HCl and HBr to give 4-chloro- and 4-bromo-butan-2-one (**34, 35**), respectively[5]. This surprisingly high reactivity of enones toward electrophilic reagents will be reconsidered in the following section in halogenation reactions.

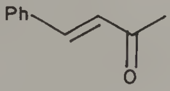
In contrast to the above examples, a β-phenyl substituted enone such as **36** reacts with dry hydroiodic acid (HI) to give the reduction product **37** in 57% yield[52]. One concludes that the primary addition product, the β-iodo species **38**, is susceptible to reduction with HI as indicated in **39**. It is interesting in this context to consider the reaction of enones with Me_3SiI or its equivalent, the system $Me_3SiCl/NaI(ROH)$[53]. The reaction of Me_3SiI with conjugated enones and 2-alkenoic acids affords β-iodo ketones and trimethylsilyl 3-iodoalkanoates, respectively[54,55]. Similarly, methyl vinyl ketone (**31**) is converted with Me_3SiCl/NaI/ethylene glycol to the acetal of 4-iodobutan-2-one (**40**)[56]. Treatment of β-phenyl α,β-unsaturated ketones, cinnamic acid (**41**) and its esters with the reagent system $Me_3SiCl/NaI/ROH$ in hexane gives the corresponding saturated carbonyl compounds[52]. It could be shown that this reduction probably involves *in situ* generated HI as indicated in **39′**. However, the yields of the reduction products are better than those obtained in reductions with HI itself.



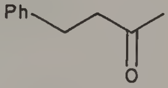
(34)



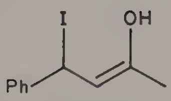
(35)



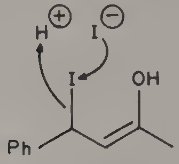
(36)



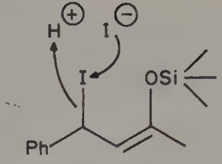
(37)



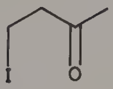
(38)



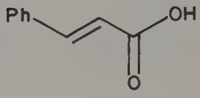
(39)



(39')

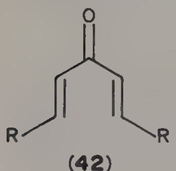


(40)

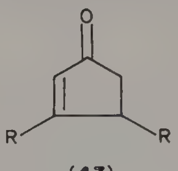


(41)

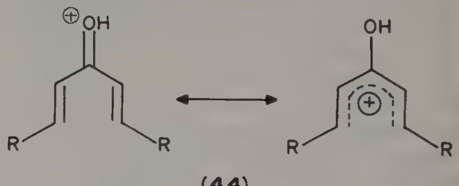
In a number of cases protonation of enones at oxygen (or complexation with a Lewis acid) has been shown to induce skeletal rearrangements[57]. The thermal conrotatory ring closure of divinyl ketones **42** in acidic media provides cyclopentenones (**43**) in excellent yields. The reaction, known as the Nazarov cyclization[58], can be described as proceeding via the carbenium ions **44** and **45**. The activation of an enone for nucleophilic attack at C_β by previous protonation at oxygen is also observed during the acid-catalyzed rearrangement of 8-(*p*-hydroxyphenyl)oct-3-en-2-one (**46**) to 2-(*p*-hydroxyphenyl)cyclohexylmethyl ketone (**47**)[59]. The key step of the reaction is a 1,5-hydride shift from the benzylic to the β-position which transforms **48** into **49**. The latter undergoes ready cyclization to **47**.



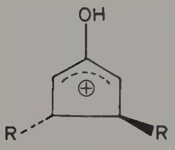
(42)



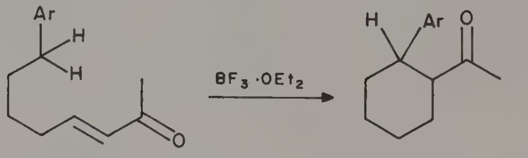
(43)



(44)

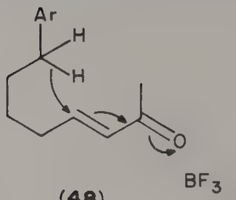


(45)

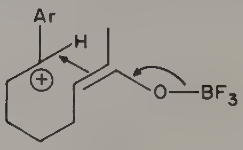


(46) **(47)**

Ar=4-HOC$_6$H$_4$



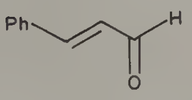
(48)



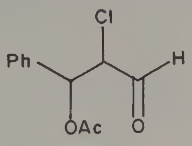
(49)

III. HALOGENATION AND HYDROXYHALOGENATION

A particularly important question within the present context is whether the halogenation of α, β-unsaturated carbonyl compounds is electrophilic or nucleophilic in nature. The possibility of nucleophilic attack was envisioned as early as 1931[60]. Subsequent studies[61–63] have revealed that the addition of bromine and chlorine to α, β-unsaturated aldehydes in acetic acid solution is catalyzed by hydrochloric and sulfuric acid whereas these acids do not influence the rate of electrophilic addition to allyl acetate[64,65]. More recent studies of the uncatalyzed and HCl-catalyzed chlorination of *trans*-cinnamaldehyde (**50**) in acetic acid included not only kinetic, but also stereochemical investigations[66]. Depending on the conditions the reaction yields up to 8 products: *erythro*- and *threo*-β-acetoxy-α-chloro-β-phenylpropionaldehyde (**51**) and (**52**), *erythro*- and *threo*-α, β-dichloro-β-phenylpropionaldehyde (**53**) and (**54**), *trans*- and *cis*-α-chloro-cinnamaldehyde (**55**) and (**56**), β-acetoxy-α, α-dichloro-β-phenylpropionaldehyde (**57**) and α, α, β-trichloro-β-phenylpropionaldehyde (**58**). The only products of the acid-catalyzed reaction are the dichlorides, the *erythro*-dichloride **53** (produced by a *trans* addition) being the major component. This outcome is in marked contrast to the uncatalyzed reaction of methyl *trans*-cinnamate (**59**) and *trans*-cinnamic acid (**41**) where the *threo*-dichloride and the *erythro*-acetoxychloride are major products. Since HCl is produced during the halogenation of **50** the products obtained in the absence of added HCl or acetate are quite similar to those of the HCl-catalyzed reaction. However, in the presence of increasing amounts of added acetate the relative yields of acetoxychlorides increase. It was concluded[66] that the uncatalyzed reaction of **50** involves at least three different pathways: (i) a direct addition of chlorine affording the *threo*-dichloride **54**, (ii) the formation of an ion pair **60** which collapses to the *threo*- and *erythro*-dichloride and (iii) the formation of the chloronium ions **61** and **62** whose reaction with the solvent gives rise to the two acetoxychlorides. Characteristic of the HCl-catalyzed reaction is the absence of products derived from reaction with the solvent and the high yield of the *erythro*-dichloride. As perchloric acid does not function as a catalyst, nucleophilic attack of chlorine on **50**, which was postulated in earlier studies (see above), could be rejected. Furthermore, the chlorine ion does not act as a catalyst on its own. The specific catalysis by hydrogen chloride was ascribed to the formation of a reactive chloroenol (**63**) via addition of HCl to **50**. The resulting 1,4-adduct is nothing else than the enol of β-chloro-β-phenylpropionaldehyde which is particularly prone to reaction with chlorine at the α-carbon.

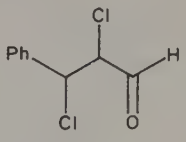


(**50**)



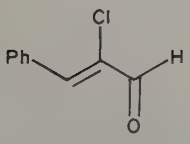
(**51**) *erythro*

(**52**) *threo*



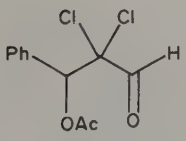
(**53**) *erythro*

(**54**) *threo*

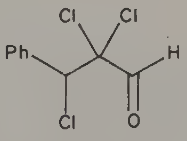


(**55**) *trans*

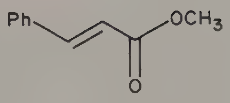
(**56**) *cis*



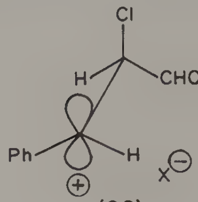
(**57**)



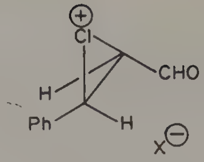
(**58**)



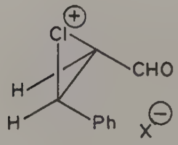
(59)



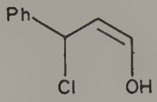
(60)



(61)

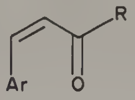


(62)

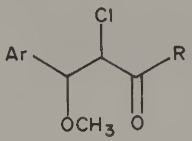


(63)

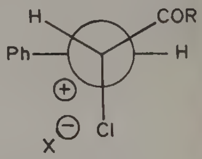
Support for an electrophilic reaction of chlorine with enone substrates such as **36** and **64** was obtained from the uncatalyzed reactions with chlorine in methanol[67]. As expected, the reaction rates depend sensitively on the nature of the *p*-substituents on the aromatic ring. The relative reaction rates of 3-(4-nitrophenyl)-1-phenylprop-2-enone (**65**) to the 4-methoxyphenyl analogue (**66**) is about 10:4, and of the nitro compound (**67**) to the methoxy compound (**68**) is about 10:3. The main products of the reaction of 1,3-diphenylprop-2-enone (chalcone) (**64**) and of 4-phenylbut-3-en-2-one (**36**) with chlorine in methanol are the *erythro*- and *threo*-methoxychlorides **69**. While chlorine is undoubtedly the effective electrophile the formation of **69** can be rationalized by the occurrence of a carbenium ion[67] (**70**,**71**) which undergoes only slow rotation about the CC bond prior to reaction with the solvent at the opposite side from the attached halogen. It should be noted, however, that these results do not distinguish unambiguously between an open intermediate cation or one which possesses some chloronium character.



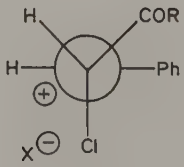
(36) Ar=Ph, R=CH_3
(64) Ar=Ph, R=Ph
(65) Ar=p-$NO_2C_6H_4$, R=Ph
(66) Ar=p-$CH_3OC_6H_4$, R=Ph
(67) Ar=p-$NO_2C_6H_4$, R=CH_3
(68) Ar=p-$CH_3OC_6H_4$, R=CH_3



(69) *erythro, threo*;
R=CH_3, Ph

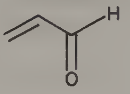


(70)

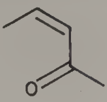


(71)

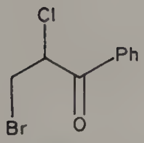
While the chlorination of cinnamaldehyde (**50**) was described as proceeding via electrophilic attack on the olefinic CC bond, the halogenation of enones without an aryl group at C_β (e.g. **2**, **31**, **72** and **73**) appeared to proceed via two alternative routes[5,68]. Two pieces of evidence are significant[5]: the reaction of a solution of bromine in methylene chloride with phenyl vinyl ketone (**2**) leads to an extremely rapid addition, and the addition of bromine chloride to **2** produces exclusively the regioisomer **74** (see below). This must be contrasted to the results that the reactions of methyl acrylate (**75**) are very slow and that BrCl addition to **75** and methyl crotonate (**76**) provides both the α-bromo-β-chloro and the α-chloro-β-bromo compound with the latter being the minor product[68]. Acrolein (**72**), methyl vinyl ketone (**31**), *cis*-3-penten-2-one (**73**) and its *trans* isomer **11** gave results similar to phenyl vinyl ketone (**2**). Competitive rate studies for the bromination of **72** and **31** with 1-heptene revealed the enhanced reactivity of the carbonyl compound: **72**/1-heptene = 2.71, **31**/1-heptene = 4.04[5]. These rate effects and the regiochemistry outlined above provide evidence that the reaction cannot involve electrophilic attack by the halogen on the CC double bond. This important conclusion is further supported by stereochemical considerations. While one expects a stereospecific addition of halogen on the CC double bond[68] (this is actually observed for the chlorination and bromination of methyl isocrotonate), chlorination of the pentenone **73** is nonstereospecific. Both **73** and its isomer **11** provide identical ratios of dichloro diastereomers. Two mechanisms (see Scheme 7) may be invoked in order to rationalize the above results. The first mechanism (A) proceeds via initial attack of halogen on the oxygen and the other (B) via initial 1,4-addition of a trace of HX to afford a highly reactive enol (see above). That chlorine and bromine chloride react via mechanism B is deduced from the following. The rates of the addition to **31** in a stirred slurry of $NaHCO_3$-methylene chloride are slowed down significantly. Evidently $NaHCO_3$ removes the catalytic amounts of HCl, since it could be established (see Section II) that HCl adds rapidly to **31** in methylene chloride to provide chlorobutan-2-one (**34**); in contrast, in the $NaHCO_3$/methylene chloride slurry the acid is neutralized before addition can occur. On the other hand, sodium bicarbonate does not affect the rate of addition of bromine to **31** which might indicate that mechanism A may be efficient. In this case, again, it could be shown that the addition of HBr to give 4-bromobutan-2-one (**35**) can be prevented when working with a $NaHCO_3$/methylene chloride slurry[5].



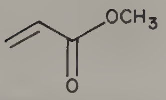
(72)



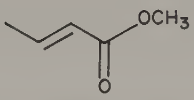
(73)



(74)

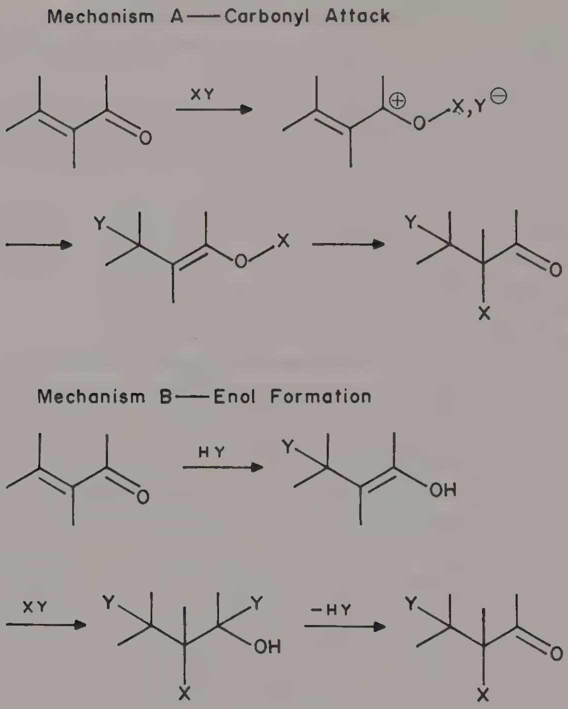


(75)



(76)

Additional arguments for the above mechanistic picture came from the electrophilic addition of dimethylbromosulfonium bromide (**77**) to conjugated enones which led to an efficient synthesis of α-bromoenones[69]. The preparative significance of such reactions will be discussed in the subsequent section. It is noteworthy in the present context that while the reagent is assumed to be an electrophile, it adds smoothly to the so-called electron-poor



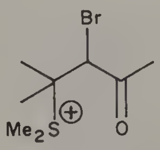
SCHEME 7

conjugated double bond in a manner very similar to conventional electrophilic reactions. Taking, e.g., **7** as substrate the complete reaction sequence involves the formation of the rather stable addition product **78** followed by base-induced elimination to yield **79**. The characteristic features are the following:

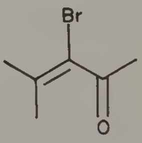
(a) The addition regiospecifically provides α-bromo-β-sulfonium carbonyl compounds.

$Me_2\overset{\oplus}{S}BrBr^{\ominus}$

(77)

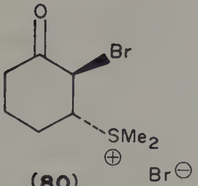


(78)

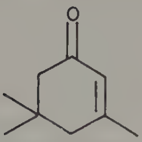


(79)

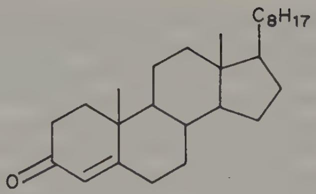
(b) The addition is stereoselective since it transforms 2-cyclohexenone (**8**) into the 2-bromo-3-sulfonium cyclohexanone adduct **80** with a (di-equatorial) *trans* configuration of the substituents. The reaction is extremely rapid since addition to acrolein (**72**) and to methyl vinyl ketone (**31**) proceeds instantaneously at −40 °C. Steric crowding is important, since addition to mesityl oxide (**7**) and 2-cyclohexenone (**8**) is only moderately rapid at 0 °C while the reaction with other enones such as 3-pentene-2-one (**11**) and crotonaldehyde (**10**) is rapid at intermediate temperatures (between −10 and −20 °C). In contrast, isophorone (**81**) and 4-cholesten-3-one (**82**) do not react at all.



(80)



(81)

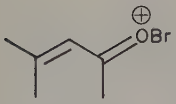


(82)

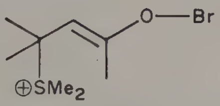
(c) Electronic factors are also operative since addition is relatively slow to conjugated esters^{70}.

It could be deduced that the process is initiated by the electrophilic attack of the bromonium ion at the carbonyl oxygen of the enone^{5,62,71,72}. This step gives the intermediate cation **83** which rapidly reacts with dimethyl sulfide to afford **84**. The stereochemistry of the adduct **78** is controlled by the transformation of the enol hypobromite **84** into **78** for which the attack of the bromide anion at C_α with removal of the bromide anion from oxygen constitutes a possible pathway.

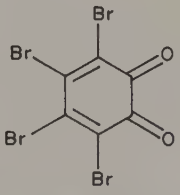
An unusual way of transforming chalcone (**64**) or its naphthyl analogues into the corresponding α,β-dibromo adducts involves the uncatalyzed reaction with tetrabromo-*o*-quinone (**85**) as halogen source^{73}.



(83)



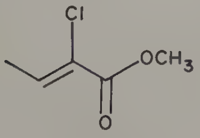
(84)



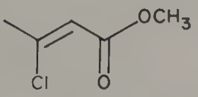
(85)

As has been pointed out already, bromine chloride adds to the CC double bond of α,β-unsaturated carbonyl compounds in such a way that bromine becomes preferentially attached to the α-position$^{5,68,74-78}$. Although BrCl tends to disproportionate in some organic solvents^{79}, the additions usually occur as if BrCl was the dominant reagent$^{78-84}$. Chloro substitution in methyl butenoates such as **86** and **87** affects the relative amounts of Br_2 and BrCl adducts and the regiochemistry of the BrCl adducts observed in reactions with BrCl^{78,80,81}. This was explained by assuming that the intermediate bromonium ions can adopt a symmetric or a strongly distorted structure (depending on the substitution).

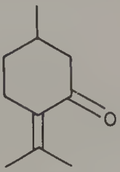
The synthesis of chlorohydrins in the reaction of hypochlorous acid with mesityl oxide (**7**), pulegone (**88**) and related compounds has been extensively studied$^{85-88}$. The product formed upon reaction of **7** possesses the general structure **22** with X = Cl and Y = OH^{24}.



(86)



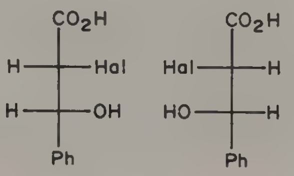
(87)



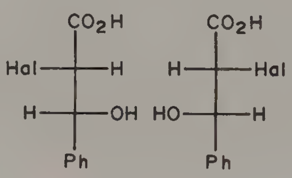
(88)

As in hydration reactions (see Section II) it is illustrative to include other α,β-

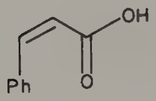
unsaturated carbonyl compounds than enones. The addition of hypochlorous or hypobromous acid to *trans*-cinnamic acid (**41**) could, in principle, afford regioisomers of chloro- or bromohydrins. However, only derivatives of **89** and **90** are obtained when methyl *trans*-cinnamate (**59**) reacts with chlorine in acetic acid$^{89-92}$. The failure of these reactions to produce the corresponding regioisomers can, again, readily be ascribed to the attack of the electrophilic species at the α-carbon. The stereochemistry of the addition, leading to the formation of the *erythro*-2-bromo-3-hydroxy adduct from *trans*-cinnamic acid (**41**) and of the analogous *threo* compound from *cis*-cinnamic acid (**91**), can be explained by a *trans* addition of hypobromous acid. The *erythro*-bromohydrin can also be obtained by hydrolysis of the corresponding *erythro*-dibromide with water. Reaction of the *erythro*-bromohydrin with alkali gives the sodium salt of the *trans*- 2,3-epoxy-3-phenylpropanoic acid (**92**) via the intramolecular S$_N$2-displacement of Br$^-$ by O$^-$ (see Section VI).



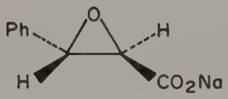
(**89**) *erythro*



(**90**) *threo*

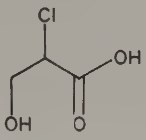


(**91**)

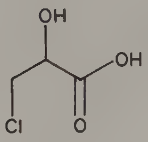


(**92**)

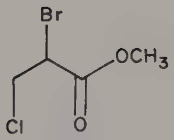
While in the addition of hypochlorous acid and chlorine acetate to cinammic acid (**41**) the intermediate chloronium ion is opened exclusively at the carbon adjacent to the phenyl rings$^{89-91}$ the addition of hypochlorous acid to acrylic acid (**32**) is not completely regiospecific since both the 2-chloro-3-hydroxy- (**93**) and the 3-chloro-2-hydroxy-propanoic acid (**94**) can be isolated^{91,92}. Likewise, addition of BrCl (in methylene chloride) to methyl acrylate (**75**) under ionic conditions provides small amounts of **97** in addition to **95** [similar results have been obtained with methyl crotonate (**76**) and methyl isocrotonate (**96**)]^{68}. On the other hand, a radical addition (reaction of BrCl with **75** in the presence of ultraviolet irradiation) gives **97**^{68}.



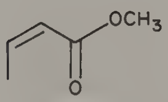
(**93**)



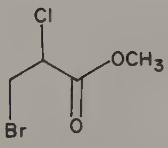
(**94**)



(**95**)



(**96**)



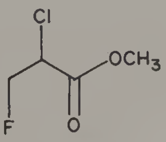
(**97**)

The above addition reactions of bromine chloride, hypochlorous acid or chlorine acetate to α,β-unsaturated carbonyl compounds have also been used to study the influence of a carbonyl group on the ring opening of the neighboring halonium ion[68,89–91]. This is relevant since the literature contains many studies of the first step in halogenation reactions, i.e. the *formation* of a halonium ion, but there have been relatively few investigations of the second step, i.e. the halonium ion ring opening[93,94,95].

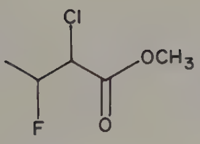
An ion pair formed from a carbonyl-substituted chloronium ion and a BF_3X^- anion has been postulated as an intermediate in the reaction of methyl hypochlorite (CH_3OCl, **98**) (in the presence of BF_3) methyl acrylate (**75**), methyl crotonate (**76**) and methyl isocrotonate (**96**)[96]. In the absence of BF_3, alkyl hypochlorite reacts with olefins in aprotic solvents by a radical mechanism[97]. Compounds **75**, **76** and **96** transform into the fluoro chlorides **99**, **100** and **101**, respectively, as major products; in addition, one observes the expected methoxychloro regioisomers (**102**–**107**). Particularly noteworthy is the completely stereospecific formation of products obtained from **75** and **96** which requires anti ring-opening of the chloronium ion in **108** by both the methoxide ion and the fluoride ion[68,98,99].

CH_3OCl

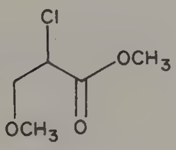
(98)



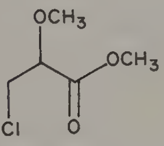
(99)



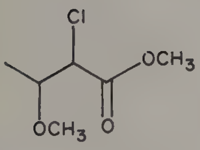
(100) *erythro*
(101) *threo*



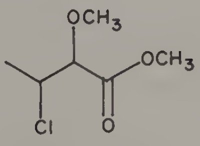
(102)



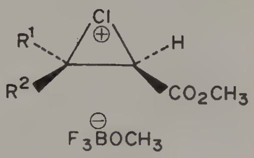
(103)



(104) *erythro*
(105) *threo*



(106) *erythro*
(107) *threo*



(108)

(from **75**: $R^1 = R^2 = H$)
(from **76**: $R^1 = CH_3, R^2 = H$)
(from **96**: $R^1 = H, R^2 = CH_3$)

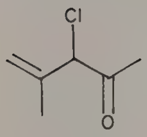
The *two-phase* reaction of hypochlorous acid with conjugated ketones leads to α-chloro-β,γ-unsaturated ketones, a class of compounds which is relatively unknown[100]. Mesityl oxide (**7**), phorone (**15**) and pulegone (**88**) cleanly react with one equivalent of HOCl to give the α-chloro ketones **109**, **110** and **111** (+**112**), respectively. 2-Phenyl-2-penten-4-one (**113**) affords a 1:1 mixture of the allylic chloride **114** and the vinyl chloride **115**. The following aspects are important:

(i) The reaction of conjugated ketones such as **116** and **117**, where an addition–elimination process can give rise to two different allylic chlorides, yields mixtures of products (**118** + **119** and **120** + **121**, respectively) with varying composition depending on the ring size and substituents of the ring.

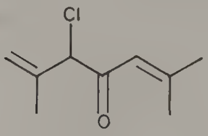
(ii) The reaction can be extended to aldehydes such as β-cyclocitral (**122**).

(iii) The process only succeeds for such conjugated carbonyl *cis*- compounds in which the *s*-conformation of the enone is accessible.

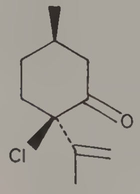
(iv) More highly unsaturated ketones such as α- or β-ionones (**123**), (**12**) provide mixtures of allylic chlorides[100].



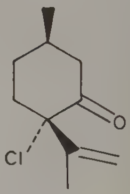
(109)



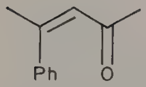
(110)



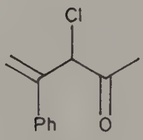
(111)



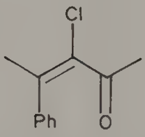
(112)



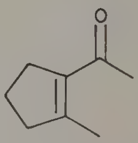
(113)



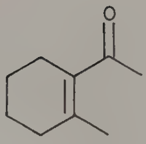
(114)



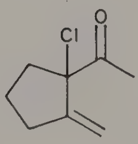
(115)



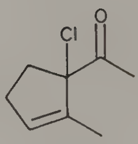
(116)



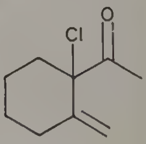
(117)



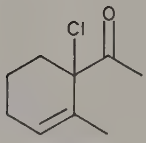
(118)



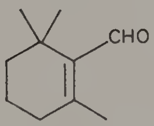
(119)



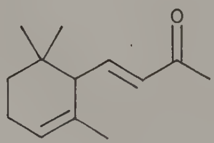
(120)



(121)

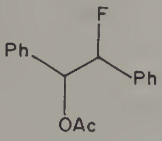


(122)

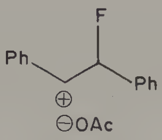


(123)

Another example of electrophilic halogenation of enones is provided by the reaction of acetyl hypofluorite (AcOF), prepared *in situ* from fluorine. In general, AcOF reacts with olefins to produce fluorohydrin derivatives. Thus the reaction of AcOF with *trans*-stilbene affords *threo*-1-acetoxy-2-fluoro-1, 2-diphenylethane (**124**) in 50% yield[4]. The predominant *syn* addition is typical for electrophilic fluorination reactions since they proceed via the tight ion pair **125** incorporating an unstable α-fluoro carbocation; the latter is expected to collapse rapidly in a *syn* addition[101–103].



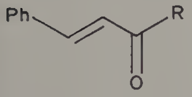
(124)



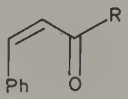
(125)

In view of the low tendency of α,β-unsaturated carbonyl compounds to undergo electrophilic addition at the CC double bond it is astonishing that acetyl hypofluorite, which is extremely mild in comparison with other fluoroxy reagents, still reacts with such compounds. Three classes of conjugated enones can be distinguished[4]:

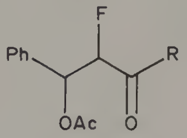
(a) Open-chain aryl-substituted α,β-unsaturated carbonyls give good yields of the expected β-acetoxy-α-fluoro derivatives. Thereby, as anticipated from a *syn* addition, *trans*-ethyl cinnamate (**126**) is converted into the *threo* (**127**), and *cis*-methyl cinnamate (**128**) into the *erythro* isomer (**129**) is about 50% yield. In a similar fashion benzalacetophenone (**36**) regio- and stereospecifically gives rise to *threo*-1, 3-diphenyl-1-acetoxy-2-fluoro-3-propanone (**130**) in 70% yield. The stereochemical result was explained by the electronic effect of the carbonyl moiety, which shortens the lifetime of the α-fluorocarbonyl cation and accelerates the collapse of the tight ion pair[4].



(126) $R{=}OCH_2CH_3$



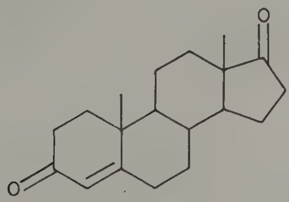
(128) $R{=}OCH_3$



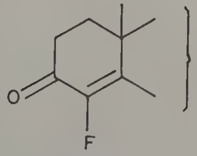
(127) *threo*; $R{=}OCH_2CH_3$
(129) *erythro*; $R{=}OCH_3$
(130) *threo*; R=Ph

(b) Rigid cyclic conjugated enones initially react in the same fashion but, because of the *anti* configuration of the acetoxy group to a relatively acidic proton adjacent to the fluorine atom and vicinal to the carbonyl group, undergo ready elimination of acetic acid. Typical examples for the formation of the otherwise difficultly accessible α-fluoroenones are the reactions of androst-4-en-3, 17-dione (**131**) to **132** and coumarin (**133**) to **134**.

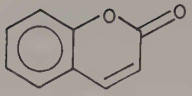
(c) On the other hand, flexible α,β-unsaturated carbonyl compounds without aryl substituents, such as cyclohexenone (**8**), 3-methylcyclohexenone (**9**), ethyl crotonate, diethyl maleinate and diethyl fumarate, do not react even with a large excess of acetyl hypofluorite[101,104].



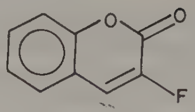
(131)



(132)

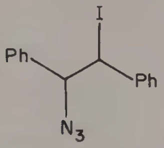


(133)

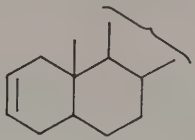


(134)

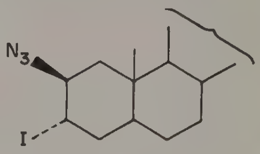
A pseudohalogen such as iodine azide, prepared *in situ* by the reaction of sodium azide and iodine monochloride in acetonitrile, adds to olefins in good yields and in a highly stereospecific manner[105]. Thus, *trans*- and *cis*-stilbene give *erythro*- and *threo*-1-azido-2-iodo-1,2-diphenylethane **135** and **136**, respectively, and the addition of IN_3 to cyclic olefins proceeds via *trans* addition, as is the case for addition of IN_3 to 2-cholestene (**137**) which results in the expected *trans*-diaxial-2β-azido-3α-iodocholestene (**138**). These findings can be explained by assuming that the electrophilic addition involves a cyclic iodonium ion, the ground state of which can be described by the structures **139** or **139a**–**c**. The ring opening of the latter would be predicted to occur in a *trans* manner leading to *trans*-addition products. The iodoazide adduct of chalcone (**64**) is formed nearly quantitatively, that of methyl cinnamate (**59**) in moderate yield[106]. The base-induced elimination of hydrogen iodide from the iodoazide adducts (see Section IV) to give unsaturated azides is very helpful in structure determination. It is also known[107] that 2-azidovinyl ketones (**140**) undergo a decomposition reaction in the presence of acids to give substituted isoxazoles (**141**) and nitriles (**142**) which probably proceeds via a vinylnitrene intermediate (**143** and its tautomer **144**). One predicts that the ground state of the intermediate iodonium ion resembles **145a** more than **145b** so that one would expect the azide ion to open the iodonium ion mainly by attack at the benzylic position.



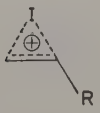
(135) *erythro*
(136) *threo*



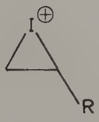
(137)



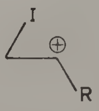
(138)



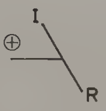
(139)



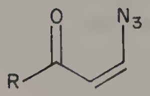
(139a)



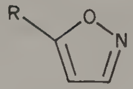
(139b)



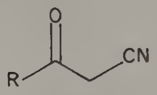
(139c)



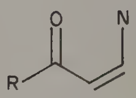
(140)



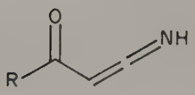
(141)



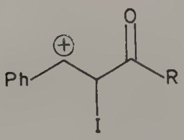
(142)



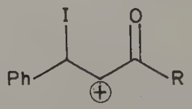
(143)



(144)

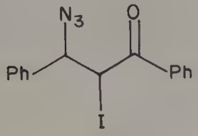


(145a)

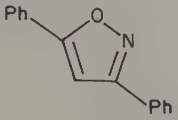


(145b)

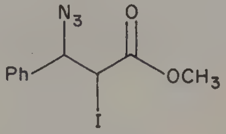
When the iodo-azide adduct of chalcone (**146**) is treated with diazabicyclooctane at room temperature, 3, 5-diphenylisoxazole (**147**) is obtained in 53% yield. Consequently, the azido group in the adduct occupies the benzylic position. On the other hand, if the methyl cinnamate adduct **148** is reacted with potassium hydroxide in methanol, only propiolic acid (**25**) can be isolated. It follows that elimination of both hydroiodic acid and hydrazoic acid can take place[106].



(146)

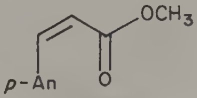


(147)



(148)

The reactions of iodine azide with α, β-unsaturated carbonyl compounds depend on whether or not air is present[108]. In the absence of air the reaction is supposed to be initiated by attack of an iodo radical. The basic question of whether the nucleophile Y^- or the electrophile X^+ attacks the substrate first in the addition of XY reagents to α, β-unsaturated carbonyl compounds has also been considered for the addition of iodine azide. From the addition of iodine isocyanate and of iodine azide to alkenes[106] it could be concluded that the former reagent is a stronger electrophile. However, the fact that only iodine azide adds to α, β-unsaturated carbonyl compounds seems inconsistent with an Ad_E mechanism for the addition. Moreover, the greater nucleophilicity of an azide ion compared with that of an isocyanate ion would also favor an Ad_N mechanism. To deal with this mechanistic problem the rates of addition of iodine azide to the *p*-methoxy derivatives **149** and **68** were compared with those of addition to methyl-*trans*-cinnamate (**59**) and 4-phenyl-but-3-en-2-one (**36**). The mesomeric effect of the *p*-methoxy substituent should decrease the rate for an Ad_N mechanism. It appears that the rates of the reaction with the *p*-methoxy derivatives are greater than those for the parent compound. Consequently[109], a rate-determining attack of an azide ion can be rejected and an electrophilic mechanism has to be assumed.

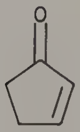


(149)

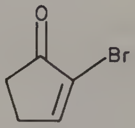
IV. HALOGENATION AND SUBSEQUENT 1, 2-ELIMINATION

The combination of addition to α, β-unsaturated carbonyl compounds and subsequent elimination reactions which have been mentioned above is important from a mechanistic and also a preparative point of view, since α-haloenone species can be prepared. This reaction shall now be considered in greater detail.

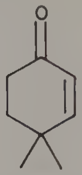
Two obvious methods have been applied for the synthesis of α-halo-α, β-unsaturated ketones[110]. Halogen is added to an α, β-unsaturated ketone and hydrogen halide is then eliminated with the aid of a base[111–114]. A typical example is the treatment of 2-cyclopentenone (**150**) with bromine and the subsequent elimination of hydrogen bromide with trialkylamine to yield **151**[115]. The latter is a useful intermediate, since it can be transformed into the labile α-bromocyclopentadiene which is used for a Diels–Alder reaction as a key step in the synthesis of homocubane. A similar example is the bromination and subsequent dehydrobromination of 4, 4-dimethylcyclohexanone (**152**) to give **153**[116]. Interestingly enough, compound **153** (together with **14**) is also obtained upon treatment of *cis*-2, 6-dibromo-4, 4-dimethylcyclohexanone (**154**) with quinoline at 170 °C. In the proposed mechanism for this transformation, the enol (**155**) of **154** undergoes a base-induced 1, 4-elimination to give **156**, the enol of **153**.



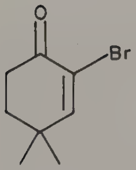
(150)



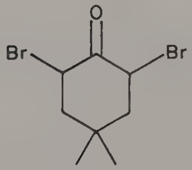
(151)



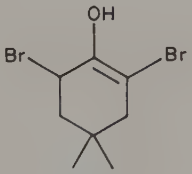
(152)



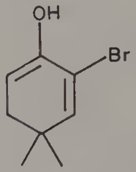
(153)



(154)

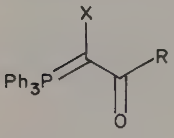


(155)



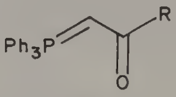
(156)

The synthesis of halophosphoranes such as **157**–**159** is closely related to that of α-haloenones. The phosphoranes **160**–**162** react rapidly with chlorine or bromine at low temperatures. The resulting halophosphonium halides **163**–**165** can then undergo base-induced elimination (pyridine or trialkylamine) to give **157**–**159**[117].

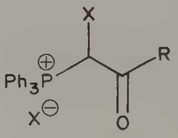


$X = Cl, Br$

(157) $R = Ph$
(158) $R = CH_3$
(159) $R = OCH_2CH_3$



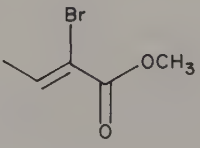
(160) $R = Ph$
(161) $R = CH_3$
(162) $R = OCH_2CH_3$



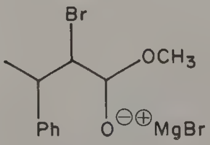
$X = Cl, Br$

(163) $R = Ph$
(164) $R = CH_3$
(165) $R = OCH_2CH_3$

It should be mentioned that an α-bromo substituent in α, β-unsaturated carbonyl compounds markedly affects the course of the addition of Grignard reagents. For example, while alkyl crotonates give exclusive 1, 2-addition, the corresponding α-bromo compound **166** undergoes 1, 4-addition with phenylmagnesium bromide through the formation of the stable bromoenolate **167**[112]. The latter can be protonated to give two diastereomeric esters.

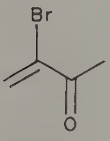


(166)

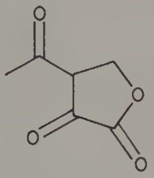


(167)

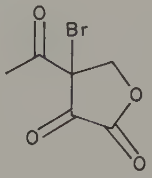
Analogous to the bromination/dehydrobromination sequence, α-halo-α,β-unsaturated ketones are also available upon the addition of hypochlorous or hypobromous acid to an α,β-unsaturated ketone followed by dehydration of the halohydrin either by heating or the use of acetic anhydride[118]. Another method for the synthesis of α-bromo-α,β-unsaturated ketones (and esters)[119] involves a degradation of butyrolactones which may be illustrated by the synthesis of methyl α-bromovinyl ketones (**168**). The α-keto-β-acylbutyrolactone (**169**) reacts with bromine in aqueous solution to give **170** and is then treated with sodium bicarbonate. The analogous preparation of α-bromo-β′,β′-dimethyldivinyl ketone (**171**) shows that bromine reacts preferentially with the double bond which is formed by enolization of the lactone **172** to give **173**.



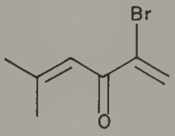
(168)



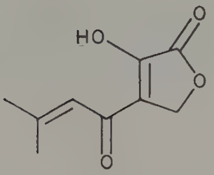
(169)



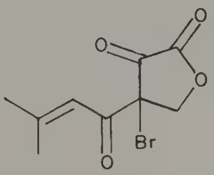
(170)



(171)

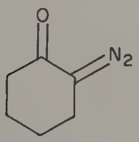


(172)

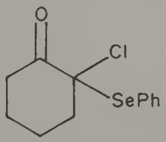


(173)

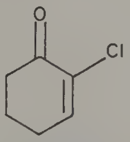
A convenient synthesis of 2-haloenones from enones uses phenylselenium halides. Diazoketones such as **174** undergo a carbenoid-like insertion reaction with phenylselenium chloride to give **175**, which can be transformed into either**176** or **177**[113]. On the other hand, enones **178** have been shown to undergo reaction with phenylselenium chloride in the presence of pyridine to give 2-phenylselenoenones **179**[120]. The latter can react further with the selenium reagent to afford adducts **180** which undergo rapid disproportionation by loss of diphenyl diselenide and, thus, transform into the target molecules **181**. This reaction can be performed under very mild conditions in high yields for a variety of cyclic and acyclic enones[121].



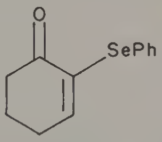
(174)



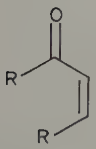
(175)



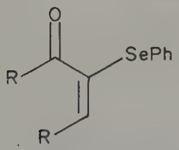
(176)



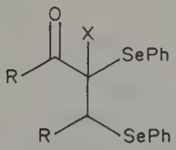
(177)



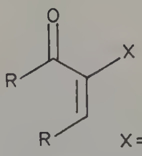
(178)



(179)



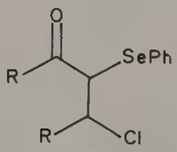
(180)



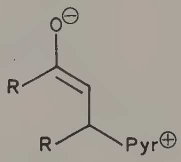
X=Cl, Br

(181)

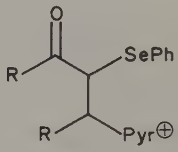
Three possible pathways were considered for the transformation of enone **178** into **179**[120]: (a) direct addition of PhSeCl to the α,β-double bond with formation of the Markownikow product **182**[122] and subsequent elimination of HCl, (b) abstraction of the enone γ-hydrogen by pyridine followed by α-selenation and double-bond isomerization, and (c) Michael addition of pyridine followed by α-selenation of the resulting enolate **183** to give **184** which would provide **179** via loss of pyridine and H^+. Since in the absence of pyridine neither the adduct **182** nor the product **179** could be observed, pathway (a) was rejected. The same holds for mechanism (b), since the product of the type **179** is still observed when starting from ketone **152**; instead, the nucleophile-initiated mechanism (c) was adopted as a working model[120].



(182)



(183)

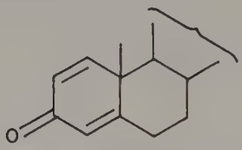


(184)

Other methods for the synthesis of α-haloenones which have already been mentioned in the previous section include the extrusion of dimethyl sulfide from sulfonium adducts of enones (see the sequence **7** → **78** → **79**) and the elimination of acetic acid from α-fluoro β-acetoxy ketones (see the transformations **131** → **132** and **133** → **134**).

V. BROMINATION AT $C_{\alpha'}$ AND C_{γ}

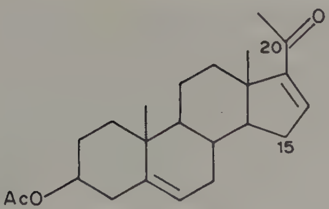
Another question in the bromination of α,β-unsaturated ketones is the attack at the sp^3-hybridized carbons $C_{\alpha'}$ or C_{γ}. This problem has played an important role in the synthesis of $\Delta^{1,4}$-dien-3-ones of the steroid series, e.g. **185**, which constitute key intermediates in the partial synthesis of, e.g., estrone and estradiol from nonaromatic precursors such as **131** possessing an angular methyl group at C-10[123–125].



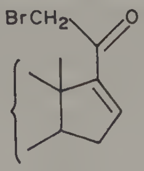
(185)

The bromination of unsaturated ketones with molecular bromine gives rise to a complex mixture of products arising from addition to the double bond, allylic displacement or addition to the enol form of the carbonyl compound. It has been shown that steroidal ketones which possess an isolated double bond can be brominated with cupric bromide in methanol without this bond being affected[126]. The reaction of 3β-acetoxypregn-5, 16-dien-20-one (**186**) with cupric bromide in tetrahydrofuran gave the C-21-bromo derivative **187** and not the C-15-bromo compound **188**. This bromination reaction proceeds via the Δ^{20}-enol[127].

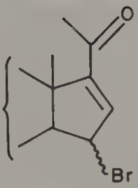
Selective bromination of the ketone function in the presence of a double bond has also been achieved by the use of phenyltrimethylammonium tribromide[128,129]; however, while dihydrocarvone **189** undergoes smooth reaction via **190** to **191**, α,β-unsaturated ketones



(186)

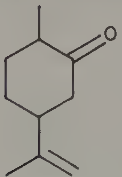


(187)

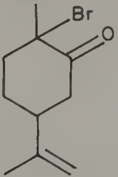


(188)

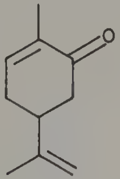
such as **131**, **186** or **192** yield addition and substitution products. Thus, in the case of the cyclohexenyl cyclohexyl ketone **192** in which enolization is slow, α-bromination is also slow and one obtains product **193**[130]. It has been demonstrated that pyrrolidone hydrotribromide (PAT) has a selectivity for α'-bromination of ketones which is superior to that of phenyltrimethylammonium tribromide[131]. The relative reactivities for bromination in tetrahydrofuran by PAT of a saturated ketone, an olefin and an enol acetate (e.g. cyclohexanone, cyclohexene and cyclohexenyl acetate) are ketone > olefin > enol acetate. Not unexpectedly, therefore, benzalacetone (**36**) could be smoothly converted with PAT in THF into the bromomethyl styryl ketone **194**[131–133]. The high keto-selectivity of PAT was rationalized in terms of an acid-catalyzed enolization, since the pyrrolidonium ion is acidic and the tetra-substituted ammonium ion is not. In the latter case the necessary catalysis of the enolization must be achieved by the HBr, which is generated when the small amount of enol originally present is brominated. It has been suggested that the keto-selectivity is due to the ability of the reagents to provide a low equilibrium concentration of molecular bromine in solvents of low dielectric constants. Indeed, the results of competition experiments for the bromination of cyclohexene and cyclohexanone with Br_2 in CCl_4 indicate that addition at the double bond can be completely suppressed by keeping a low effective concentration of molecular bromine. Since the ketone contains only 10^{-2} to $10^{-6}\%$ of the enol, it follows that the enol under the prevailing reaction conditions is at least 10^6 times more reactive than the olefin.



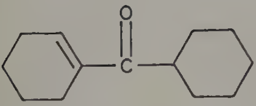
(189)



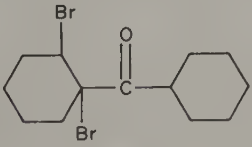
(190)



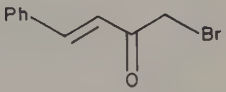
(191)



(192)

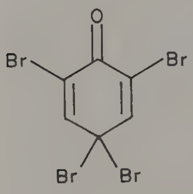


(193)

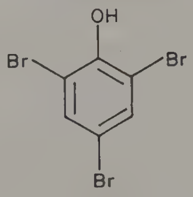


(194)

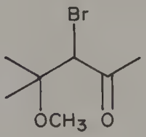
α,β-Unsaturated ketones have been brominated with high keto-selectivity in good yields with the reagent 2,4,4,6-tetrabromocyclohexadienone (**195**) in ether[134]. Thus the reaction of **36** with **195** provides **194** and the phenol **196**. The rate of this reaction is enhanced by the addition of a small amount of gaseous HCl or HBr whereby the acid catalyzes the enolization of the ketone and the aromatization of the halocyclohexadienone to the phenol[134]. This mechanism is similar to that of the reduction of α-bromoketones[135,136]. While the reaction of **36** affords exclusively 1-bromo-4-phenyl-3-buten-1-one (**194**), complications arise for mesityl oxide (**7**) where the regiochemistry of the bromination depends sensitively upon the experimental conditions. The formation of **197** in methanol is probably due to a slight enolization of the ketone **7**. Nevertheless, product **198** can be obtained in 80% yield from the reaction of **195** in ether with only traces of HBr. The reaction of **195** with the steroid ketone **82** gives 2-α-bromocholest-4-en-3-one (**199**) as the main product. Under the same reaction conditions **200** yields exclusively 4α-bromo-1-methylandrost-1-en-3-one-17β-olacetate (**201**).



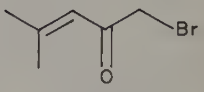
(195)



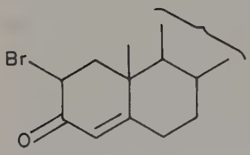
(196)



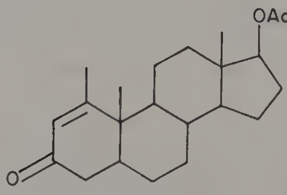
(197)



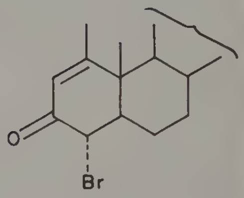
(198)



(199)

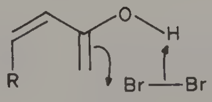


(200)

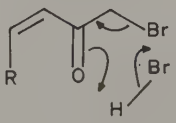


(201)

It has been mentioned above that at very low bromine concentrations the enol undergoes bromination at least 10^6 times faster than the olefin. This can be explained by assuming a six-center transition state (**202**) for the reaction of the enol. It can be seen from **202** that this mechanism of the bromination of ketones is the complete reverse of the reduction of bromoketones with HBr (see structure **203**)[136]; in the presence of an α, β-double bond the halogen can react slowly under irreversible addition. Thus, the keto-selective reaction is favored not only by a low equilibrium concentration of the halogen from the reagent (comparable to the enol concentration), but also by the neutralization of the hydrobromic acid (without affecting the keto-enol equilibrium).



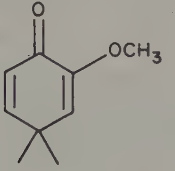
(202)



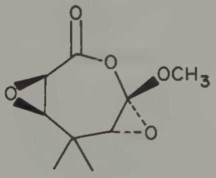
(203)

VI. EPOXIDATION

As is known from ample experience, epoxidation reactions via electrophilic attack of peracids on alkenes are rendered much more difficult by electron-withdrawing substituents[1]. Due to the low reactivities of these substrates towards electrophiles, competing side-reactions can lead to products other than the desired epoxides[2]. A frequently encountered side-reaction is the Baeyer–Villiger oxidation, which prevents, e.g., the conversion of 2-methoxy-4, 4-dimethyl-2, 5-cyclohexadienone (**204**) with *m*-chloroperbenzoic acid in 1, 1, 1-trichloroethane into the corresponding bis-oxirane, but produces the 2, 3, 5, 6-diepoxy-6-methoxy-4, 4-dimethyl-6-hexanolide (**205**)[137]. Consequently, α, β-unsaturated carbonyl compounds are usually converted into the corresponding epoxides by other methods, e.g. by oxidation with alkaline hydrogen peroxide[3] (known as the Weitz–Scheffer reaction) or by elimination of hydrogen halides from halohydrin precursors[138] (see, e.g., the transformation of **89** into **92** in Section III).



(204)

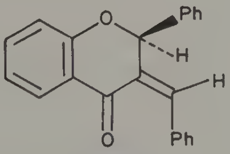


(205)

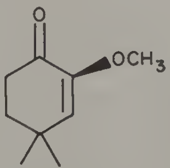
From a mechanistic standpoint the Weitz–Scheffer epoxidation is a typical Michael-type reaction involving nucleophilic attack of the anion OOH^- at C_β of the conjugated system and will therefore not be discussed here in detail. The method has been reviewed by Berti[3] and has gained new interest since 1976, when the preparation of optically active epoxyketones via asymmetric catalysis was first reported[139,140].

The electronic requirements of the peracid oxidation and the alkaline peroxide method are opposite. While the former proceeds best with electron-rich alkenes, the latter is only feasible with olefins bearing electron-attracting substituents. Thus it is possible to epoxidize double bonds conjugated with carbonyl functions regioselectively in the presence of 'normal' olefinic bonds, and vice versa, by choosing the appropriate reaction conditions. When, e.g., α-ionone (**123**) is subjected to epoxidation by perbenzoic acid, only the CC double bond within the cyclohexene moiety is attacked, while under Weitz–Scheffer conditions the oxirane ring is exclusively formed from the olefinic bond conjugated to the carbonyl group[1,3].

It has been shown that the reactivity of olefins towards peracids depends sensitively upon the substitution pattern of the alkene[141]. Accordingly, this epoxidation method is only useful in practice when the electron-attracting effect of the carbonyl group is counteracted by the simultaneous presence of electron-releasing groups either at the same double bond[137,142,143] or at the carbonyl oxygen, thus reducing its carbonyl activity[144]. Examples are found in the epoxidation of flavoindogenides[143] (e.g. **206**) and some cyclohexenones[137] (e.g. **207**) with *m*-chloroperbenzoic acid.



(206)



(207)

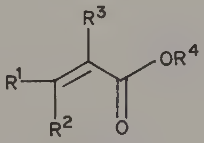
α, β-Unsaturated esters and acids represent substrates with reduced carbonyl activity. Not surprisingly, therefore, the reaction conditions required for their epoxidation with peracids are less severe. These compounds can be converted into the corresponding glycidic esters (respectively acids) by reaction with peracetic acid[144], trifluoroperacetic acid[145], 3, 5-dinitroperbenzoic acid[146] or potassium peroxymonosulfate/acetone[151].

The application of different peracids will now be considered separately.

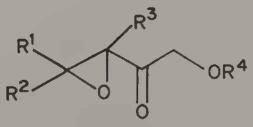
A. Peracetic Acid

Epoxide formation with peracetic acid still requires long reaction periods at elevated temperatures, so that special care has to be taken regarding the stabilities of the employed peracid and the desired epoxide[144]. Peracetic acid made by the oxidation of acetaldehyde is free of impurities such as traces of heavy metal ions, which cause decomposition of the peracid, and free of mineral acids, salts, water, and larger amounts of carboxylic acid[147] which can destroy the epoxide products by participating in or catalyzing the opening of the oxirane rings.

For several reasons this method is often superior to the conventional Darzens method for the preparation of glycidic esters. Aldol condensation of the employed alkanals[148] or the self-condensation of ketones[149] do not compete with the epoxidation; α-arylglycidic esters, which are not accessible by condensations with carbonyl compounds having α-hydrogen[150], can be prepared in good yields. In addition, the progress of the reaction can easily be followed by a simple iodimetric technique. Under these conditions, the α, β-unsaturated esters **208** of Table 1 have been converted into the corresponding glycidic esters **209**. It should be noted, however, that the relatively low electrophilicity of the peracetic acid requires the presence of (electron-donating) substituents at the olefinic bond known to accelerate epoxidations by peracids. In fact, the product yield correlates with the number of such groups and is poorest for the unsubstituted ethyl acrylate (22%).



(208)



(209)

B. Trifluoroperacetic Acid

The use of trifluoroperacetic acid as oxidant enables the pH value to be controlled, so that the resulting oxirane product does not undergo ring opening and the stability of

TABLE 1. Glycidic esters **209** from α, β-unsaturated esters **208** and peracetic acid[11]

R^1	R^2	R^3	R^4	Yield (%)
Methyl	H	H	ethyl	74
H	H	methyl	methyl	47
H	H	H	ethyl	22
Methyl	methyl	H	ethyl	84
Ethyl	H	H	ethyl	57
Phenyl	H	H	ethyl	69
Phenyl	H	methyl	ethyl	87
H	$—(CH_2)_4—$		butyl	87
Propyl	H	ethyl	methyl	72
Propyl	H	ethyl	ethyl	79
Methyl	H	phenyl	ethyl	95

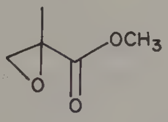
TABLE 2. Epoxidation of α, β-unsaturated esters[146a]

Substrate	Product	Time (h)	Yield (%)
Methylmethacrylate	Methyl-α-methylglycidate	(i) 0.5 (ii) 7.75	(i) 84 (ii) 80
Ethyl crotonate	Ethyl β-methylglycidate	(i) 0.5 (ii) 9.5	(i) 73 (ii) 87
Ethyl acrylate	Ethyl glycidate	(i) 0.5 (ii) 8	(i) 54 (ii) 79

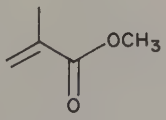
[a] (i) With trifluoroperacetic acid; (ii) with 3, 5-dinitroperbenzoic acid.

the peracid is not affected. This is ascribed to the large difference in acidity between trifluoroperacetic acid and the liberated trifluoroacetic acid, which makes it possible to buffer the reaction mixture with the weak base disodium hydrogen phosphate[145]. This buffer is not sufficiently basic to destroy the trifluoroperacetic acid very rapidly; due to the increased concentration of the peracid in the reaction medium the relatively unreactive olefins can now be epoxidized at a practicable rate. Alkyl acrylates, crotonates and methacrylates (see Table 2) have been converted into the corresponding oxiranes in 54–84% yield.

The importance of the buffer basicity is revealed by the fact that the yield of methyl α-methylglycidate (**210**) from oxidation of methyl methacrylate (**211**) drops from 84% to 13% when the dihydrogen phosphate is replaced by sodium carbonate.



(210)



(211)

C. 3, 5-Dinitroperbenzoic Acid

3, 5-Dinitroperbenzoic acid (3, 5-DNPBA) is a less reactive oxidant than trifluoroperacetic acid, but its application provides several distinct advantages[146] since no buffers are needed and since 3, 5-DNPBA is a crystalline solid which can be stored without significant loss of active oxygen content for up to one year at −10 °C.

Due to the lower reactivity of 3, 5-DNPBA, the reaction times for α, β-unsaturated esters are by a factor of approximately 15–20 times longer than those with trifluoroperacetic acid. The yields of glycidic esters, however, seem to be comparable with, sometimes even higher than, the 3, 5-DNPBA-reagent (see Table 2 for a comparison of trifluoroperacetic acid and 3, 5-DNPBA).

D. Potassium Peroxymonosulfate (Potassium Caroate)

It is the characteristic feature of potassium caroate ($KHSO_5$) that its epoxidizing power is greatly increased in the presence of ketones[151]. Thus, while the caroate alone is not capable of oxidizing, e.g., *trans*-cinnamic acid (**41**), the conversion into the *trans*-epoxide proceeds smoothly in the presence of acetone in over 90% yield[151]. Under the mild reaction conditions (pH 7.5; 2–10 °C) side-reactions due to the facile opening of the oxirane ring are largely suppressed.

As indicated by kinetic, stereochemical and ^{18}O-labeling experiments[152], the formation of dioxirane intermediates **212** is assumed to be responsible for the higher oxidation activity of this system. This suggestion was confirmed through isolation of some methyldioxiranes (**212**) (R = methyl, ethyl, propyl, butyl) in solutions of the parent ketone[153]. The utilization of these solutions gave similar results in the epoxidation of olefins. Recently ^{17}O and ^{13}C NMR spectra of dimethyldioxirane have been recorded in acetone solution[156].

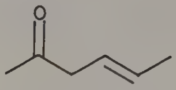
The side-reaction involving Baeyer–Villiger oxidation of the employed ketone is insignificant for most ketones (dialkyl ketones, acetophenone) if the pH value is maintained at 7.5 during the conversion. This can be achieved by continuous addition of a base or by buffering the reaction mixture with $NaHCO_3$[154].

The high stereospecificity of the reaction is demonstrated by the fact that *cis*-cinnamic acid (**91**) could also be converted into the *cis*-epoxide under the same conditions[151].

The epoxidation of water-insoluble olefins can be conducted in a biphasic benzene–water mixture under phase-transfer catalysis[155].

Though the caroate/acetone method seems to be of great versatility, its application to the epoxidation of α, β-unsaturated ketones could not be found in the literature. In these cases the addition of acetone may be expected to be superfluous, because these compounds possess an olefinic double bond and a ketone group within the same molecule, so that the oxidation could occur intramolecularly after dioxirane formation. This has been observed[151] to be the case for 4-hexen-2-one (**213**), which the CC and CO double bonds are not conjugated.

(212)



(213)

VII. HYDROXYLATION

The electron-attracting effect of the carbonyl group is responsible for the fact that not all reagents which can hydroxylate isolated CC double bonds are able to achieve the analogous conversion with α, β-unsaturated carbonyl compounds. Very potent electrophiles are therefore required for the transformation of enones into keto-alcohols.

Depending on the position into which the alcohol functions are introduced, three different hydroxylation pathways will be considered:

(a) *Cis*-hydroxylation of the CC double bonds, reflecting the olefinic character of the substrates. These oxidations occur with the reagents osmium tetraoxide, permanganate and hypervalent iodine.

(b) Hydroxylations at the α′-position of the carbonyl function in enolizable enones, emphasizing their ketonic properties. Representative examples are the hydroxylations with peroxomolybdenum compounds, hypervalent iodine and silyl-protected enone enolates.

(c) Hydroxylation at the γ-position of the enone by selenium dioxide. (A three-step synthesis has been published to accomplish the same transformation with α, β-unsaturated esters.)[157].

Another indirect method of the hydroxylation of α, β-unsaturated compounds is the ring-opening of oxirane precursors[158]. *Trans*-diols are formed in this case in contrast to the *cis*-diols obtained by the reaction with the transition-metal oxides. The reader may refer to the previous section for information concerning the epoxidation of enones.

A. Osmium Tetraoxide

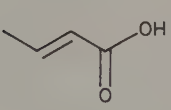
Though the *cis*-hydroxylation of alkenes by osmium tetraoxide has been known since 1912[159], considerable research effort is still focused on this procedure, especially on variations leading to enantioselective product formation.

The mechanism of this reaction has been studied in great detail[160]. The most commonly employed catalysts in the hydroxylation of α,β-unsaturated carbonyl compounds are metal chlorates, H_2O_2 (the mixture of OsO_4, H_2O_2 and *t*-butanol known as Milas' reagent)[60].

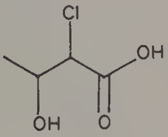
With some metal chlorates, the formation of chlorohydroxy compounds occurs as a side-reaction, presumably due to the intermediate formation of free hypochlorous acid[161]. An example is the reaction of crotonic acid (**214**) with $OsO_4/Ba(ClO_3)_2$ to yield chlorohydroxycrotonic acid (**215**)[161].

Better results can therefore be obtained when silver chlorate is used as a source of chlorate ions. In this case, any free hypochlorous acid is trapped by the formation of the insoluble silver salt. Because this reaction is usually performed in aqueous solvents, it proceeds most readily with substrates having some water solubility.

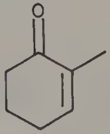
Enones which have been converted[160] into the corresponding keto diols by this method are, e.g., *p*-benzoquinone and 2-methylcyclohexenone (**216**).



(214)

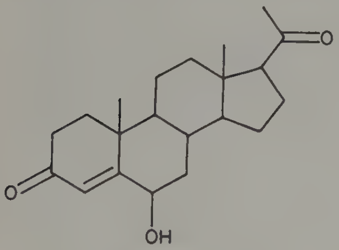


(215)

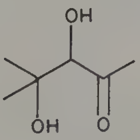


(216)

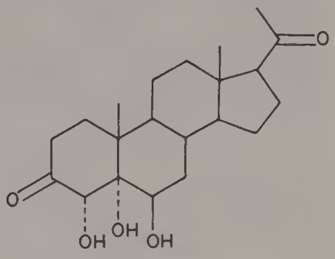
With the more reactive Milas reagent mesityl oxide (**7**) and 6-hydroxyprogesterone (**217**) have been *cis*-hydroxylated to yield **218** and **219**, respectively[162,163]. One major disadvantage of this procedure is that overoxidation sometimes occurs to give rise to carbonyl products thus lowering the yield of *cis*-diol. In all cases, however, an olefinic bond conjugated to a carbonyl group is attacked only in the absence of other CC double bonds having a higher π-electron density (except those which belong to an aromatic π system)[164]. Recently[165,166] it has been shown that the hydroxylation of enones can occur with high stereoselectivity. Steric effects either in the reagent or the substrate can be responsible for the preference of one certain isomer out of many theoretically possible isomers.



(217)

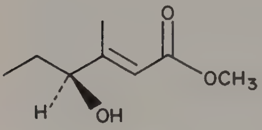


(218)

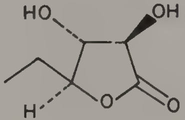


(219)

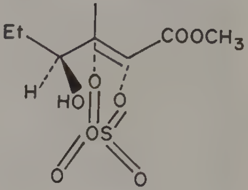
An intramolecularly induced stereoselectivity is observed in the reaction of OsO_4 with 4-hydroxy-3-methyl-2-hexenoic acid methyl ester (**220**) (*E*-isomer) leading to the specific formation of **221** as the single diol (yield 73%)[165]. In order to explain these results a transition state **222** has been suggested. It has been assumed that the prevailing conformation results from an interaction between the π orbitals of the double bond and an unshared electron pair on the γ-hydroxy group due to the electron-withdrawing carbomethoxy function. Approach of the OsO_4 from the least hindered side between the hydrogen and oxygen functions in the γ-position would thus lead to the observed stereochemistry. According to this view the *Z*-isomer of **220** should render the conformation **222** less favorable, with the hydrogen atom now eclipsing the olefinic bond (see **223**). The corresponding *Z*-ester **223** is indeed transformed into the dihydroxylactone **224** which again results from the approach of the osmium reagent between OH and H in **222**. The importance of the presence of the electron-withdrawing carbomethoxy group is demonstrated by the fact that the isopropenyl analogue of **220** (i.e. **225**) shows considerably less stereoselectivity[165].



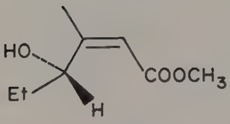
(220)



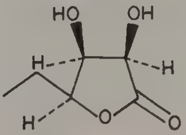
(221)



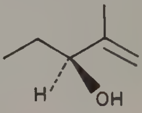
(222)



(223)



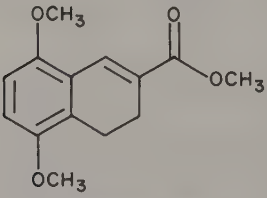
(224)



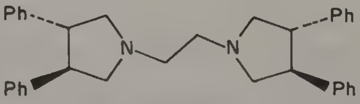
(225)

The conversion of olefins into *cis*-diols with OsO_4 can also be conducted enantioselectively by adding a chiral catalyst. The catalytic effect of tertiary amines in the hydroxylation reaction is well known[160]. By choosing optically active tertiary amines it has been possible to generate asymmetric induction in the reaction of several olefins with OsO_4[167–169].

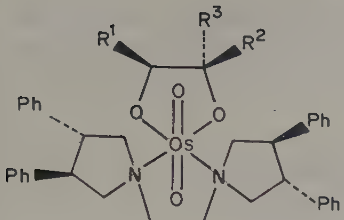
Dimethyl fumarate (yield 67%, ee = 93%) and the ester **226** (yield 89%, ee = 85%) have been transformed into the corresponding *cis*-diols with high enantioselectivity in the presence of the chiral diamine **227**[166]. In this case the hydroxylation is assumed to proceed via the intermediate **228**, which is then reductively cleaved with $LiAlH_4$ or $NaHSO_3$ to generate the diol product. Steric effects have been reported to be responsible for the observed stereoselectivity in the *cis*-hydroxylations of the enones **229** and **230**, which yield **231** and **232** respectively as the single diols through approach of OsO_4 from the least hindered side of the starting compounds[170]. Stereoselective *cis*-hydroxylation of an enone has also been a key step in the total synthesis of pentenomycin[171] (**233**) which is accessible through reaction of **234** with OsO_4 in pyridine to yield **235**.



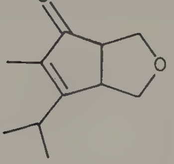
(226)



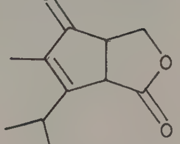
(227)



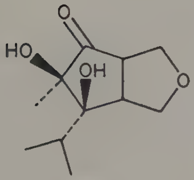
(228)



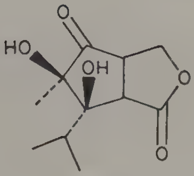
(229)



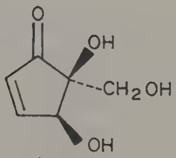
(230)



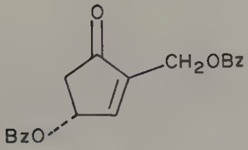
(231)



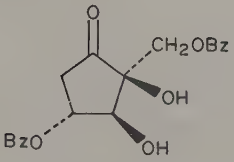
(232)



(233)



(234)



(235)

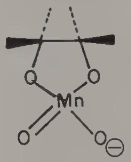
B. Potassium Permanganate

The oxidation of alkenes by permanganate ions to yield the *cis*-hydroxylated products has been known for nearly a century[172], and despite its limitations it is still widely used. Careful control of the reaction conditions is required if the substrate is not to be consumed by extensive side-reactions, such as cleavage of the CC double bond due to further oxidation of the formed diol or due to acid- or base-catalyzed isomerizations. Though the reaction has been extensively studied, its exact mechanistic pathway is still a matter of controversy[173]. After Criegee had shown[174] that the analogous reaction with OsO_4 occurs through cyclic osmate esters (see above), a similar mechanism was adopted for the MnO_4^- oxidation.

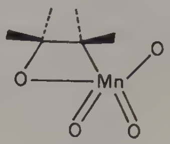
The cyclic manganate(V)ester **236** is still elusive, but its formation is supported by recent kinetic investigations showing that the reaction is determined by low energies of activation, large negative entropies of activation, steric effects and an inverse secondary deuterium kinetic isotope effect[175]. By using ^{18}O-labeled permanganate it was demonstrated that both glycol oxygens come from the oxidizing agent[176].

The very similar rate constants measured for the hydroxylation of salts of various substituted cinnamic acids show that the reaction in this series is essentially independent of electronic factors; accordingly, a decisive answer as to whether the MnO_4^- reagent is electrophilic[177], nucleophilic[178] or ambiphilic[173] in nature cannot be given.

The combination of the kinetic findings has led to the conclusion[175] that the permanganate ion undergoes cycloaddition with the CC double bond to yield the metallacyclooxetane **237** or the cyclic manganate(V) diester **236**.



(236)

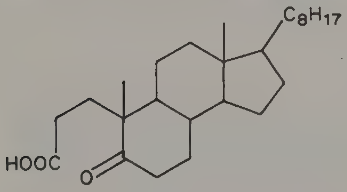


(237)

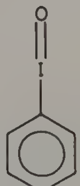
According to the hydrophilic nature of the oxidant this hydroxylation reaction is usually performed in aqueous media with substrates having a certain water solubility, most often α,β-unsaturated acids. More lipophilic olefins [e.g. mesityl oxide (**7**) or cinnamic acid esters such as **59**] can be hydroxylated in mixtures of organic solvents such as ethanol, *t*-butanol or acetone with water[179] or by employing quaternary ammonium permanganates[180,181]. The latter method allows the reaction to be performed in purely organic solvents (e.g. methylene chloride). $KMnO_4$ has also been used in catalytic amounts together with sodium metaperiodate as co-oxidant to cleave the olefinic bond in enones with formation of keto acids[182,183]. Treatment of cholest-4-en-3-one (**82**) with this reagent[183] yields the keto acid **238** (80%).

C. Hypervalent Iodine Compounds

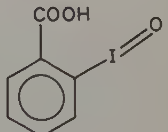
Iodosobenzene (**239**) and *o*-iodosylbenzoic acid (**240**) are known to convert enolizable ketones in the presence of a base (methanol/KOH) into α-hydroxydimethyl acetals[184] (see below). When no acidic α-hydrogens are available, as in α, β-unsaturated ketones, the reaction follows a different pathway.



(238)

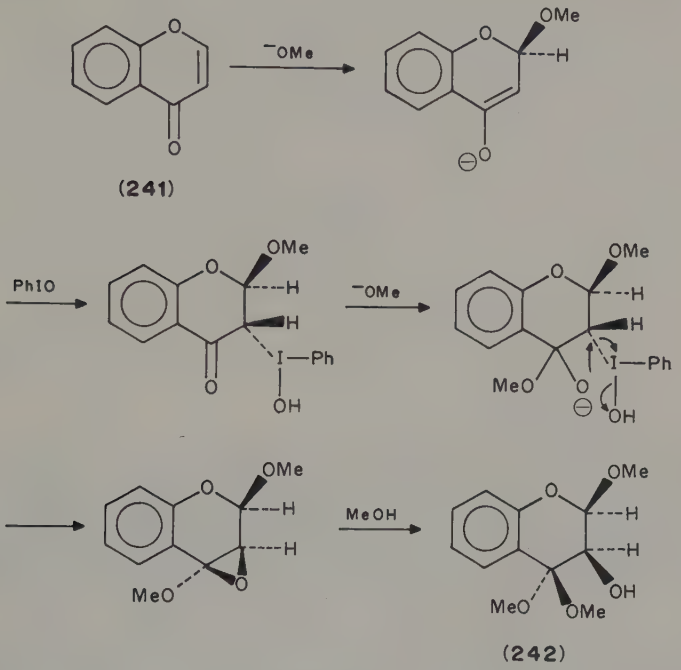


(239)



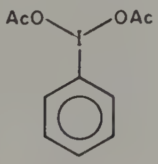
(240)

In the case of enones the product is the β-alkoxylated, dimethyl acetal derivative[185]. Though the reaction mechanism does not include an electrophilic attack of the oxidant on the olefinic bond, but rather involves an initial Michael addition of the base at C_β of the unsaturated system, this conversion has been included in this section because the products belong to the same family as those obtained from the hydroxylations with OsO_4 or $KMnO_4$, namely α-keto glycol derivatives. The course of the reaction shall be exemplified for chromone (**241**), which regio- and stereospecifically yields compound **242** upon treatment with **239** in methanol/KOH (Scheme 8)[184]. The proposed mechanism proceeds via initial Michael addition of a methoxide ion (MeO^-) on the unsaturated system followed by electrophilic *anti* addition of iodosobenzene to the resulting enolate anion. Addition of another equivalent of MeO^- to the carbonyl oxygen generates an alkoxide which stabilizes itself by S_Ni attack on the C_α. The resulting epoxide undergoes ring opening by another molecule of the base generating **242** (after subsequent protonation) (see Scheme 8). The yield is 60%. The stereochemistry has been confirmed through X-ray crystallography, indicating the *cis* position of the methoxy and the hydroxy group added to the double bond.

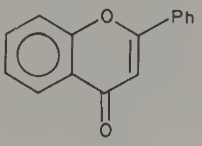


SCHEME 8

Analogous products have been obtained from the reaction of PhI(OAc)$_2$ (**243**) methanol/KOH with flavone (**244**) and chalcone (**64**)[185], showing its general applicability to the oxidation of α,β-unsaturated ketones.



(243)

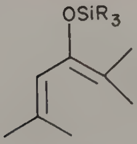


(244)

VIII. α'-HYDROXYLATION OF ENOLIZABLE ENONES

α'-Hydroxylation of unsaturated (see Scheme 9) and saturated ketones is a key step in the synthesis of several natural products[186,187]. Three recent methods which have been developed for this purpose are the oxidations of ketone enolates employing (a) the peroxomolybdenum system MoO$_5$/pyridine/hexamethylphosphoric acid[188,189] ('MoOPH'), (b) hypervalent iodine compounds such as iodosylbenzene (**239**) and diacetoxyphenyliodine(III) (**243**) and (c) the epoxidation of silylenolates such as **245**. These methods are also useful in the series of enolizable α, β-unsaturated carbonyl compounds.

SCHEME 9



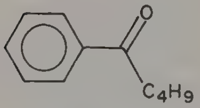
(**245**)

A. Molybdenum Peroxide/Pyridine/HMPA

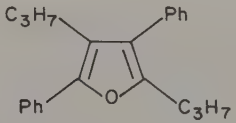
The MoOPH system can easily be prepared[190] from molybdenum trioxide, 30% H_2O_2 and hexamethylphosphoric acid (HMPA). The resulting complex is dehydrated (in a desiccator) and dissolved in THF; addition of pyridine precipitates the oxidant, which is stable over a long period when stored in the dark at low temperature. MoOPH has been reported to decompose violently after storage at ambient temperature under the influence of light[188].

The hydroxylation reaction is performed via the enolate of the carbonyl compound which is generated by deprotonation of the neutral precursor with strong bases, e.g. lithium diisopropylamide (LDA), at low temperatures (−22 to −78 °C, depending on the substrate). Possible side-reactions are the overoxidation to α-diketones and the aldol condensation of the enolate with the formed α-hydroxy product.

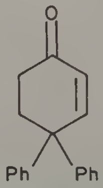
The latter complication becomes especially important in the oxidation of sterically unhindered enolates (e.g. enolates of methyl ketones). Valerophenone (**246**), for instance, yields up to 42% of the furan derivative **247** (formed after cyclization and dehydration of the primary aldol adduct) under unfavorable reaction conditions[188]. In these cases an inverse addition technique (addition of enolate to MoOPH) or working in high dilution can minimize the amount of by-products formed by aldolization. With these precautions valerophenone (**246**) and 4, 4-diphenylcyclohexenone (**248**) have been converted into the corresponding acyloins (**249**, **250**) in 70% and 53% yield, respectively. An inverse addition procedure has also been reported to be essential for the conversion of 3-β-methoxypregna-5,16-dien-20-one (**251**) into the C-21-hydroxylated product **252**[188].



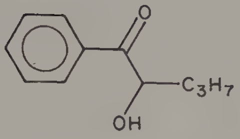
(**246**)



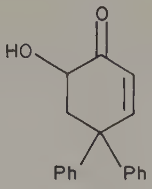
(**247**)



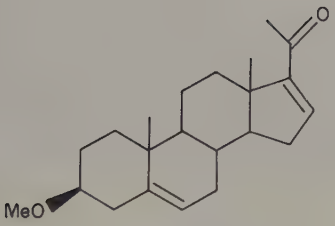
(**248**)



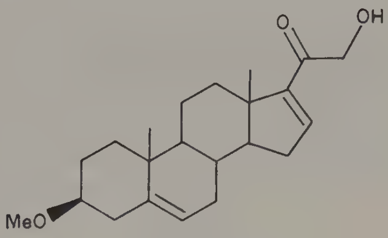
(249)



(250)



(251)

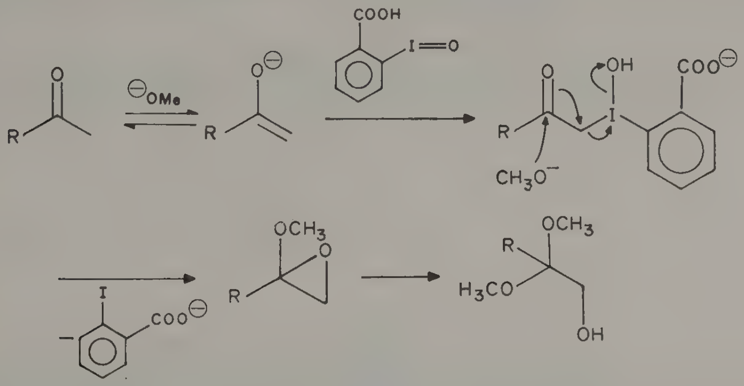


(252)

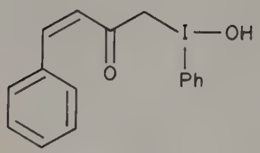
B. Hypervalent Iodine Compounds

The α′-hydroxylation of unsaturated ketones with the aid of hypervalent iodine compounds such as iodosylbenzene (**239**)[191], diacetoxyphenyliodine (**243**)[191,192] or *o*-iodosylbenzoic acid (**240**)[192] is a valuable synthetic tool, especially in those cases where the application of peroxomolybdenum oxidants does not lead to the desired acyloins (see above).

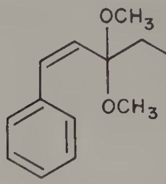
Treatment of, e.g., benzalacetone **36** with a base (KOH/methanol) generates an equilibrium concentration of the corresponding enolate which is attacked by the subsequently added iodine reagent as depicted in Scheme 10. Addition of one equivalent of the base to the carbonyl oxygen cleaves the intermediate **253** with concomitant epoxide formation. This epoxide is finally solvolyzed by methanol to yield the product α′-hydroxybenzalacetone dimethyl acetal (**254**). The acyloin can then be isolated in the acetal form or deprotected *in situ* with 5% H_2SO_4 to yield the free keto alcohol **255**[191].



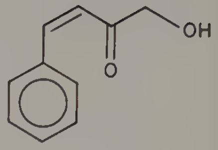
SCHEME 10



(253)



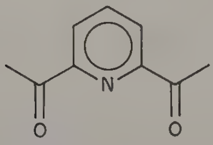
(254)



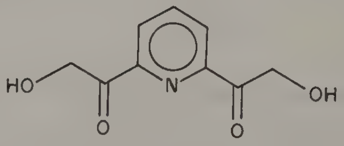
(255)

This transformation is most conveniently performed with the commercially available *o*-iodosylbenzoic acid (**240**) which is reduced to *o*-iodobenzoic acid. Purification of the acyloin is in this case achieved by simple extraction with water, whereas the other iodine reagents mentioned require separation from the reaction products by chromatography[192].

In bifunctional systems such as diacetylpyridine (**256**) both functionalities take part in the reaction[191] to yield the bis-acyloin **257**. Compounds of this structure are potentially important precursors in the synthesis of macrocycles.



(256)

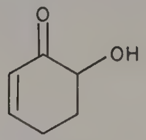


(257)

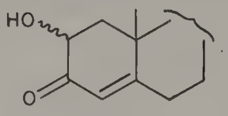
C. Oxidation of Silyl Enol Ethers

Another method for the transformation of enones into the corresponding α′-hydroxy enones is provided by the peracid oxidation of silyl enol ethers which serve as enolate equivalents[193,194]. The *O*-silylated enone[195] is treated with, e.g., *m*-chloroperbenzoic acid which attacks the electron-richest double bond (i.e. the one bearing the $OSiR_3$ group). Cleavage of the O—Si bond with triethylammonium fluoride[196] and hydrolysis or acetylation of the oxirane intermediate generates the acyloin or the α′-acetoxy compound, respectively. The mildness of the procedure allows the isolation of labile compounds such as α′-hydroxycyclohexenones **258** in high yields.

As indicated by the transformation of cholest-4-en-3-one (**82**) into the acyloin **259**, the reaction is not stereospecific but yields a mixture of the α- and β-isomers[194].



(258)

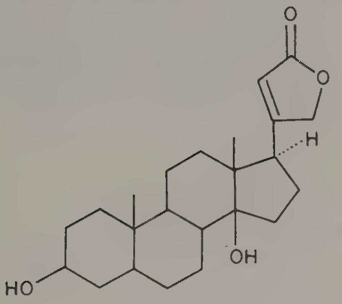


(259)

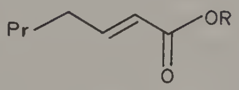
IX. γ-OXIDATION WITH SELENIUM DIOXIDE[197]

A methylene group in the γ-position of enones constitutes another reactive site which can regioselectively be attacked by electrophiles. Depending on the reaction conditions γ-hydroxy derivatives or γ-oxo enones are obtained upon oxidation with selenium dioxide. In the case of α, β-unsaturated acids or esters the introduced alcohol function frequently induces further transformation of the starting material into α, β-unsaturated lactones by intramolecular esterification or transesterification as illustrated in the synthesis of digitoxigenin **260**[198].

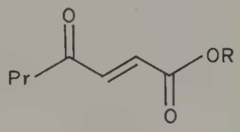
The oxidation of 2-heptenoic acid esters **261** in dioxane provides an example for the possible control of the product spectrum (γ-alcohol or γ-oxo compound). Working under nonaqueous conditions leads to the formation of 4-oxoheptenoic acid ester **262** while the same reaction in dioxane containing 3% water yields the 4-hydroxyheptenoic acid ester **263**[199]. This principle has been applied in the synthesis of some macrolid antibiotics, e.g. norpyrenophorin **264**[199].



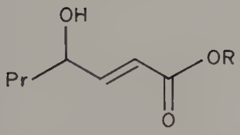
(260)



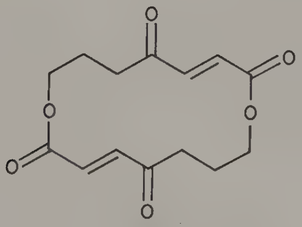
(261)



(262)

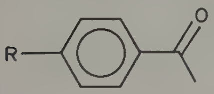


(263)

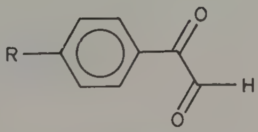


(264)

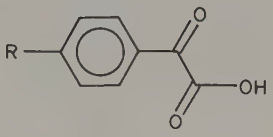
Enones which do not possess a methylene group allylic to the CC double bond but an α′-methyl group such as the substituted acetophenones **265** are attacked at this ('hetero-allylic') position[200] with formation of glyoxals **266** or, with an excess of the oxidant[201], α-keto acids **267**.



(265)



(266)



(267)

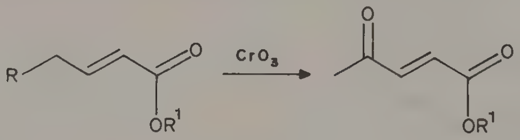
Regioselective γ-hydroxylation of α, β-unsaturated esters has also been described via electrophilic attack at the γ-position of the corresponding enolate anion[157].

X. MISCELLANEOUS

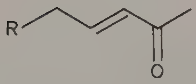
Numerous oxidation reactions of enones which do not follow a general pattern exist in the literature. Some examples have been chosen arbitrarily and are listed below. This list, however, is by no means intended to be comprehensive.

A. Allylic Oxidation with Chromium Trioxide

The use of chromium trioxide as an oxidant has enabled the conversion of α,β-unsaturated esters into γ-oxo-α,β-unsaturated esters[202], important intermediates in the preparation of cyclopentenone derivatives[203] (Scheme 11). This reaction is comparable to the analogous transformation employing selenium dioxide (see previous section), except that hydroxylated species are not accessible due to the greater oxidizing power of the chromium reagent. In the series of α,β-unsaturated ketones the method has been applied to 3-alkene-2-ones **268** with R representing long-chain alkyl groups. In these cases the yields were considerably poorer due to a side-reaction involving cleavage of the olefinic bond which leads to the formation of aliphatic acids[202].



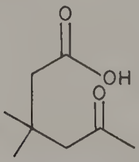
SCHEME 11



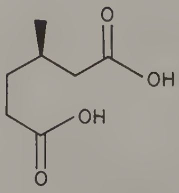
(268)

B. Oxidation with Ruthenium Tetraoxide

The olefinic bond in enones can be cleaved with ruthenium tetraoxide to yield diacids or keto acids[204,205]. Any aldehyde groups present are usually oxidized to acids. The ruthenium tetraoxide is applied in either stoichiometric amounts[204] or in catalytic amounts together with a co-oxidant such as $NaIO_4$[205,206]. Examples[205] are the conversions of isophorone (**81**) to 3, 3-dimethyl-5-oxohexanoic acid (**269**) and of pulegone (**88**) to (+)-3-methyladipic acid (**270**).



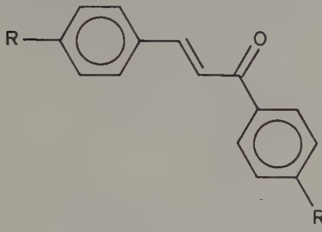
(269)



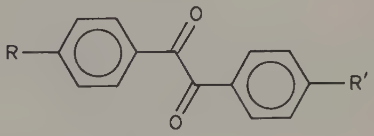
(270)

C. Oxidation with Thallium(III) Compounds

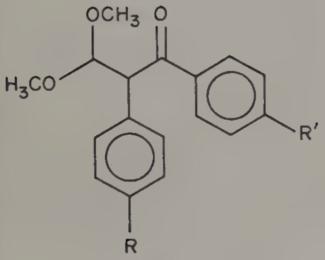
The oxidation of differently substituted chalcones **271** with thallium(III) salts such as $Tl(OAc)_3$ or the more electrophilic $Tl(NO_3)_3$ produces a variety of products dependent on the nature of the substituents and on the reaction conditions. Unsymmetric benzils **272**, for example, are formed during the reaction of chalcones with three equivalents of $Tl(NO_3)_3$ in aqueous acidic dimethoxyethane (glyme)[207]. The use of one equivalent of the oxidant in acidic methanol as solvent affords, in contrast, 3, 3-dimethoxy-1, 2-diarylpropan-1-ones (**273**)[208]. Compounds **273** derived from chalcones bearing an *o*-methyl group within the benzoyl moiety are key intermediates in the synthesis of isoflavones **274**[209]. Tl(III) oxidation of deactivated chalcones (i.e. those possessing electron-attracting substituents) affords methyl 2, 3-diaryl-3-methoxypropanoates **275** in acidic methanol or, better, in trimethyl orthoformate as solvents[209].



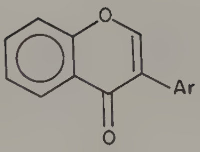
(271)



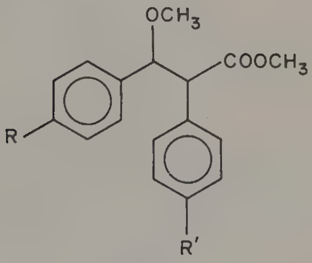
(272)



(273)



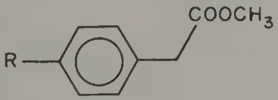
(274)



(275)

The influence of these variations of the reaction conditions on the product selectivity has been rationalized in terms of three competing reaction pathways[209]. Each of these pathways involves a 1, 2-aryl migration and has been studied by ^{14}C-labeling experiments in the case of the synthesis of compounds **273**.

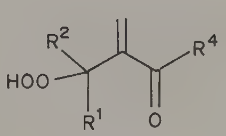
The adsorption of $Tl(NO_3)_3$ on montmorillonite clay enhances the versatility of the reagent[211]. Substituted acetophenones **265** have been converted into methyl arylacetates **276** in excellent yield with this reagent. Oxidations of cinnamic acid esters were successful only with this form of the oxidant[211].



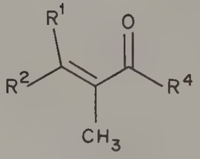
(276)

D. Oxidation with Singlet Oxygen

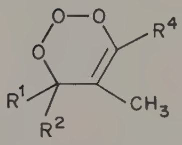
Singlet oxygen has been used to oxidize α,β-unsaturated ketones[210] and esters[212] leading to the formation of the hydroperoxides **277**. A characteristic feature of both classes of compounds is the common regiochemistry encountered in this conversion. In enones of the general structure **278** the newly formed CC double bond is directed to the allylic carbon in a geminal position to the carbonyl functionality (i.e. towards R^3). The other possible isomers are formed only in minor amounts. This result has also been observed for cyclohexenones[210] and is in marked contrast to the analogous reaction of cyclohexenes which usually yield olefins with exocyclic double bonds[213]. A plausible explanation for the geminal effect assumes initial [4 + 2]cycloaddition of singlet oxygen and the enone with formation of the 1, 2, 3-trioxine **279**. Thermolytic cleavage of a weak OO bond could then occur to yield the stabilized diradical **280**. Subsequent abstraction of a β-hydrogen generates the major product **277**[210].



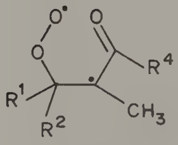
(277)



(278)



(279)



(280)

The reaction is of considerable synthetic utility[214]. If the hydroperoxide is reduced to the alcohol (e.g. with triethyl phosphite[210]) it constitutes, in addition to the transformations described in Section IX, another method of introducing a hydroxyl group regioselectively into an enone.

XI. REFERENCES

1. D. Swern, *Chem. Rev.*, **45**, 1 (1949).
2. H. O. House, *Modern Synthetic Reactions*, 2nd edn., W. A. Benjamin, Menlo Park, Calif., 1972, p. 306.
3. G. Berti, *Top. Stereochem.*, **7**, 166 (1973).
4. S. Rozen, O. Lerman, M. Kol and D. Hebel, *J. Org. Chem.*, **50**, 4753 (1985).
5. V. L. Heasley, D. F. Shellhamer, T. L. Carter, D. E. Gipe, R. K. Gipe, R. C. Green, J. Nordeen, T. D. Rempel and D. W. Spaite, *Tetrahedron Lett.*, **22**, 2467 (1981).
6. J. L. Jensen and D. J. Carré, *J. Org. Chem.*, **39**, 2103 (1974).
7. N. C. Deno, H. G. Richey, N. Friedman, J. D. Hodge, J. J. Houser and Ch. U. Pittman, Jr., *J. Am. Chem. Soc.*, **85**, 2991 (1963).
8. R. I. Zalewski and G. E. Dunn, *Can. J. Chem.*, **46**, 2469 (1968).
9. R. I. Zalewski and G. E. Dunn, *Can. J. Chem.*, **47**, 2264 (1969).
10. R. I. Zalewski and G. E. Dunn, *Can. J. Chem.*, **48**, 2538 (1970).
11. E. M. Arnett, *Prog. Phys. Org. Chem.*, **1**, 223 (1963).
12. (a) C. C. Greig and C. D. Johnson, *J. Am. Chem. Soc.*, **90**, 6453 (1968).
    (b) T. G. Bonner and J. Phillips, *J. Chem. Soc. (B)*, 650 (1966).

13. H. J. Campbell and J. T. Edward, *Can J. Chem.*, **38**, 2109 (1960).
14. G. C. Levy, J. D. Cargioli and W. Racela, *J. Am. Chem. Soc.*, **92**, 6238 (1970).
15. E. M. Arnett, R. P. Quirk and J. W. Larsen, *J. Am. Chem. Soc.*, **92**, 3977 (1970).
16. J. L. Jensen and A. T. Thibeault, *J. Org. Chem.*, **42**, 2168 (1977).
17. K. Müllen, E. Kotzamani, H. Schmickler and B. Frei, *Tetrahedron Lett.*, **25**, 5623 (1984).
18. G. Olah, Y. Halpern, Y. K. Mo and G. Liang, *J. Am. Chem. Soc.*, **94**, 3554 (1972).
19. R. F. Childs, E. F. Lund, A. G. Marshall, W. J. Morrisey and C. V. Rogerson, *J. Am. Chem. Soc.*, **98**, 5924 (1976).
20. R. F. Childs, D. L. Mulholland and A. Nixon, *Can. J. Chem.*, **60**, 801 (1982).
21. J. V. Greenhill, *Chem. Soc. Rev.*, **6**, 277 (1977); H. E. A. Kramer and R. Gompper, *Z. Phys. Chem. (Frankfurt am Main)*, **43**, 349 (1964); H. Böhme and M. Tränka, *Liebigs. Ann. Chem.*, 149 (1985).
22. N. J. Leonard and J. A. Adamcik, *J. Am. Chem. Soc.*, **81**, 595 (1959); A. I. Meyers, A. H. Reine and R. Gault, *J. Org. Chem.*, **34**, 698 (1969); G. H. Alt and A. J. Speziale, *J. Org. Chem.*, **30**, 1407 (1965); H. Bredereck, F. Effenberger, D. Zeyfang and K.-A. Hirsch, *Chem. Ber.*, **101**, 4036 (1968); H. Böhme and J. Grätzel von Grätz, *Tetrahedron*, **33**, 841 (1977).
23. B. Singer and G. Maas, *Chem. Ber.*, **120**, 485 (1987).
24. M. Hauser, *Chem. Rev.*, **63**, 311 (1963).
25. J. L. Jensen and D. J. Carré, *J. Org. Chem.*, **36**, 3180 (1971).
26. (a) W. M. Schubert and J. R. Keefe, *J. Am. Chem. Soc.*, **94**, 559 (1972).
    (b) W. M. Schubert and J. L. Jensen, *J. Am. Chem. Soc.*, **94**, 566 (1972).
27. A. J. Kresge, Y. Chiang, P. H. Fitzgerald, R. S. McDonald and G. H. Schmid, *J. Am. Chem. Soc.*, **93**, 4907 (1971).
28. J. J. Scott and K. R. Brower, *J. Am. Chem. Soc.*, **89**, 2682 (1967).
29. R. P. Bell, J. Preston and R. B. Whitney, *J. Chem. Soc.*, 1166 (1962).
30. D. Pressman and H. J. Lucas, *J. Am. Chem. Soc.*, **62**, 2069 (1940).
31. D. S. Noyce and K. E. DeBruin, *J. Am. Chem. Soc.*, **90**, 372 (1968).
32. L. R. Fedor and J. McLaughlin, *J. Am. Chem. Soc.*, **91**, 3594 (1969).
33. D. M. Jones and N. F. Wood, *J. Chem. Soc.*, 5400 (1964).
34. E. J. Stamhuis, W. Drenth and H. van den Berg, *Rec. Trav. Chim. Pays-Bas*, **83**, 167 (1964).
35. T. H. Fife, *J. Am. Chem. Soc.*, **87**, 1084 (1965).
36. A. J. Kresge, D. S. Sagatys and H. L. Chen, *J. Am. Chem. Soc.*, **90**, 4174 (1968).
37. A. J. Kresge and Y. Chiang, *J. Chem. Soc.* (B), 58 (1967).
38. L. R. Fedor, N. C. De and S. K. Gurwara, *J. Am. Chem. Soc.*, **95**, 2905 (1973).
39. D. S. Noyce and W. L. Reed, *J. Am. Chem. Soc.*, **80**, 5539 (1958).
40. D. S. Noyce and M. J. Jorgenson, *J. Org. Chem.*, **28**, 3208 (1963).
41. P. D. Bartlett and G. D. Sargent, *J. Am. Chem. Soc.*, **87**, 1297 (1965).
42. J. E. Vik, *Acta Chem. Scand.*, **27**, 251 (1973).
43. J. L. Jensen and H. Hashtroudi, *J. Org. Chem.*, **41**, 3299 (1976).
44. C. F. Bernasconi and G. D. Leonarduzzi, *J. Am. Chem. Soc.*, **104**, 5133 (1982).
45. C. F. Bernasconi and G. D. Leonarduzzi, *J. Am. Chem. Soc.*, **104**, 5143 (1982).
46. A. Hoffman, *J. Am. Chem. Soc.*, **49**, 530 (1927).
47. J. B. Tindall, U.S. Patent 2, 430, 436; *Chem. Abstr.*, **42**, 1964 (1948).
48. D. Pressman and H. J. Lucas, *J. Am. Chem. Soc.*, **64**, 1953 (1942).
49. D. S. Noyce, H. S. Avarbock and W. L. Reed, *J. Am. Chem. Soc.*, **84**, 1647 (1962).
50. H. Rupe and S. Kessler, *Chem. Ber.*, **42**, 4715 (1909).
51. G. Richard, M. Mirjolet and P. Gschwind, *Compt. Rend.*, **223**, 1007 (1946).
52. T. Sakai, K. Miyata, M. Utaka and A. Takeda, *Bull. Chem. Soc. Jpn.*, **60**, 1063 (1987).
53. G. A. Olah and S. C. Narang, *Tetrahedron*, **38**, 2225 (1982).
54. R. D. Miller and D. R. McKean, *Tetrahedron Lett.*, 2305 (1979).
55. T. Azuhata and Y. Okamoto, *Synthesis*, 461 (1983).
56. G. L. Larson and R. Klesse, *J. Org. Chem.*, **50**, 3627 (1985).
57. Y. S. Rao and R. Filler, *J. Chem. Soc., Chem. Commun.*, 471 (1976).
58. C. Santelli-Rouvier and M. Santelli, *Synthesis*, 429 (1983).
59. R. S. Atkinson and R. H. Green, *J. Chem. Soc., Perkin Trans 1*, 394 (1974).
60. C. K. Ingold and E. H. Ingold, *J. Chem. Soc.*, 2354 (1931); S. V. Anantakrishnan and C. K. Ingold, *J. Chem. Soc.*, 1396 (1935).
61. E. P. White and P. W. Robertson, *J. Chem. Soc.*, 1509 (1939).
62. P. B. D. de la Mare and P. W. Robertson, *J. Chem. Soc.*, 888 (1945).

63. P. W. Robertson, R. M. Dixon, W. G. M. Goodwin, I. R. McDonald and J. F. Scaife, *J. Chem. Soc.*, 294 (1949).
64. P. B. D. de la Mare and P. W. Robertson, *J. Chem. Soc.*, 2838 (1950).
65. I. R. C. McDonald, R. M. Milburn and P. W. Robertson, *J. Chem. Soc.*, 2836 (1950).
66. M. C. Cabaleiro, C. J. Cooksey, M. D. Johnson, B. E. Swedlund and J. G. Williams, *J. Chem. Soc. (B)*, 1026 (1968); M. C. Cabaleiro, M. D. Johnson, B. E. Swedlund and J. G. Williams, *J. Chem. Soc. (B)*, 1022 (1968).
67. M. C. Cabaleiro and A. B. Chopa, *J. Chem. Soc., Perkin Trans. 2*, 452 (1974).
68. V. L. Heasley, D. W. Spaite and D. F. Shellhamer, *J. Org. Chem.*, **44**, 2608 (1979).
69. Y. L. Chow and B. H. Bakker, *Can. J. Chem.*, **60**, 2268 (1982).
70. R. P. Bell and M. Pring, *J. Chem. Soc. (B)*, 1119 (1966).
71. F. C. Fahey, *Top. Stereochem.*, **3**, 237 (1968).
72. H. P. Rothbaum, I. Ring and P. W. Robertson, *J. Chem. Soc.*, 980 (1945).
73. N. Latif and K. El-Bayouki, *Chem. Ind.*, 316 (1975).
74. R. E. Buckles and J. W. Long, *J. Am. Chem. Soc.*, **73**, 998 (1951).
75. R. E. Buckles, J. L. Forrester, R. L. Burham and T. W. McGee, *J. Org. Chem.*, **25**, 24 (1960).
76. A. Bruckner, *Acta Chim. Acad. Sci. Hung.*, **49**, 287 (1966).
77. S. Groszkowski and J. Sienkicwicz, *Rocz. Chem.*, **45**, 1779 (1971); *Chem. Abstr.*, **76**, 99043v (1972).
78. I. O. O. Korhonen, M. Pitkänen and J. N. J. Korvola, *Tetrahedron*, **38**, 2837 (1982).
79. A. I. Popov and J. J. Mannion, *J. Am. Chem. Soc.*, **74**, 222 (1952).
80. M. Pitkänen and I. O. O. Korhonen, *Tetrahedron*, **39**, 3367 (1983).
81. M. Pitkänen and I. O. O. Korhonen, *Tetrahedron*, **41**, 4707 (1985).
82. H. J. Hageman and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, **85**, 1143 (1966).
83. G. Bellucci, G. Ingrosso, F. Marioni, E. Mastrorilli and I. Morelli, *J. Org. Chem.*, **39**, 2562 (1974).
84. V. L. Heasley, D. F. Shellhamer, J. A. Iskikian and D. L. Street, *J. Org. Chem.*, **43**, 3139 (1978).
85. M. Pastureau and H. Bernard, *Bull. Soc. Chim. Fr.*, **33**, 1440 (1923).
86. G. Cauquil and P. Mion, *Bull. Soc. Chim. Fr.*, **D**, 659 (1940).
87. S. Marmor, *J. Org. Chem.*, **30**, 3556 (1965).
88. Z. Jedlinski and J. Majnusz, *Chem. Abstr.*, **73**, 44840k (1970).
89. P. B. D. de la Mare and M. A. Wilson, *J. Chem. Soc., Perkin Trans. 2*, 653 (1973).
90. P. B. D. de la Mare, M. A. Wilson and M. J. Rosser, *J. Chem. Soc., Perkin Trans. 2*, 1480 (1973).
91. P. B. D. de la Mare, C. J. O'Connor and M. A. Wilson, *J. Chem. Soc., Perkin Trans. 2*, 1150 (1975).
92. P. Melikoff, *Chem. Ber.*, **12**, 2227 (1879); **13**, 2153 (1880).
93. J. E. Dubois and J. R. Chretien, *J. Am. Chem. Soc.*, **100**, 3506 (1978).
94. E. S. Gould, *Mechanism and Structure in Organic Chemistry*, Holt, Rinehart and Winston, New York, 1959, p. 284.
95. G. A. Olah, *Halonium Ions*, Wiley, New York, 1975 p. 114.
96. V. L. Heasley, D. F. Shellhamer, R. K. Gipe, H. C. Wiese and M. L. Oakes and G. E. Heasley, *Tetrahedron Lett.*, **21**, 4133 (1980).
97. G. E. Heasley, V. M. McCully, R. T. Wiegman, V. L. Heasley and R. A. Skidgel, *J. Org. Chem.*, **41**, 644 (1976).
98. V. L. Heasley, G. E. Heasley, P. D. Davis, D. M. Ingle and K. D. Rold, *J. Org. Chem.*, **39**, 736 (1974).
99. R. C. Fahey, *J. Am. Chem. Soc.*, **88**, 4681 (1966).
100. S. G. Hegde and J. Wolinsky, *Tetrahedron Lett.*, **22**, 5019 (1981).
101. S. Rozen and O. Lerman, *J. Org. Chem.*, **45**, 672 (1980).
102. D. H. R. Barton, R. H. Hesse, G. P. Jackman, L. Ogunkoya and M. M. Pechet, *J. Chem. Soc., Perkin Trans. 1*, 739 (1974).
103. O. Lerman and S. Rozen, *J. Org. Chem.*, **45**, 4122 (1980).
104. R. H. Hesse, *Isr. J. Chem.*, **17**, 60 (1978).
105. F. W. Fowler, A. Hassner and L. A. Levy, *J. Am. Chem. Soc.*, **89**, 2077 (1967).
106. A. Hassner, M. Lorber and C. H. Heathcock, *J. Org. Chem.*, **32**, 540 (1967).
107. A. N. Nesmeyanov and M. I. Rybinskaya, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 816 (1962).
108. R. C. Cambie, J. L. Jurlina, P. S. Rutledge, B. E. Swedlund and P. D. Woodgate, *J. Chem. Soc., Perkin Trans. 1*, 327 (1982).
109. R. C. Cambie, R. C. Hayward, P. S. Rutledge, T. Smith-Palmer, B. E. Swedlund and P. D. Woodgate, *J. Chem. Soc., Perkin Trans. 1*, 180 (1979).

110. H. Pauly and H. V. Berg, *Chem. Ber.*, **34**(2), 2092 (1901).
111. K. Mitsuhashi and K. Nomura, *Chem. Pharm. Bull.* (*Tokyo*), **13**, 951 (1965).
112. J. Klein and S. Zitrin, *J. Org. Chem.*, **35**, 666 (1970).
113. D. J. Buckley, S. Kulkowit and A. McKervey, *J. Chem. Soc., Chem. Commun.*, 506 (1980).
114. N. H. Cromwell, D. J. Cram and C. E. Harris, *Org. Synth., Coll. Vol.* 3, 125 (1962).
115. G. L. Dunn, V. J. DiPasquo and J. R. E. Hoover, *J. Org. Chem.*, **33**, 1454 (1968).
116. F. G. Bordwell and K. M. Wellman, *J. Org. Chem.*, **28**, 2544 (1963).
117. D. B. Denney and S. T. Ross, *J. Org. Chem.*, **27**, 998 (1962).
118. L. W. Metzger and O. Bayer, *Chem. Abstr.*, (Ger. 708, 371) **37**, 3105 (1943).
119. C. H. Nield, *J. Am. Chem. Soc.*, **67**, 1145 (1945).
120. G. Zima and D. Liotta, *Synthetic Commun.*, **9**, 697 (1979).
121. S. V. Ley and A. J. Whittle, *Tetrahedron Lett.*, **22**, 3301 (1981).
122. D. Liotta and G. Zima, *Tetrahedron Lett.*, 4977 (1978).
123. H. H. Inhoffen, *Angew. Chem.*, **53**, 473 (1940); **59**, 207 (1947).
124. A. Butenandt, G. Schramm and H. Kudsus, *Liebigs Ann. Chem.*, **531**, 176 (1937).
125. C. Djerassi, G. Rosenkranz, J. Romo, S. Kaufmann and J. Pataki, *J. Am. Chem. Soc.*, **72**, 4534 (1950).
126. E. R. Glazier, *J. Org. Chem.*, **27**, 4397 (1962).
127. P. B. Sollman and R. M. Dodson, *J. Org. Chem.*, **26**, 4180 (1961).
128. A. Marquet and J. Jacques, *Tetrahedron Lett.*, 24 (1959).
129. A. Marquet, M. Dvolaitzky, H. B. Kagan, L. Mamlok, C. Ouannes and J. Jacques, *Bull. Soc. Chim. Fr.*, 1822 (1961).
130. A. Marquet and J. Jacques, *Bull. Soc. Chim. Fr.*, 90 (1961).
131. D. V. C. Awang and S. Wolfe, *Can. J. Chem.*, **47**, 706 (1969).
132. P. L. Southwick, L. A. Pursglove and P. Numerof, *J. Am. Chem. Soc.*, **72**, 1600 (1950).
133. N. L. Allinger, L. W. Chow and R. A. Ford, *J. Org. Chem.*, **32**, 1994 (1967).
134. V. Calo, L. Lopez, G. Pesce and P. E. Todesco, *Tetrahedron*, **29**, 1625 (1973).
135. B. R. Kennedy and K. U. Ingold, *Can. J. Chem.*, **45**, 2632 (1972).
136. M. S. Newman, *J. Am. Chem. Soc.*, **73**, 4993 (1951).
137. K. Matoba, N. Karibe and T. Yamazaki, *Chem. Pharm. Bull.*, **32**, 2639 (1984).
138. W. P. Evans, *Z. Phys. Chem.*, **7**, 337 (1891).
139. R. Helder, J. C. Hummelen, R. W. P. M. Laane and J. C. Wiering, *Tetrahedron Lett.*, 1831 (1976).
140. H. Wynberg, *Top. Stereochem.*, **16**, 113 (1986).
141. D. Swern, *Organic Reactions*, Vol. 7, Wiley, New York, 1953, p. 378.
142. H. Hart, M. Verma and I. Wang, *J. Org. Chem.*, **38**, 3418 (1973).
143. D. D. Keane, W. I. O'Sullivan, E. M. Philbin, R. M. Simons and P. C. Teague, *Tetrahedron*, **26**, 2533 (1970).
144. D. L. MacPeek, P. S. Starcher and B. Phillips, *J. Am. Chem. Soc.*, **81**, 680 (1959).
145. W. D. Emmons and A. S. Pagano, *J. Am. Chem. Soc.*, **77**, 89 (1955).
146. W. H. Rastetter, T. J. Richard and M. D. Lewis, *J. Org. Chem.*, **43**, 3163 (1978).
147. B. Phillips, F. C. Frostick and P. S. Starcher, *J. Am. Chem. Soc.*, **79**, 5982 (1957).
148. G. Darzens, *Compt. Rend.*, **142**, 214 (1906).
149. H. A. Weidlich and G. H. Daniels, *Chem. Ber.*, **72**, 1596 (1939).
150. H. H. Morris, R. H. Young, Jr., C. Hess and T. Sottery, *J. Am. Chem. Soc.*, **79**, 411 (1957).
151. R. Curci, M. Fiorentino, L. Troisi, J. O. Edwards and R. H. Pater, *J. Org. Chem.*, **45**, 4758 (1980).
152. J. O. Edwards, R. H. Pater, R. Curci and F. DiFuria, *Photochem. Photobiol.*, **30**, 63 (1979).
153. R. W. Murray and R. Jeyaraman, *J. Org. Chem.*, **50**, 2847 (1985).
154. P. F. Corey and F. E. Ward, *J. Org. Chem.*, **51**, 1925 (1986).
155. G. W. Gokel and H. D. Durst, *Synthesis*, 168 (1976).
156. L. Cassidei, M. Fiorentino, R. Mello, O. Sciacovelli and R. Curci, *J. Org. Chem.*, **52**, 699 (1987).
157. P. R. Ortiz de Montellano and C. K. Hsu, *Tetrahedron Lett.*, 4215 (1976).
158. A. H. Haines, *Methods for the Oxidation of Organic Compounds*, Academic Press, London, 1985, p. 92.
159. K. A. Hofmann, *Chem. Ber.*, **45**, 3329 (1912).
160. M. Schröder, *Chem. Rev.*, **80**, 204 (1980).
161. G. Braun, *J. Am. Chem. Soc.*, **51**, 228 (1929).
162. F. D. Gunstone, in *Advances in Organic Chemistry*, Vol. 1, Interscience, New York, 1960, p. 110ff.

163. A. D. Tait, *Steroids*, **20**, 531 (1972).
164. A. Butenandt and H. Wolz, *Chem. Ber.*, **71B**, 1483 (1938).
165. G. Stork and M. Kahn, *Tetrahedron Lett.*, **24**, 3951 (1983).
166. K. Tomioka, M. Nakajima and K. Koga, *J. Am. Chem. Soc.*, **109**, 6213 (1987).
167. S. G. Hentges and K. B. Sharpless, *J. Am. Chem. Soc.*, **102**, 4263 (1980).
168. C. R. Johnson and M. R. Barbachyn, *J. Am. Chem. Soc.*, **106**, 2459 (1984).
169. M. Tokles and J. K. Snyder, *Tetrahedron Lett.*, **27**, 3951 (1986).
170. A. B. Smith III and D. Boschelli, *J. Org. Chem.*, **48**, 1217 (1983).
171. M. Hetmanski, N. Purcell, R. J. Stoodley and M. N. Palfreyman, *J. Chem. Soc., Perkin Trans. 1*, 2089 (1984).
172. G. J. Wagner, *Russ. Phys. Chem. Soc.*, **27**, 219 (1895).
173. F. Freeman and J. C. Kappos, *J. Org. Chem.*, **51**, 1654 (1986) and references cited therein.
174. R. Criegee, *Liebigs Ann. Chem.*, **522**, 75 (1936).
175. F. Freeman and L. Y. Chang, *J. Am. Chem. Soc.*, **108**, 4504 (1986).
176. K. B. Wiberg and K. A. Saegebarth, *J. Am. Chem. Soc.*, **79**, 2822 (1957).
177. K. B. Sharpless, A. Y. Teranishi and J. E. Bäckvall, *J. Am. Chem. Soc.*, **99**, 3120 (1977).
178. K. Polgar, M. Jáky and L. I. Simándy, *React. Kinet. Catal. Lett.*, **5**, 489 (1976).
179. F. D. Gunstone, *Advances in Organic Chemistry*, Vol. 1, Interscience, New York, 1960, p. 107.
180. D. G. Lee and K. C. Brown, *J. Am. Chem. Soc.*, **104**, 5076 (1982).
181. H. J. Schmidt and H. J. Schäfer, *Angew. Chem., Int. Ed. Engl.*, **18**, 68, 69, 787 (1979).
182. L. Milewich and L. R. Axelrod, *Org. Synth.*, **55**, 67 (1976).
183. J. T. Edward, D. Holder, W. H. Lunn and I. Puskas, *Can. J. Chem.*, **39**, 599 (1961).
184. R. M. Moriarty and K. C. Hou, *Tetrahedron Lett.*, **25**, 691 (1984).
185. R. M. Moriarty, O. Prakash and W. A. Freeman, *J. Chem. Soc., Chem. Commun.*, 927 (1984).
186. H. U. Reissig, *Nachr. Chem. Techn. Lab.*, **34**, 328 (1986).
187. F. A. Davis, L. C. Vishwakarma, J. M. Billmers and J. Finn, *J. Org. Chem.*, **49**, 3241 (1984).
188. E. Vedejs, D. A. Engler and J. E. Telschow, *J. Org. Chem.*, **43**, 188 (1978).
189. E. Vedejs and S. Larsen, *Org. Synth.*, **64**, 127 (1985).
190. M. Mimoun, L. Seree de Roch and L. Sajus, *Bull. Soc. Chim. Fr.*, 1481 (1969).
191. R. M. Moriarty, H. Hu and S. C. Gupta, *Tetrahedron Lett.*, **22**, 1283 (1981).
192. R. M. Moriarty and K. C. Hou, *Tetrahedron Lett.*, **25**, 691 (1984).
193. G. M. Rubottom and J. M. Gruber, *J. Org. Chem.*, **43**, 1599 (1978).
194. G. M. Rubottom, J. M. Gruber, H. D. Juve, Jr. and D. A. Charleson, *Org. Synth.*, **64**, 118 (1985).
195. C. Ainsworth, F. Chen and Y. N. Kuo, *J. Organomet. Chem.*, **46**, 59 (1972).
196. S. Hünig and G. Wehner, *Synthesis*, 391 (1975).
197. N. Rabjohn, *Org. React.*, **64**, 261 (1984).
198. M. Danieli, Y. Mazur and F. Sondheimer, *Tetrahedron Lett.*, 3189 (1966).
199. H. J. Bestmann and R. Schobert, *Angew. Chem.*, **97**, 785 (1985).
200. H. Schubert, I. Eissfeldt, R. Lange and F. Treffich, *J. prakt. Chem.*, **33**, 265 (1966); J. W. G. de Meester, H. C. van der Plas and W. J. Middelhoven, *J. Heterocycl. Chem.*, **24**, 441 (1987).
201. G. Hallmann and K. Hägele, *Ann. Chem.*, **662**, 147 (1963).
202. M. Nakayama, S. Shinke, Y. Matsushita, S. Ohira and S. Hayashi, *Bull. Chem. Soc. Jpn.*, **52**, 184 (1979).
203. L. Novák, G. Baán, J. Marosfalvi and C. Szántany, *Tetrahedron Lett.*, 487 (1978).
204. D. G. Lee and M. van den Engh, in *Oxidation in Organic Chemistry*, Part B (Ed. W. S. Trahanovsky), Academic Press, New York, London, 1973, p. 186.
205. F. X. Webster, J. Rivas-Enterrios and R. M. Silverstein, *J. Org. Chem.*, **52**, 689 (1987).
206. P. H. J. Carlsen, T. Katsuki, V. S. Martin and K. B. Sharpless, *J. Org. Chem.*, **46**, 3936 (1981).
207. A. McKillop, B. P. Swann, M. E. Ford and E. C. Taylor, *J. Am. Chem. Soc.*, **95**, 3641 (1973).
208. W. D. Ollis, K. L.Ormand and I. O. Sutherland, *J. Chem. Soc. (C)*, 119 (1970).
209. E. C. Taylor, R. A. Conley, D. K. Johnson, A. McKillop and M. E. Ford, *J. Org. Chem.*, **45**, 3433 (1980).
210. H. E. Ensley, R. V. C. Carr, R. S. Martin and T. B. Pierce, *J. Am. Chem. Soc.*, **102**, 2836 (1980).
211. E. C. Taylor, C. S. Chiang, A. McKillop and J. F. White, *J. Am. Chem. Soc.*, **98**, 6750 (1976).
212. M. Orfanopoulos and C. S. Foote, *Tetrahedron Lett.*, **26**, 5991 (1985).
213. C. S. Foote, *Acc. Chem. Res.*, **1**, 104 (1968).
214. R. W. Denny and A. Nickon, *Org. React.*, **20**, 133 (1973).

The Chemistry of Enones
Edited by S. Patai and Z. Rappoport

CHAPTER 13

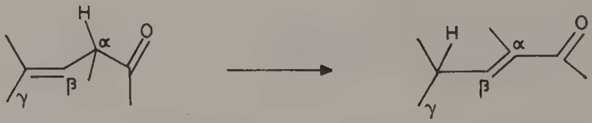
Chemical and enzymatic conversion of β,γ-enones to α,β-enones

RALPH M. POLLACK, PATRICIA L. BOUNDS and CHARLES L. BEVINS

Laboratory for Chemical Dynamics, Department of Chemistry, University of Maryland Baltimore County, Baltimore, MD 21228, USA and Center for Advanced Research in Biotechnology, 9600 Gudelsky Drive, Rockville, MD 20850, USA

I. INTRODUCTION

The isomerization of β,γ-unsaturated ketones to their α,β-unsaturated isomers (equation 1) is an example of a variety of reactions which may be formally regarded as 1,3-proton shifts. This reaction differs from other examples, such as the interconversions of ketones/enols, imines/enamines and aci/nitro forms by requiring a proton transfer between two carbon atoms rather than between a carbon atom and a hetero atom. Although the mechanism of the isomerization could, in principle, be either stepwise or concerted, in all systems so far investigated a stepwise pathway operates. The general mechanism involves abstraction of a proton from the α carbon to generate an enol, enolate or enamine (for catalysis by acid, base and amine, respectively) followed by reprotonation at the γ carbon. Thus, the overall reaction is enolization, followed by ketonization at a different carbon atom.



(1)

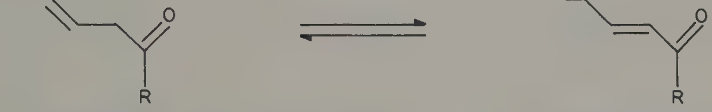
The simplicity of this reaction has made the isomerization an attractive reaction for examining the effect of variation of structure on the rates of protonation and deprotonation at carbon. Studies of the isomerization have provided insight into the nature of a variety of phenomena, including stereoelectronic effects, electrostatic catalysis, nucleophilic catalysis, and conformational effects on rates and equilibria. These results will be discussed in the context of the equilibrium constants for the isomerization, the mechanism of reaction in the presence of acids, bases and amines, and the factors that control the partitioning of the intermediate dienol in the acid- and base-catalyzed reactions. In addition, the photochemically induced deconjugation of α,β-unsaturated ketones to β,γ-unsaturated ketones will be briefly discussed (Section III.D).

Finally, a review of the mechanism of action of 3-oxo-Δ^5-steroid isomerase will be presented. This enzyme catalyzes the conversion of 3-oxo-Δ^5-steroids to the corresponding conjugated Δ^4-isomers. The mechanism of this reaction is of particular interest, since the isomerase is one of the most active enzymes known. The second-order rate constant (k_{cat}/K_m) for the isomerization of 5-androstene-3,17-dione is $2.3 \times 10^8\ M^{-1}\,s^{-1}$ [1,2], which suggests that catalysis by the isomerase may be close to diffusion-controlled[3]. Enzymes that operate at the diffusion limit are intrinsically interesting from a mechanistic standpoint, as they are thought to have evolved to be near catalytic perfection[4,5].

II. EQUILIBRIUM CONSTANTS

A. Acyclic Systems

A cursory inspection of the isomerization leads to the conclusion that the conjugation of the double bond with the carbonyl in the α,β-unsaturated ketone should cause it to be more stable than the β,γ-isomer in virtually all cases. Although this conclusion is correct in the majority of cases, the preference for the α,β-isomer is not always large. Hine and coworkers have determined the equilibrium constant for the isomerization of *trans*-4-hexen-2-one (**1**) to *trans*-3-hexen-2-one (**2**) and found an equilibrium constant of 4.8 ± 0.5 at 25 °C, favoring the conjugated isomer. This difference corresponds to a ΔG of only about $1\,\mathrm{kcal\,mol^{-1}}$ between the conjugated and unconjugated isomers. Similarly, the equilibrium constant for isomerization of *trans*-3-pentenal (**3**) to *trans*-2-pentenal (**4**), extrapolated to 25 °C, is 24[7] (equation 2).



(2)

(**1**) R = Me 18% (**2**) R = Me 82%

(**3**) R = H 4% (**4**) R = H 96%

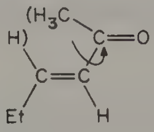
Hine[8,9] has calculated a 'double bond stabilization parameter' (D) for a variety of substituents based on statistical analysis of equilibrium constants for reactions of the type shown in equation 3 over a range of temperatures and in different solvents. Owing to the lack of standardization of temperature and solvent, an assumption inherent in this method is that entropy effects and differences in solvation between the four species are negligible. Hine[6,9] used the results of the isomerization of the *trans* hexenones to calculate the value of D for the acetyl group ($D = 3.36\,\mathrm{kcal\,mol^{-1}}$). The corresponding D value for the formyl substituent is $4.34\,\mathrm{kcal\,mol^{-1}}$.

$$trans\text{-}\mathrm{XCH{=}CHCH_2Y \rightleftharpoons XCH_2CH{=}CHY} \qquad (3)$$

Interestingly, the double bond stabilization parameter for simple primary alkyl groups ($D = 3.2$) is similar to that for the acetyl group, indicating that the stabilization of a double bond by a ketonic carbonyl is quite small and similar to that for an alkyl group. Similar small values of D are seen with other conjugating substituents, such as MeO (5.2), F (3.3), CN (2.3) and NO_2 (2.9). Hine[8] suggested that these low values are due to destabilization of the double bond from the inductively electron-withdrawing σ bonds, counteracting the resonance stabilization of the π bonds. Thus, the value of D for the $CH_2CO_2CH_3$ group is 2.1, compared to 3.2 for the CH_3 group, showing substantial ($1.1\,\mathrm{kcal\,mol^{-1}}$) inductive destabilization of the carbomethoxy substituent (and presumably the acetyl group) relative to a hydrogen, even one atom removed from the double bond.

The better stabilizing ability of the formyl group relative to acetyl and carboalkoxy was explained in terms of some destabilizing cross-conjugation in esters and ketones, as well as steric hindrance between the methyl group of the acetyl and the hydrogen *cis* to it in the preferred transoid conformation (**5**)[7]. This steric interaction presumably causes some twisting of the single bond between the carbonyl and the carbon–carbon double bond, resulting in less favorable resonance interaction.

The severity of these steric interactions can be appreciated from a comparison of the equilibria for the corresponding *cis* compounds derived from Hine's data[6] (equation 4). Surprisingly, the unconjugated isomer (**6**) in the *cis* hexenones is substantially more stable



(5)

than the conjugated isomer (7). Steric hindrance with R = Me is clearly much more important for the *cis* 2-hexenones than for the *trans* isomers. Even in the case of the conjugated aldehyde (**9**), there is apparently substantial interaction across the double bond between the formyl hydrogen and the methylene group, since at equilibrium **9** is present in approximately a 1:1 ratio with the unconjugated isomer (**8**).

(4)

(**6**) R = Me 100% (**7**) R = Me 0%

(**8**) R = H 52% (**9**) R = H 48%

B. Five- and Six-membered Ring Systems

Although substantial amounts of the unconjugated isomer are in equilibrium with the conjugated isomer in simple acyclic systems, Δ^5(6)- and Δ^5(10)-unsaturated 3-oxosteroids react virtually quantitatively to give Δ^4-unsaturated steroids with either chemical (acid or base) or enzymatic catalysis (equations 5 and 6)[10]. Measurements of the equilibrium constants for isomerization of 3-cyclohexenone (**14**) and 3-cyclopentenone (**16**) to the conjugated isomers show that these equilibria, too, lie far toward the conjugated isomers. At equilibrium, less than 1% of the mixture of cyclohexenones is present as the unconjugated isomer[11,12]. Similarly, less than 0.01% of the equilibrium mixture of cyclopentenones is 3-cyclopentenone[12]. In the case of cyclic ketones, there is no destabilization due to steric hindrance in the conjugated isomers. In addition, the conjugation of an acyclic β,γ-unsaturated ketone involves a loss of entropy due to the loss of rotational freedom in the bond between the carbonyl and the carbon–carbon double bond. It has been estimated that freezing out of one bond rotation is equivalent to a factor of about 10- to 100-fold[13–16].

(10) (11)

(5)

(12) (13)

(6)

(14) (15)

< 1% > 99%

(7)

(16) (17)

< 0.01% > 99.99%

(8)

Whalen and coworkers[12] have explained the variation in equilibrium constants for cyclopentenones and cyclohexenones in terms of differences in planarity of the two conjugated isomers. The more planar 2-cyclopentenone allows better overlap of the π orbitals of the double bond with the π orbitals of the carbonyl. A slight puckering of the cyclohexenone system causes twisting of the bond between the carbonyl and double bond, resulting in diminished conjugation.

C. Medium Ring Systems

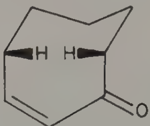
Extension of the series of unsaturated ketones to include seven-, eight- and nine-membered ring 2-cycloalkenones and 3-cycloalkenones shows a dramatic shift in the equilibrium constants with ring size (Table 1). As the ring size increases, the proportion of unconjugated ketone also increases until for the eight- and nine-membered rings the unconjugated isomer predominates. In fact, in the nine-membered ring, no conjugated isomer can be detected at equilibrium. Heap and Whitham[11] explained the preference of the larger ring systems for the unconjugated isomer by postulating a destabilization of the conformation of the conjugated isomer in which the double bond and the carbonyl group are coplanar. In the eight-membered ring system a coplanar arrangement of these groups

TABLE 1. Equilibrium composition of mixtures of 2- and 3-cycloalkenones

Ring size	% Δ^2	% Δ^3	Reference
5[a]	> 99.99	> 0.01	12
6[a]	99.64	0.36	12
6[b]	99	1	11
7[b]	73	27	11
8[b]	20	80	11
9[b]	<0.3	> 99.7	11

[a] Aqueous solution.
[b] Benzene solution.

is prohibited by a severe transannular interaction between hydrogens at $C_{(4)}$ and $C_{(8)}$ (**18**). Similar interactions are important in the nine-membered ring, although it is not obvious from model building that the steric interactions are more severe than they are in the eight-membered ring, as is suggested by the observed equilibrium constants.



(**18**)

III. MECHANISMS

A. Acid-catalyzed Isomerization

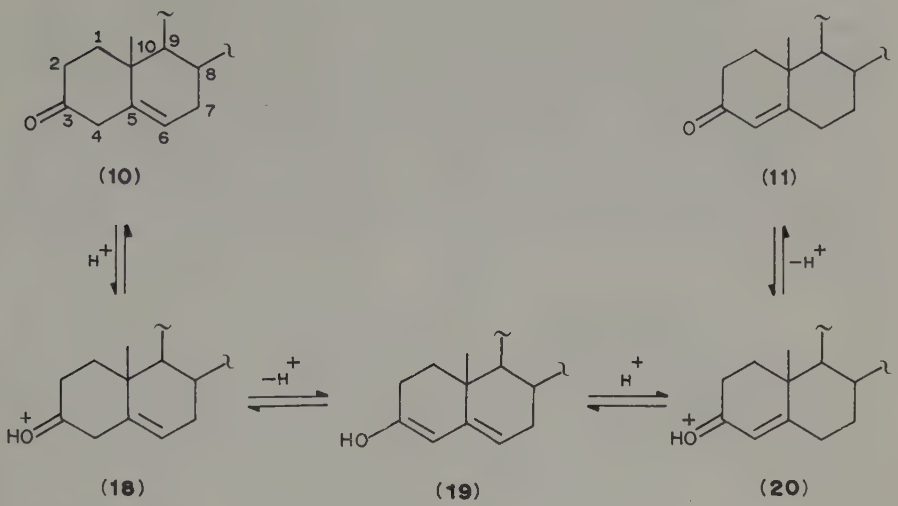
1. General mechanism

In the acid-catalyzed isomerization of β,γ-unsaturated ketones, a proton is removed from $C_{(\alpha)}$ of the protonated ketone to form a neutral dienol, followed by reprotonation at $C_{(\gamma)}$ to form the protonated product (equation 9)[10,12,17–23]. Protonation of the intermediate dienol can occur at either $C_{(\alpha)}$ or at $C_{(\gamma)}$. If protonation at $C_{(\gamma)}$ occur faster than at $C_{(\alpha)}$, then the dienol is converted rapidly to product (α,β-unsaturated ketone) rather than reverting to reactant (β,γ-unsaturated ketone). Thus, formation of the dienol, rather than a subsequent step, is the rate-limiting step in the overall reaction. Alternatively, if protonation at $C_{(\gamma)}$ is slower than at $C_{(\alpha)}$, then partitioning of the intermediate favors the reactant and the breakdown of the dienol to form product is rate-limiting.

Initial mechanistic studies of the isomerization of β,γ-unsaturated ketones were carried out on steroidal ketones. Nes and collaborators[10] examined the kinetics of the isomerization of a series of $\Delta^{5(6)}$ and $\Delta^{5(10)}$ 3-oxosteroids at pH 0.5 to 2.5. They found that the reaction is first-order in both steroid and acid, with the $\Delta^{5(6)}$ systems reacting about 30-fold faster that the $\Delta^{5(10)}$ steroids. They also found, in agreement with previous work by Talalay and Wang[24], that isomerization of 5-androstene-3, 17-dione in D_2O results in the incorporation of 1 atom of deuterium per mol, suggesting that proton removal from $C_{(4)}$ is the rate-limiting step.

Malhotra and Ringold[18] carried out the first detailed mechanistic studies on the isomerization of β,γ-unsaturated ketones. They proposed that the acid-catalyzed isomerization of 3-oxo-Δ^5-steroids proceeds according to the pathway outlined in equation 9. A substantial primary kinetic isotope effect at $C_{(4)}$ ($k_H/k_D = 4.1$) and an inverse solvent isotope effect ($k_{H_2O}/k_{D_2O} = 0.61$)[18] are consistent with equilibrium protonation on oxygen, followed by rate-limiting formation of the dienol, rapid reprotonation at $C_{(6)}$ and deprotonation at oxygen. The inverse solvent deuterium isotope effect rules out the alternative mechanism of rate-limiting protonation at $C_{(6)}$, followed by loss of a proton at $C_{(4)}$. Direct protonation at $C_{(6)}$ may also be safely eliminated, since simple model olefins, such as isobutylene, are protonated several orders of magnitude too slowly to account for the observed rate of isomerization[25]. Okuyama and coworkers[26] examined the analogous isomerization of Δ^5-testosterone in acidic solution and obtained similar results.

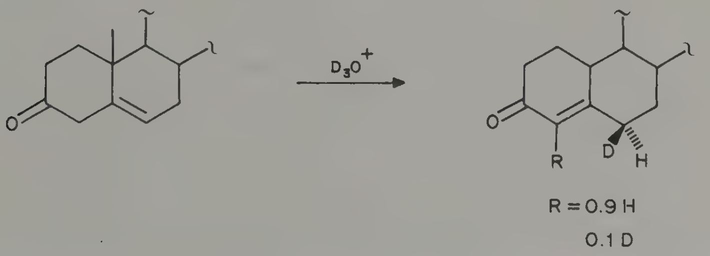
The stereochemical aspects of this reaction were also investigated by Malhotra and Ringold[18]. It was shown that the 4α (equatorial) proton is removed in slight preference to the 4β (axial) proton ($k_{4\alpha}/k_{4\beta} \simeq 1.2$). This small discrimination between axial and equatorial proton loss in enolization is consistent with the stereoelectronic effect observed



(9)

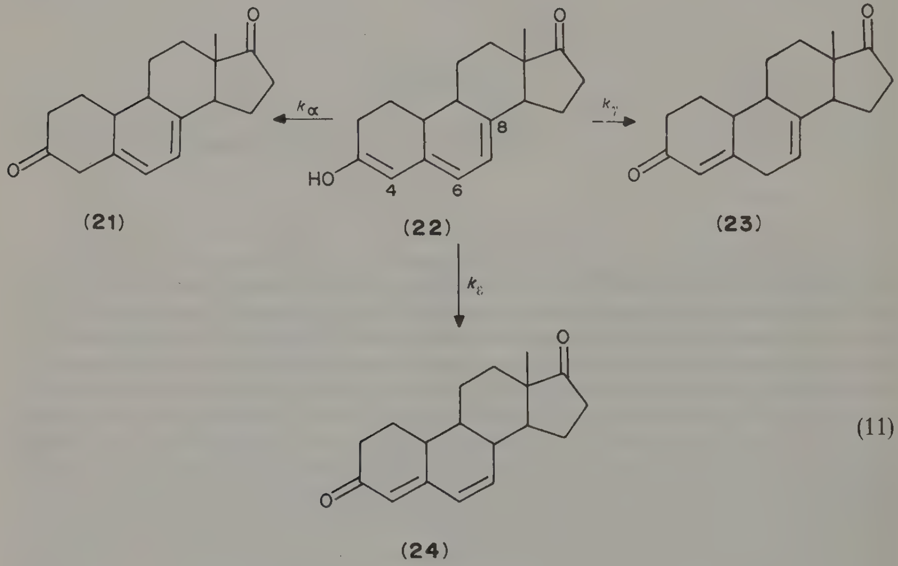
in simple systems, in which axial proton loss is generally favored but only by modest factors. Malhotra and Ringold interpreted the lack of a large stereoelectronic effect in terms of a transition state that has considerable enolic character. They reasoned that a transition state that resembles the protonated ketone should give preferential removal of the axial (4β) proton which, although it is presumably in a more hindered location (due to the diaxial interaction with the $C_{(10)}$ methyl group), allows more favorable orbital overlap with the carbonyl carbon[27]. However, recent X-ray crystallographic studies indicate that carbons $C_{(3,4,5,\text{ and }6)}$ are approximately coplanar, and that the 4α and 4β protons are symmetrically oriented with respect to the $C_{(3)}$ keto group[28]. If this conformation is maintained in solution for the protonated ketone, then neither of the $C_{(4)}$ protons is oriented axially and steric factors rather than stereoelectronic factors would be expected to govern the relative rates of proton removal.

Further evidence that protonation of the dienol intermediate occurs at $C_{(6)}$ much faster than at $C_{(4)}$ came from a determination of the deuterium content of both starting material and product when 5-cholestene-3-one was partially isomerized in deuterated acidic medium (equation 10). The product contained one atom of deuterium per molecule, which was located at $C_{(6)}$ and almost exclusively at the β position[18]. The conjugated ketone also contained less than 0.1 atom deuterium per molecule at $C_{(4)}$ and recovered β,γ-unsaturated ketone contained negligible quantities of deuterium at $C_{(4)}$ (or elsewhere).



(10)

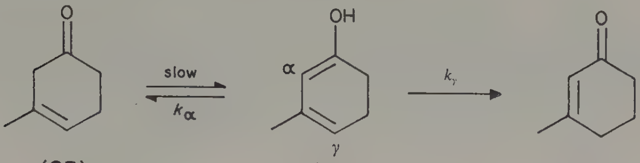
Similar results (equation 11) have been observed with the trienol intermediate for the analogous isomerization of 5, 7-estradiene-3, 17-dione (**21**) to 4, 7-estradiene-3, 17-dione (**23**). The putative intermediate trienol (**22**) can be isolated[29] and its partitioning has been examined in acidic solutions[30]. This enol can ketonize in three different ways, by protonation at $C_{(4)}$, $C_{(6)}$ or $C_{(8)}$. Surprisingly, there is no detectable protonation at $C_{(8)}$ to give the most stable ketone (**24**). Instead, ketonization is primarily at $C_{(6)}$ to give the 4, 7-dienone (**23**). Protonation at C-8 presumably in inhibited by steric interactions at the tertiary carbon. Thus, in the isomerization of the 5, 7-isomer to the 4, 7-isomer, deprotonation of the conjugate acid must be rate-limiting, in analogy to the isomerization of simple Δ^5-3-oxosteroids, although the k_γ/k_α ratio is higher for the dienol than for the trienol.



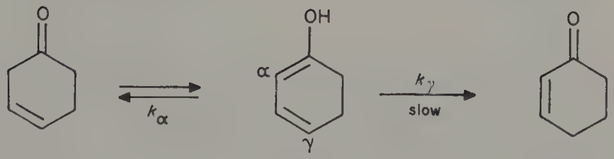
(11)

2. *Factors that influence the rate-determining step*

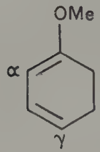
a. Alkyl substitution at the β-carbon. Noyce and Evett[19,20] have investigated the mechanism of isomerization of several β,γ-unsaturated ketones with different substitution patterns at $C_{(\beta)}$. An inverse solvent isotope effect ($k_{D_3O^+}/k_{H_3O^+} = 1.3$) was observed[19] (equation 12) in the acid-catalyzed isomerization of 3-methyl-3-cyclohexenone (**25**) to 3-methyl-2-cyclohexenone (**27**), consistent with rate-limiting proton abstraction at $C_{(\alpha)}$ ($k_\gamma > k_\alpha$). However, the isomerization of 3-cyclohexenone (**14**) to 2-cyclohexenone (**15**) exhibits (equation 13) a solvent isotope effect ($k_{D_3O^+}/k_{H_3O^+}$) of 0.2 and reprotonation of the dienol at $C_{(\alpha)}$ is much faster than the rate of isomerization ($k_\alpha > k_\gamma$)[19]. Noyce and Evett concluded that this latter reaction occurs through a rate-determining protonation at the γ carbon of the dienol. Thus, the presence of a methyl group at the β carbon changes the relative rate of protonation of the intermediate dienol from favoring $C_{(\alpha)}$ in the isomerization of **14** to favoring $C_{(\gamma)}$ in the isomerization of **25**. Substitution of a methyl group at the β carbon similarly effects the relative rates of protonation at $C_{(\alpha)}$ and $C_{(\gamma)}$ of the intermediate in other β,γ-unsaturated ketone isomerizations[20] and during acid-catalyzed hydrolysis of dienol ethers[31]. The presence of a methyl group at $C_{(\beta)}$ shifts the relative protonation ratio (k_α/k_γ) from 1.9 for **29** to 0.1 for **30**[31].



(25) **(26)** **(27)** (12)

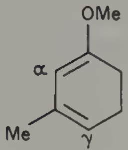


(14) **(28)** **(15)** (13)



(29)

k_α/k_γ 1.9



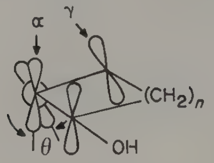
(30)

0.1

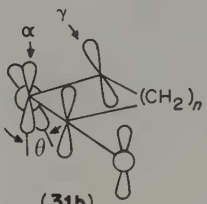
Noyce and Evett[19,20] interpreted these results in terms of the effects of alkyl substitution on the rates of olefin protonation. A methyl group at $C_{(\beta)}$ tends to stabilize the positive charge developed in the transition state by protonation at $C_{(\gamma)}$ but will have minimal effect on protonation at $C_{(\alpha)}$. Thus, methyl substitution at $C_{(\beta)}$ will enhance protonation at $C_{(\gamma)}$ relative to $C_{(\alpha)}$. In general, when $C_{(\beta)}$ is tertiary, protonation of the dienol occurs preferentially at $C_{(\gamma)}$ and enolization of the β,γ-unsaturated ketone is rate-determining. If $C_{(\beta)}$ is secondary, protonation of the dienol at $C_{(\alpha)}$ is faster than at $C_{(\gamma)}$ and k_γ is rate-determining.

Theoretical considerations are in accord with this model. Molecular orbital calculations by Rogers and Sattar[31] for a series of homoannular methyl-substituted dienol ethers (including compounds **29** and **30**) have yielded satisfactory predictions of $C_{(\gamma)}/C_{(\alpha)}$ protonation rates based on the relative charge density at each of the two carbons.

b. Diene conformation. Although the acid-catalyzed isomerization of 3-cyclohexenone proceeds by rate-limiting protonation of the dienol intermediate, the isomerization of 3-cyclopentenone (**16**) shows rate-limiting formation of a dienol intermediate[12]. Thus, the dienol intermediate from 3-cyclopentenone violates the generalization that $k_\alpha > k_\gamma$ for compounds in which $C_{(\beta)}$ is secondary. The difference between the rate-determining step in the isomerization of these two compounds has been rationalized by Whalen and coworkers[12] based on structural considerations of the respective intermediate dienols. The ratio of protonation rates (k_γ/k_α) for a dienol is a result of the relative abilities of the respective transition states to stabilize the developing positive charge. The conformation of a dienol may be represented by structure **31a**. The dihedral angle θ formed by the double bonds determines the extent to which positive charge can be delocalized onto the oxygen atom. The relative rate of protonation of a dienol at $C_{(\gamma)}$ compared to $C_{(\alpha)}$ will depend on this dihedral angle. For θ equal to 0°, all p orbitals are aligned and therefore positive charge generated by addition of a proton at $C_{(\gamma)}$ will be effectively transmitted to the oxygen. As θ increases, overlap between the orbitals of $C_{(\alpha)}$ and $C_{(\beta)}$ decreases and the positive charge cannot be as effectively stabilized by the hydroxyl group.



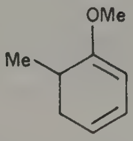
(31a)



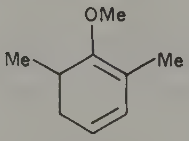
(31b)

For θ equal to 90°, protonation at $C_{(\gamma)}$ is comparable to protonation of an isolated double bond, whereas protonation at $C_{(\alpha)}$ resembles the much more favorable protonation of an enol ether. This model predicts that the ratio of protonation rates, k_γ/k_α, will be a maximum at $\theta = 0°$ and will then decrease as θ increases. Since the structures for the dienols are not available, Whalen's group[12] used the molecular structures of cyclopentadiene and cyclohexadiene as models for the dienols derived from 3-cyclopentenone and 3-cyclohexenone, respectively. For cyclopentadienol, where θ is nearly zero, the positive charge generated from protonation at $C_{(\gamma)}$ can be effectively stabilized by the oxygen, and protonation at this carbon is more favorable than at $C_{(\alpha)}$. For cyclohexadienol, where θ is probably near 18°, the positive charge generated by protonation at $C_{(\gamma)}$ cannot be as effectively stabilized by the hydroxyl group and, consequently, protonation at $C_{(\alpha)}$ is favored.

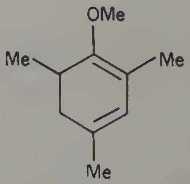
c. Steric hindrance at the site of protonation. The k_γ/k_α protonation rate ratio of dienols (and dienol ethers) is significantly affected by alkyl substitution at $C_{(\alpha)}$ and $C_{(\gamma)}$. Substitution of a methyl group at $C_{(\alpha)}$ of 1-methoxy-5-methyl-1,3-cyclohexadiene (**32** vs. **33**) increases k_γ/k_α by a factor of 28. The secondary $C_{(\gamma)}$ in **19** is protonated faster than $C_{(\alpha)}$, but methyl substitution at $C_{(\gamma)}$ substantially reduces the relative rate of protonation. The decreased rate of protonation at a tertiary $C_{(\gamma)}$ compared to a secondary $C_{(\gamma)}$ is also evident in a comparison of **33** ($k_\gamma/k_\alpha = 19$) and **34** ($k_\gamma/k_\alpha = 0.14$). The major factor in all these examples is undoubtedly steric hindrance to protonation.



(32)

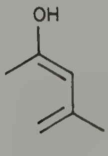


(33)



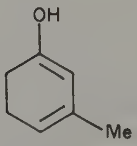
(34)

k_γ/k_α 0.69 (Ref. 31) 19 (Ref. 31) 0.14 (Ref. 31)



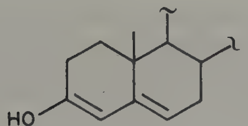
(35)

v. large (Ref. 20)



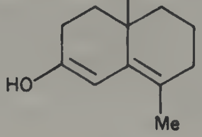
(26)

v. large (Ref. 19)



(19)

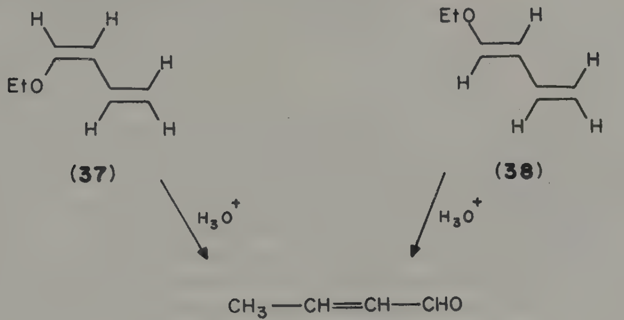
>20 (Ref. 32)



(36)

ca 1 (Ref. 32)

d. Configuration of the diene. When *cis* and *trans* isomers of 1-ethoxy-1, 3-butadiene (**37** and **38**, respectively) are hydrolyzed in acidic medium, crotonaldehyde (**39**) is formed[34] (equation 14). In deuterated medium, **39** produced from the hydrolysis of the *trans* compound contains deuterium exclusively at $C_{(\gamma)}$. However, **39** produced from the *cis* isomer contains, in addition to 1 atom of deuterium at $C_{(\gamma)}$, 0.2 atom of deuterium at $C_{(\alpha)}$. Thus, the k_γ/k_α protonation rate ratio is much larger for the *trans* isomer than for the *cis* isomer. Surprisingly, the *trans* isomer reacts *ca* 15-fold more rapidly than the *cis* isomer[34], even though the *trans* isomer is more stable by almost 1 kcal mol^{-1} in the liquid phase[35]. It was proposed[34] that charge density at $C_{(\alpha)}$ and $C_{(\gamma)}$ determines the site of protonation in these two compounds, but no satisfactory explanation for the structural basis of the charge density difference between these two compounds was offered.



(39)

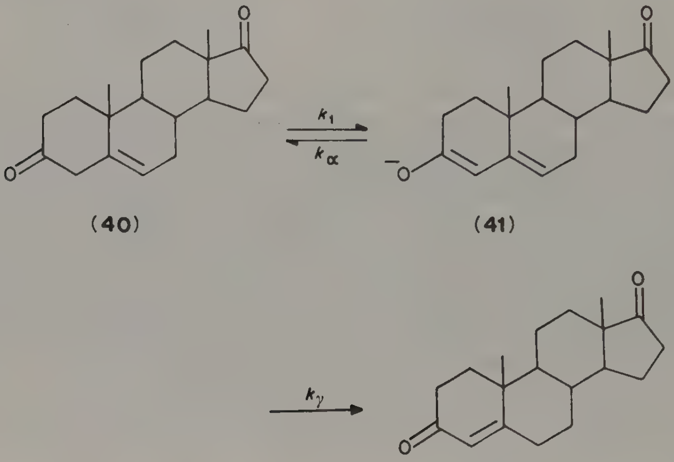
(14)

Examination of molecular models reveals that the olefinic proton on $C_{(3)}$ may have an unfavorable steric interaction with the ethoxy group in the *cis* isomer that is more severe than the corresponding proton–proton interaction in the *trans* isomer. The bond between $C_{(2)}$ and $C_{(3)}$ would likely rotate to relieve this interaction, thereby reducing the overlap of the π orbitals of the diene. Protonation at $C_{(4)}$ of the *trans* isomer then would be more favorable than for the *cis* isomer, due to better charge delocalization to the oxygen.

B. Base-catalyzed Isomerization

1. General considerations

The simplest mechanism for interconversion of β,γ- and α,β-unsaturated ketones in base is abstraction of a proton from $C_{(\alpha)}$ of the β,γ-unsaturated ketone to generate a dienolate ion, followed by protonation of this intermediate at $C_{(\gamma)}$ (equation 15). It has been known for some time that deconjugation of 3-oxo-Δ^4-steroids can be effected by irreversible protonation of the conjugate anion. In 1962, Ringold and Malhotra[36] showed that the dienolate ions of a variety of 3-oxo-Δ^4-steroids can be generated by treatment with potassium *t*-butoxide in *t*-butyl alcohol. Protonation of the dienolate by acetic acid generates the β,γ-unsaturated isomer, showing that kinetic protonation of the dienolate occurs primarily at $C_{(\alpha)}$. Thus, in the thermodynamically favorable direction (isomerization of the β,γ-unsaturated ketone), the reaction must take place by rate-limiting protonation of a dienolate ion that is in rapid equilibrium with the starting β,γ-unsaturated ketone.



(40) **(41)** **(42)** (15)

Subsequently, Jones and Wigfield[21] examined the base-catalyzed isomerization of 5-androstene-3,17-dione (**40**) in aqueous solution. They found a linear dependence on hydroxide ion concentration in the pH range 10.6 to 11.7, consistent with the protonation–deprotonation mechanism. These authors investigated the kinetic isotope effect using the 4,4-dideutero derivative and found a curved pseudo-first-order plot, indicating that exchange of the $C_{(4)}$ hydrogens is competitive with isomerization. Similarly Okuyama and coworkers[26] investigated the reaction of Δ^5-testosterone in base and found a solvent isotope effect (k_{OH^-}/k_{OD^-}) of 3.1, consistent with preequilibrium formation of a dienolate ion.

Perera, Dunn and Fedor[37] investigated the isomerization of both 5-androstene-3,17-dione and 17α-ethynyl-17β-hydroxy-5(10)-estren-3-one. They found general base catalysis by tertiary amines, with a solvent isotope effect of *ca* 6, indicating rate-limiting protonation of the dienolate for both systems. The greater reactivity of 5-androstene-3,17-dione was attributed to a greater concentration of the dienolate at equilibrium.

More recent work in our laboratory has enabled us to characterize this reaction in greater detail[38]. By rapidly adding 5-androstene-3,17-dione to aqueous 1.0 M sodium hydroxide, we were able to observe the formation of a dienolate ion as a transient intermediate at 257 nm. As the reaction proceeds, this intermediate is transformed to the product conjugated ketone, which absorbs at 248 nm. The rate of formation of this intermediate was determined by monitoring the initial phase of this reaction by stopped-flow spectrophotometry. Analysis of these observed rate constants, along with the overall rate constants for isomerization, gave values for the microscopic rate constants (k_1, k_α and k_γ). From these results, the partitioning of the intermediate ($k_\alpha/k_\gamma = 25$) and the pK_a of the starting ketone could be obtained ($pK_a = 12.7$). In agreement with prediction[37], we were unable to observe the formation of the dienolate ion from 5(10)-estrene-3,17-dione.

The surprisingly low pK_a of 5-androstene-3,17-dione may be compared to that for several saturated ketones. The aqueous pK_a values are substantially higher for isobutyrophenone (18.3)[39], acetone (19.2)[40] and acetophenone (18.1)[41]. Thus, it appears that the acidifying effect of a β,γ-double bond on an α hydrogen is about 10^5- to 10^6-fold. A similar effect on acidity may be seen in the effect of a phenyl group on the α carbon. The pK_a of 2-tetralone has been found to be 12.9, although the acidity for the analogous acyclic compound, benzyl methyl ketone, is several orders of magnitude weaker[42].

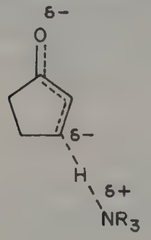
2. Factors that influence the site of protonation in dienolate intermediates

The factors that influence the relative rates of protonation of dienolates at $C_{(\alpha)}$ and $C_{(\gamma)}$ are likely to be similar to those factors that influence the relative protonation rate ratio at these carbons in dienols and dienol ethers. Thus, alkyl substitution at $C_{(\beta)}$, diene conformation and steric hindrance at the site of protonation may all play some role in determining the ratios of protonation rates at $C_{(\alpha)}$ and $C_{(\gamma)}$ in dienolates. However, the relative importance of these factors in the protonation of dienolates is not necessarily the same as their contribution in the protonation of neutral dienols. At present, there are not enough data to comment on the contribution of each of these factors to the site of protonation. In all of the studies to date, protonation at $C_{(\alpha)}$ is more rapid than at $C_{(\gamma)}$[12,26]. This result indicates that the relative charge density is greater at $C_{(\alpha)}$, as suggested by Birch[43].

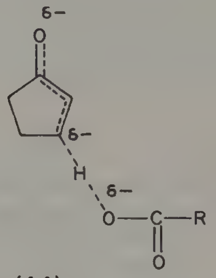
Whalen and coworkers[12] have examined the mechanism of general-base-catalyzed isomerization of 3-cyclopentenone and 3-cyclohexenone. The rate-limiting step in the isomerization of 3-cyclohexenone is protonation of the intermediate dienolate ion (k_α/k_γ is large), analogous to the conjugation of 5-androstene-3,17-dione. (The rate of exchange of the α-protons in deuterium oxide is 575-fold larger than the rate of isomerization[12]). However, for 3-cyclopentenone, the partitioning of the intermediate favors return to reactants over conversion to products by only a factor of about 3. Although part of this difference in the partitioning ratio is undoubtedly due to the difference in equilibrium constants for the two reactions (Table 1), Whalen and coworkers suggest that there is also a substantial difference in the relative charge densities at $C_{(\alpha)}$ and $C_{(\gamma)}$ in the two systems. The large difference in k_α/k_γ implies that there is significantly higher charge density at $C_{(\alpha)}$ of the cyclohexadienolate ion than the cyclopentadienolate ion. Using reasoning similar to that for the corresponding acid-catalyzed reaction, these authors postulated that the difference in protonation rate ratios is due to greater twisting in the six-membered ring dienolate compared to the five-membered ring (**31b**). In the cyclopentadienolate ion, with the dihedral angle near 0°, the negative charge can be partially delocalized to $C_{(\gamma)}$. As the dienolate system becomes twisted in the cyclohexadienolate ion, increasing θ, less charge can be delocalized to $C_{(\gamma)}$ and protonation becomes more favored at $C_{(\alpha)}$.

3. Electrostatic effects in general base catalysis

Whalen and coworkers[12] also examined the efficiency of various general bases in catalyzing the isomerization of 3-cyclopentenone. They found that neutral bases (tertiary amines) are about 100-fold more effective catalysts than negatively charged bases (hydroxide, phosphate, carbonate), although each charge type gives a good Brønsted plot with a β value of 0.5. These investigators suggested that electrostatic effects might explain the greater efficiency of tertiary amines relative to bases that are negatively charged. Their reasoning is that the transition state would have a favorable electrostatic interaction between the partial negative charge on the substrate and the partial positive charge on the amine catalyst (**43**). When the catalyst is a negatively charged base, however, both the substrate and the catalyst will have some negative charge in the corresponding transition state (**44**). These electrostatic interactions would be unfavorable in the latter case and might explain why negatively charged bases are less efficient than tertiary amines in catalyzing the isomerization.

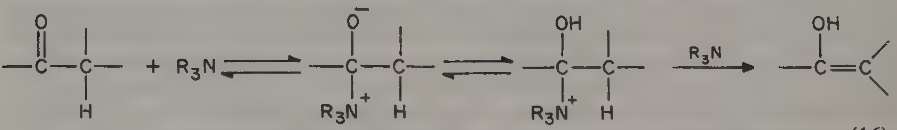


(43)



(44)

It should be noted, however, that Bruice and Bruice[44,45] have proposed that tertiary amine catalyzed enolization of oxaloacetic acid occurs by nucleophilic attack of the amine on the carbonyl compound to generate a carbinolamine. A second molecule of the tertiary amine then catalyzes the elimination of a proton and neutral amine to yield the enol (equation 16). Initial reports that suggested this mechanism were criticized[46], but a reinvestigation by P. Y. Bruice is consistent with the proposed nucleophilic mechanism[47]. It is possible that the greater ability of tertiary amines to catalyze the isomerization of β,γ-unsaturated ketones compared to the other general bases could be due, at least in part, to a nucleophilic component of the overall catalytic mechanism. Two pieces of evidence, however, argue against a significant contribution of nucleophilic catalysis to the rate enhancement demonstrated by tertiary amines. (1) Upward curvature in rate vs. buffer plots at low buffer concentration is predicted for a component in the rate expression that is second order with respect to buffer (e.g. a nucleophilic component). Whalen and coworkers[12] saw no such deviations. (2) Steric factors might significantly alter the efficiency by which tertiary amines could serve as nucleophilic catalysts. Deviations from the Brønsted lines generated by the five tertiary amines that might be attributable to steric effects are seen, but these deviations are relatively small (*ca* 0.5 log units).



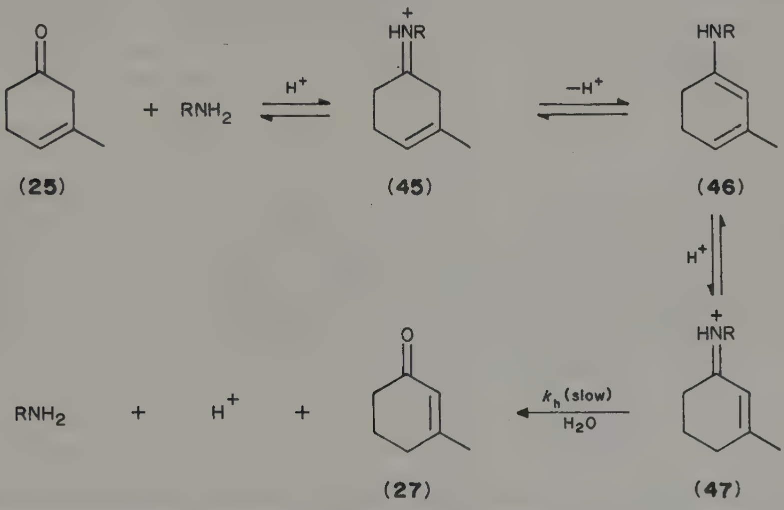
(16)

Kresge and Chiang[48] have observed that in the acid-catalyzed hydrolysis of vinyl ethers, general acids that contain negative charged or dipolar substituent groups are more effective catalysts than neutral acids of the same pK_a. Electrostatic effects analogous to those suggested by Whalen's group[12] were proposed to explain these results. However, the magnitude of the electrostatic effect (*ca* 0.5 log units) is smaller than that seen by Whalen (*ca* 2 log units). P. Y. Bruice[49] has observed that tertiary amines are better catalysts than oxyanions of the same pK_a in the ionization of nitroethane by 13-fold (p$K_a = 10.0$) to 130-fold (p$K_a = 6.2$). These rate ratios, which are similar to those observed by Whalen, are also attributed to electrostatic effects.

C. Nucleophilic Catalysis

Primary amines such as 2,2,2-trifluoroethylamine (TFEA) efficiently catalyze the isomerization of β,γ-unsaturated ketones to their α,β-unsaturated isomers[50,51]. When

3-methyl-3-cyclohexenone (**25**) is added to aqueous TFEA buffer near neutral pH, 3-methyl-2-cyclohexenone (**27**, $\gamma_{\max}$ 240 nm) is formed. At moderate concentrations of buffer (<0.4 M) the appearance of **27** is a pseudo-first-order process. However, an initial induction period is observed, and another ultraviolet-absorbing species ($\lambda_{\max} = 268$ nm) transiently accumulates during the course of the reaction. When the reaction is monitored at 268 nm, a rapid initial absorbance increase (without an induction period) is seen followed by a slower decay. The rate of this decay corresponds to the rate of formation of the α,β-unsaturated ketone. These results strongly suggest the involvement of an intermediate in the reaction pathway. This intermediate was isolated and identified as the protonated α,β-unsaturated Schiff base **47** (equation 17). The rate of formation of **47** could be assessed by absorbance changes at 251 nm, the isosbestic point for the conversion of **47** → **27**, and was found to be *ca* 100 times faster than the rate of the overall (**25** → **27**) reaction (at 1 M amine). Furthermore, **47** hydrolyzes exclusively to **27** with a rate constant indistinguishable from the rate of the overall reaction. The results are consistent with a mechanism where the protonated Schiff base **47** is formed in a very rapid reaction, followed by slower hydrolysis to yield **27**. After initial formation of the β,γ-unsaturated Schiff base **45**, the isomerization of the double bond to form **47** probably proceeds in a manner analogous to that described earlier for the acid-catalyzed reaction.



(17)

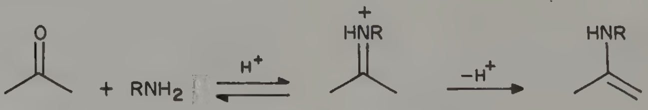
The overall catalytic efficiency of a primary amine such as TFEA in the isomerization of **25** is limited by k_h, since the rate of hydrolysis of **47** to **27** is much slower than the preceding steps at all but very low concentrations of TFEA. The rate constant, k_h, for this reaction at pH 6 (with 1 M TFEA) is *ca* $1 \times 10^{-3}\,\mathrm{s}^{-1}$. A comparison of this rate constant with the estimated rate constant for spontaneous isomerization of **25** at neutrality (*ca* $2 \times 10^{-7}\,\mathrm{s}^{-1}$) gives a rate enhancement of about 10^4-fold[50]. A comparison with the corresponding acid-catalyzed[19] and base-catalyzed processes at this pH shows that the amine catalysis is more efficient by a factor of 10^6-fold and 10^5-fold, respectively[50]. Since the actual bond migration (**25** → **47**) is *ca* 100 times faster than the hydrolysis step (**47** → **27**), primary amines are excellent catalysts for the double-bond migration of β,γ-unsaturated ketones.

The rate-limiting hydrolysis reaction of the Schiff base has been studied in some detail and two important conclusions can be drawn. (1) The hydrolysis of **47** is subject to general base catalysis[52,53]. Thus, the rate of the hydrolysis reaction (and hence the overall isomerization rate) is increased by increasing the buffer concentration at a given pH. (2) A lowered solvent polarity produces a marked increase in the hydrolysis rate, even though the concentration of water is diminished[52,54]. For example, the observed rate constant for attack of water on **47** in 90% dioxane is 18-fold larger than in pure water. This rate enhancement is probably due to preferential solvation of the transition state with a positive charge on oxygen relative to both reactants and products, which have positive charge on a nitrogen. Interestingly, a combination of general base catalysis and reduced solvent polarity is considerably more effective than would be predicted from the magnitude of these effects acting individually[52]. For example, the rate constant for hydrolysis extrapolated to 1 M chloroacetate in 70% dioxane is 350-fold greater than in pure water. If both the solvent effect (11-fold) and the effect of 1 M chloroacetate catalysis in water (2.5-fold) were acting independently, a rate increase of only 28-fold would be predicted. The synergism of these two effects could explain part of the very rapid rate of Schiff base hydrolysis that is observed with many enzymes.

Benisek and Jacobson[55] have shown that isomerization of 3-oxo-Δ^5-steroids to their conjugated isomers is also catalyzed by primary amines. The reaction of 5-androstene-3, 17-dione in glycine buffer presumably follows a mechanism analogous to that for 3-methyl-3-cyclohexenone, but a detailed kinetic analysis of this reaction was not undertaken. The accumulation of a Schiff base as an intermediate in the reaction was suggested by the rapid, but transient, appearance of an ultraviolet chromophore with an absorbance maximum at 275 nm. The identification of the intermediate was established by chemical trapping with sodium borohydride. The primary amine catalyzed isomerization of 3-oxo-Δ^5-steroids was also described in later reports by the groups of Okuyama[26] and of Fedor[37].

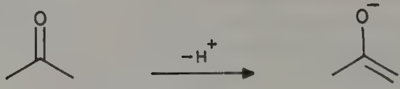
The efficiency by which primary amines catalyze the isomerization of β,γ-unsaturated ketones is attributable to their ability to rapidly and reversibly form Schiff base intermediates in aqueous solution with the carbonyl group of the β,γ-unsaturated ketone[56]. Since simple Schiff bases are somewhat less basic (*ca* 3pK_a units) than the amines from which they are derived[57–59], the Schiff base exists substantially in the protonated form near neutral pH, and thereby gives the molecule an electron sink into which an electron pair may be put during the cleavage of the $C_{(\alpha)}$—H bond. Alternatively, when this reaction is catalyzed by base, the electron pair is placed on the carbonyl function itself, but the resultant enolate intermediate is relatively unstable at neutral pH. In the acid-catalyzed reaction, the electron pair is placed on a protonated ketone to form a stable enol intermediate, but a carbonyl group is not readily protonated at neutral pH. The existence of a reasonably good electron sink, the protonated Schiff base, which rapidly and reversibly forms in high concentration near neutral pH, makes the Schiff base mechanism a favorable reaction pathway. The rate enhancement afforded by this mechanism is particularly significant when enolization and subsequent isomerization are restricted to solutions with pH values at or near neutrality, such as that found in biological systems.

Schiff Base Catalysis:



(18)

Base Catalysis:

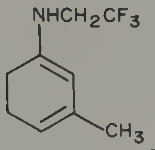


(19)

Acid Catalysis:

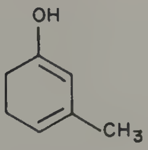
(20)

It is of interest to compare the k_γ/k_α ratio for the trifluoroethylamine enamine of 3-methyl-3-cyclohexenone with the corresponding enol and enol ether. In the case of both **26** and **30** protonation is predominantly at $C_{(\gamma)}$, yet **48** protonates slightly faster at $C_{(\alpha)}$ than $C_{(\gamma)}$. Because of the twisting between the double bonds of the nonplanar diene system[12], the conjugation of the heteroatom with $C_{(\gamma)}$ is inhibited relative to $C_{(\alpha)}$. Thus, the additional electron-donating ability due to the nitrogen of **48** (compared to the oxygens of **26** and **30**) is transmitted more effectively to $C_{(\alpha)}$ than $C_{(\gamma)}$, and k_α is increased more than k_γ on going from **26** or **30** to **48**.



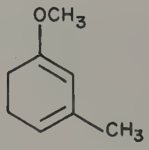
(48)

k_γ/k_α 0.7 (Ref.31)



(26)

v. large (Ref.19)

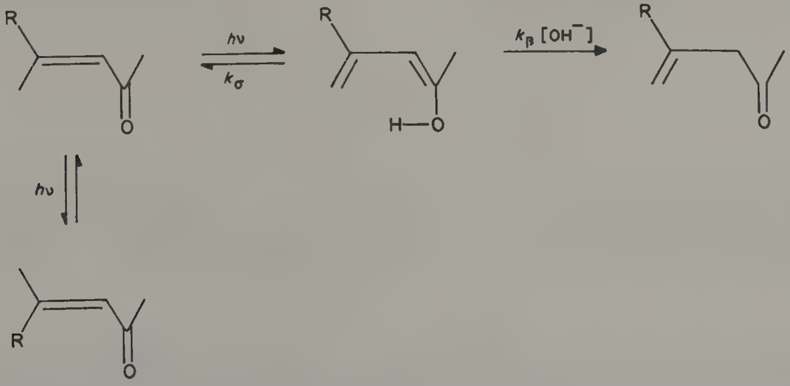


(30)

9 (Ref.31)

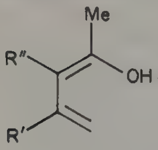
D. Photochemical Isomerization

Irradiation of α,β-unsaturated esters and ketones with substituents at the β carbon results in *cis–trans* isomerization through the triplet state[60–67] and slower isomerization to the β,γ-unsaturated isomers through the singlet state. Isomerization to the unconjugated isomer occurs through initial abstraction of a hydrogen from $C_{(\gamma)}$ to produce an intermediate dienol that rapidly ketonizes to produce the β,γ-unsaturated product in base or to regenerate the starting α,β-unsaturated carbonyl compound in neutral solution.

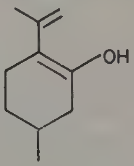


(21)

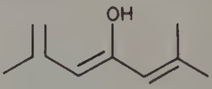
The intermediacy of a dienol in the deconjugation has been shown by chemical trapping experiments in which mesityl oxide was irradiated in the presence of chlorotrimethylsilane and imidazole. The trimethylsilyl ether of (*Z*)-4-methyl-2,4-pentadienol was isolated as the major initial product, confirming that a dienol is formed[64]. In addition, the dienolate ions of **49**–**53** have been directly observed by Duhaime and Weedon[66,67] in the ultraviolet spectrum, upon flash photolysis of a series of simple unsaturated ketones.



(**49**) R′ = Me, R″ = H
(**50**) R′ = *t*-Bu, R″ = H
(**51**) R′ = R″ = Me



(**52**)



(**53**)

Duhaime and Weedon[66,67] measured the rates of ketonization of several dienols in aqueous solution as a function of base concentration. The reaction shows kinetic behavior consistent with two reactions, a base-catalyzed process (probably protonation of the dienolate ion by water) and an uncatalyzed process. The observed rate constant for protonation of the dienolate ions by water is about $10^3\,s^{-1}$ (ambient temperature) for dienols **49**–**53**. These values are similar to the corresponding values for the rate constant for protonation of simple enolate ions such as those derived from acetone ($k = 5 \times 10^4\,s^{-1}$)[40], acetaldehyde ($8.8 \times 10^2\,s^{-1}$)[68], isobutyrophenone ($69\,s^{-1}$)[39] and acetophenone ($7.2 \times 10^3\,s^{-1}$)[41], as might be expected for reactions occurring by similar mechanisms.

In contrast to the base-catalyzed rate constants, the rate constants for the neutral reaction of these dienols are substantially higher than the corresponding rate constants for simple enols. For compounds **50**–**53**, rate constants for the uncatalyzed reaction are in the range 10–$50\,s^{-1}$, whereas typical rate constants[*] for simple enols under these conditions are *ca* 10^{-4} to $10^{-1}\,s^{-1}$[39,69]. The enhanced lifetime for simple enols in neutral solution compared to these dienols was interpreted in terms of a ketonization mechanism available to dienols that is unavailable to simple enols. Duhaime and Weedon proposed that these dienols ketonize by an intramolecular 1,5-hydrogen shift (equation 22) to give the α,β-unsaturated compounds directly.

(22)

In support of this mechanism, we have found that 1,3-cyclohexadienol, a dienol locked in a conformation such that a 1,5-hydrogen shift cannot occur, has a lifetime comparable to simple enols in slightly acidic solution[70]. Furthermore, the uncatalyzed ketonization of 1,3-cyclohexadienol yields the β,γ-unsaturated isomer, rather than the α,β-unsaturated isomer obtained with dienols that ketonize by the cyclic mechanism.[†]

---

[*] The rate constant for acetophenone has been reported to be greater than that for other simple enols ($1.9\,s^{-1}$)[41]. However, more recent measurements of this rate constant give a value of $0.18\,s^{-1}$.

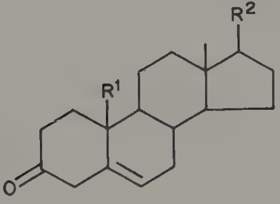
[†] *Note added in proof*: Recently, it has been concluded that this pathway is not important for the ketonization of the acyclic dienol (*Z*)-1-hydroxy-1,3-butadiene (B. Capon and B. Guo, *J. Am. Chem. Soc.*, **110**, 5144 (1988)).

IV. 3-OXO-Δ^5-STEROID ISOMERASE

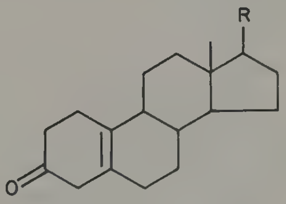
A. Background

Much of the impetus for the investigations into the acid- and base-catalyzed mechanisms of isomerization of β,γ-unsaturated ketones comes from a desire to understand the mechanism of action of the enzyme 3-oxo-Δ^5-steroid isomerase[1]. Enzyme-catalyzed isomerization of 3-oxo-Δ^5-steroids to their 3-oxo-Δ^4-isomers was first described by Talalay and Wang in 1955[24]. This enzymatic activity was found in soluble extracts of *Pseudomonas testosteroni*, a soil bacterium capable of growing in a medium containing any one of a variety of steroids as the sole carbon source[1]. By 1960, the 3-oxo-Δ^5-steroid isomerase was obtained in a crystalline form[71] and a decade later the entire amino acid sequence of this enzyme had been determined[72]. This enzyme has received much attention since the conversion of 3-oxo-Δ^5-steroids to their conjugated Δ^4 isomers is a necessary step in the biosynthesis of all classes steroid hormones.

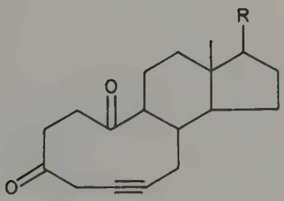
The bacterial isomerase has a rather broad specificity (Table 2). Not only does it catalyze the isomerization of 3-oxo-Δ^5-steroids, such as 5-androstene-3, 17-dione (**40**) and 5-pregnene-3, 20-dione (**54**), but it also isomerizes $\Delta^{5(10)}$ steroids and $\Delta^{5,6}$ acetylenes. In addition, more than sixty steroids and related compounds have been shown to be competitive inhibitors of isomerase activity[73], demonstrating that the active site interactions with steroids are relatively nonspecific.



(**40**) $R^1 = Me$, $R^2 = O$
(**54**) $R^1 = Me$, $R^2 = \beta\text{-}COCH_3$
(**55**) $R^1 = H$, $R^2 = O$



(**56**) $R = O$
(**57**) $R = \beta\text{-}OH$
(**58**) $R = \alpha\text{-}C{\equiv}CH,\ \beta\text{-}OH$



(**59a**) $R = O$
(**59b**) $R = \beta\text{-}COCH_3$

The 3-oxo-Δ^5-steroid isomerase from *Psuedomonas testosteroni* is an inducible enzyme with a monomer molecular weight of 13, 394[1,72]. The subunits of the isomerase readily undergo association and the enzyme exists as a dimer over the concentration range 0.05 to 1.0 mg protein/ml[74–76]. Above a concentration of 2 mg/ml, the dimeric enzyme undergoes

TABLE 2. Kinetic parameters of substrate isomerization[a]

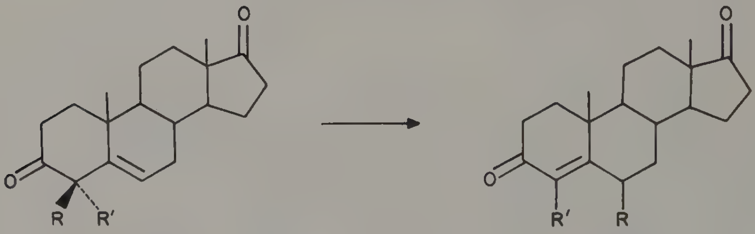
Substrate	$k_{cat}(s^{-1})$	$K_m(M)$	k_{cat}/K_m $(M^{-1}s^{-1})$	References
40	7.0×10^4	3.1×10^{-4}	2.3×10^8	84[b], 115, 137
40[c]	1.2×10^4	3.8×10^{-4}	3.0×10^7	105
54	2.7×10^3	8.2×10^{-6}	3.3×10^8	115
54[c]	3.5×10^3	6.8×10^{-5}	5.1×10^7	115
55	2.7×10^4	8.3×10^{-5}	3.3×10^8	84[b]
56	6.1×10^1	4.8×10^{-5}	1.4×10^6	84[b], 115
57	1.7×10^1	4.0×10^{-5}	4.3×10^5	84[b]
58[d]	9.1×10^1	1.4×10^{-4}	6.5×10^5	84[b]
59a[c]	1.2×10^3	4.1×10^{-4}	2.8×10^6	105
59b[c]	7.5×10^2	4.8×10^{-5}	1.6×10^7	105

[a] These values are kinetic constants calculated assuming one active site per monomer at pH 7, 25.0 °C in 3.3% methanol, unless otherwise stated. Where more than one reference is given, the reported parameters may differ slightly.

[b] The k_{cat} values for Reference 84 have been divided by a factor of 2, as it appears that they are based on dimeric enzyme.

[c] 8.1% acetonitrile.

[d] 5.0% methanol.



(23)

(**40**)

(a) R = R′ = H

(b) R = D, R′ = H

(c) R = H, R′ = D

(**42**)

(a) R = R′ = H

(b) R = D, R′ = H

(c) R = H, R′ = D

(d) R = R′ = D

further aggregation, although some controversy exists over whether the isomerase is monomeric or dimeric at concentrations below 0.05 mg/ml. 'Half-of-the-sites' reactivity has been reported for the isomerase[77], but it has been established that there is one steroid binding site per enzyme monomer[78–82]. The isomerase contains no tryptophan or cysteine residues, and requires no cofactors, prosthetic groups, or metal ions for catalysis.

B. Intramolecular Proton Transfer and Stereochemistry

The migration of the double bond of 3-oxo-Δ^5-steroids to the Δ^4 position occurs with transfer of a proton from $C_{(4)}$ to $C_{(6)}$. Talalay and coworkers[24,71,83] showed that, although the corresponding base-catalyzed reaction carried out in deuterated solvent gives rise to product with incorporation of one or more atoms of deuterium, isomerization catalyzed by the enzyme in D_2O proceeds with incorporation of only 0.1 atoms of deuterium into product. They concluded that the enzyme catalyzes the isomerization via an intramolecular proton transfer in the enzyme–substrate complex, involving a single active site base shielded from solvent. Utilizing $C_{(4)}$ deuterated substrates, Malhotra and Ringold[18] confirmed the intramolecular nature of the proton transfer, and further demonstrated that the reaction involves stereospecific transfer of the 4β proton to the 6β position.

Comparison of the catalytic rate constants for isomerization of 5-androstene-3, 17-dione and its 4β-deuterium analogue reveals a large primary isotope effect $(k_{cat}/K_m)^H/(k_{cat}/K_m)^D = 2.9$[84]. Since the isomerization proceeds predominantly, if not exclusively, by a $C_{(4\beta)}$ to $C_{(6\beta)}$ intramolecular transfer[18,85], the primary isotope effect suggests that either proton removal at $C_{(4)}$ or reprotonation at $C_{(6)}$ is at least partially rate-determining. Thus, at least in the case of 5-androstene-3, 17-dione as a substrate, the enzymatic reaction is not totally diffusion-controlled.

More recently, the stereospecificity of the enzyme was reinvestigated by Viger and coworkers[85,86], who demonstrated that the reaction is more complex than previously thought. The isomerase-catalyzed reaction of 4β-deutero-5-androstene-3, 17-dione (**40b**) yields an isotopic mixture of products (**42b**, 50%, **42a**, 25% and **42c**, 25%), showing that the two hydrogens at $C_{(4)}$ are competitively abstracted. The formation of **42b** exhibits the expected transfer of the axial 4β hydrogen, but the appearance of **42a** shows that the substrate undergoes a significant amount of exchange of this hydrogen with the medium. Significantly, the formation of **42c** requires that there be a mechanism for abstraction of the 4α hydrogen. However, the 4α-deuterium abstracted during isomerization of 4α-deutero-5-androstene-3, 17-dione (**40c**) is lost to the medium and is not incorporated into the product. Isomerization of **40a** in D_2O gives both some **42c** and **42d**. These results were interpreted in terms of two bases at the active site, one that abstracts the 4β proton in the catalytic reaction and one that acts to abstract the 4α proton, but cannot donate this proton to $C_{(6)}$, although this latter base may simply be a solvent molecule.

Somewhat different results were obtained from analogous experiments with 5-pregnene-3, 20-dione (**54**) as the substrate. Enzymatic isomerization of this compound in D_2O leads to the incorporation of 0.25 atoms D per molecule, all at $C_{(6)}$[85]. When 4β-D-**54** is isomerized in H_2O, 40% of the deuterium remains in the product, all at $C_{(6)}$. A comparison of the catalytic constants for 4β-deutero-5-pregnene-3, 20-dione and the analogous undeuterated substrate reveals a primary deuterium isotope effect of unity for k_{cat}. These results indicate that neither removal of the $C_{(4\beta)}$ proton nor protonation at C-6 is rate-determining, consistent with a rate-limiting product dissociation or conformational change of the enzyme for this substrate.

With 4β-deutero-5(10)-estrene-3, 17-dione (4β-D-**56**) as a substrate, 27% of the deuterium is retained in the product (0.16 atom at $C_{(10)}$ and 0.11 atom at $C_{(4)}$). The localization of deuterium at C-10 demonstrates that intramolecular transfer is also possible with this substrate. This result is significant because it implies that the basic group which mediates the proton transfer has access to $C_{(10)}$ in addition to $C_{(4)}$ and $C_{(6)}$, suggesting mobility of this group relative to substrate within the active site. However, intramolecular transfer accounts for only 16% of the reaction with the 5(10) isomer (**56**), compared to 50% in the case of 5-androstene-3, 17-dione. These results may be due to a less suitable location of the basic residue that mediates the proton transfer for protonation of $C_{(10)}$ compared to $C_{(6)}$. Alternatively, the decreased amount of intramolecular transfer could be due to a slower intrinsic rate of protonation at a tertiary carbon $C_{(10)}$ relative to a secondary carbon $C_{(6)}$. In either case, the slower rate of protonation could allow more extensive proton exchange with solvent to occur. Furthermore, deuterated 5(10)-estrene-3, 17-dione shows only a small primary isotope effect ($k_{4\beta\text{-D}}/k_{4\beta\text{-H}} < 2$[84])*. If the rate of

---

*The report of a negligible isotope effect does not state whether it is for k_{cat} or k_{cat}/K_m. Since **56** is a slowly reactive substrate, we may assume that $K_m^H \sim K_m^D$, and thus both k_{cat} and k_{cat}/K_m should have small isotope effects.

deprotonation at $C_{(4)}$ is similar for the 5(10) and 5(6) unsaturated steroids, then it would be expected that reprotonation at $C_{(10)}$ should be rate-limiting for the 5(10) isomer. Since protonation at $C_{(6)}$ occurs predominantly with hydrogen derived from the medium in this compound (*ca* 84%), only a small isotope effect would be expected.

C. pH Dependence

Weintraub and collaborators[87] determined the pH dependence of $V_{\max}$ and K_m for the reaction of the isomerase with the specific substrate 5-androstene-3,17-dione. From a plot of log $V_{\max}$ vs. pH, a pK_a for the enzyme–substrate complex (pK_{ES}) of 5.6 was determined, and a pK_a for the free enzyme (pK_E) of 4.7 was obtained from a plot of log K_m^{-1} vs. pH. A pK_E of 4.9 was determined from a study of the pH dependence of competitive inhibition of the isomerase by estradiol (**60a**) and estrone (**60b**)[87]. They also observed a second titratable group having a pK_{ES} of 9.3, but did not firmly establish that the decrease in rate near pH 9 is not due to irreversible inactivation of the enzyme.

As has been pointed out by several authors[88–90], the pH–rate profile for an enzyme acting at or near the diffusion-controlled limit (such as the isomerase) does not necessarily give correct values for the ionization constants of the amino acids involved in the mechanism. We have reexamined the pH–rate profile of the isomerase with both 'sticky' and 'nonsticky' substrates, that is substrates that are converted to products at near diffusion-controlled rates and those that react more slowly. The pH–rate profiles for the sticky substrates 5-androstene-3,17-dione and 5-pregnene-3,17-dione do not correspond to simple titration curves, as predicted for an enzymatic reaction near the diffusion limit. The pH–rate profiles of the nonsticky substrate 5(10)-estrene-3,17-dione, however, both give an excellent fit with a titration curve, giving p$K_E = 4.57$ (from k_{cat}/K_m) and p$K_{ES} = 4.74$ (from k_{cat}). Since the second-order rate constant for 5(10)-estrene-3,17-dione is about 10^3-fold slower than that for 5-androstene-3,17-dione[84], this reaction is well below the diffusion-controlled limit, and these pK values likely represent the true ionization constants for the free enzyme and the enzyme–substrate complex. On the base side of the profile, measurements could not be made higher than pH 8.7, due to rapid loss of enzyme activity, in contrast to the results reported by Weintraub and coworkers[87].

D. Amino Acid Residues Implicated in the Reaction

1. Lysine

The remarkably efficient mechanism by which primary amines can catalyze the isomerization of β,γ-unsaturated ketones to their α,β-isomers[50,51,55] makes it of interest to determine whether the isomerase can function in the same manner. The enzyme contains five primary amines which could conceivably function as the key amine group in Schiff base catalysis (four ε-amino groups of lysine and one α-amino group of the terminal methionine group)[72]. A classical approach used to gain evidence in support of this type of mechanism is to trap the Schiff base intermediate by reduction with sodium borohydride. Attempts to reduce the complex of isomerase and radioactively labelled competitive inhibitor 19-nortestosterone (**61a**) with borohydride at pH 6 and 0 °C were unsuccessful[1]. There was no loss of enzymatic activity and no significant incorporation of radioactivity into the protein. Furthermore, treatment of the enzyme with borohydride in the presence of the substrate 5-androstene-3,17-dione also showed no loss of activity[91]. Substrate reduction occurs faster than inactivation. Attempts to trap a possible Schiff base intermediate with cyanide were also unsuccessful[91]. Although these results argue against a mechanism which involves a Schiff base intermediate, there is precedent for enzymes that function via Schiff base formation not being amenable to trapping by either borohydride or cyanide[92,93].

Further evidence concerning the involvement of a primary amine in the catalytic mechanism of the isomerase comes from the results of Benisek and Jacobson[55] on the effect of the modification of amine residues of the isomerase on activity. Trinitrobenzenesulfonate and maleic anhydride, two reagents that modify primary amine groups of proteins, both completely inactivate the enzyme. On the other hand, treatment of the enzyme at pH 8.5 for 2 h with methyl acetimidate, another reagent that modifies primary amine groups, does not inactivate the enzyme. This latter result was interpreted as showing that a Schiff base is not involved in the enzymatic reaction[55].

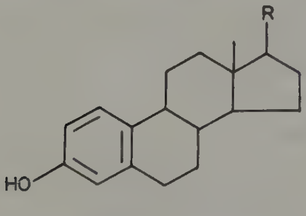
2. *Histidine*

Weintraub and coworkers[87] suggested that the group observed by them having pK_a of 4.7–4.9 in the free enzyme and 5.6 in the enzyme–substrate complex might be histidine or a carboxylic acid residue. Talalay and colloborators[1] reported that diethyl pyrocarbonate, a reagent which specifically acylates imidazole side-chains of histidine at pH 6 or below[94,95], causes inactivation of the isomerase at pH 6. Also, the isomerase undergoes a pH-dependent photoinactivation in the presence of methylene blue, in which the pH–rate profile for the photoinactivation parallels that for the ionization of imidazole. Talalay[1,96] has proposed that the imidazole side-chain of a single histidyl residue might function simultaneously both to protonate the 3-oxo group of substrate and to carry out the 4β–6β proton transfer. However, Jones and Wigfield[21] criticized this proposal. Upon examination of molecular models they concluded that the geometry of the transition states could probably not support the proposed bifunctional activity of a single imidazole side-chain.

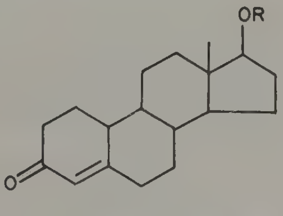
In contrast to the above results implicating histidine in the catalytic mechanism, Benisek and Ogez[97] found that binding of the competitive inhibitor 17β-estradiol produces no significant change in the chemical shifts of the protons of the isomerase histidine residues in the NMR. These results indicate that histidine may not be present at the active site, or at least does not interact with bound steroid. If 17β-estradiol binds to the isomerase in the same manner as substrate, it might be expected that the aromatic ring current would perturb the resonances from nearby protons of the enzyme.

3. *Tyrosine*

In early work Wang, Kawahara and Talalay[83] suggested that a tyrosine residue is present at the active site, on the basis of changes in the fluorescence spectrum of the isomerase upon binding of the competitive inhibitor 19-nortestosterone (**61a**). Moreover, nitration of the tyrosines of the enzyme by tetranitromethane causes inactivation of the



(60a) R = β-OH
(60b) R = O



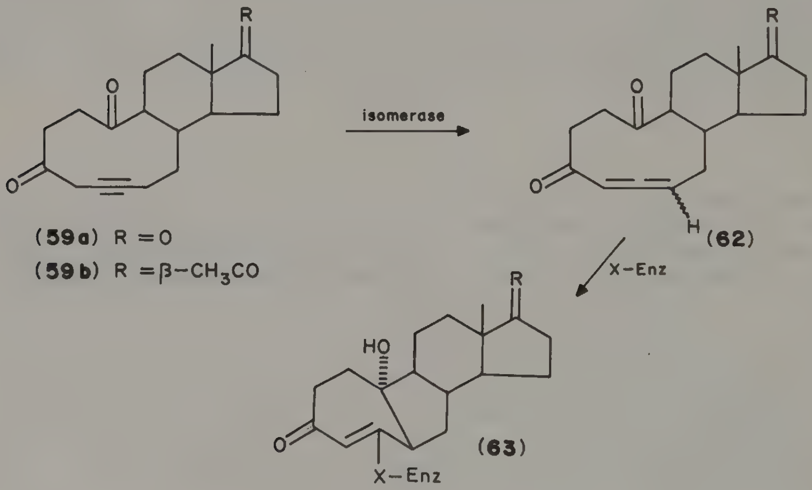
(61a) R = β-OH
(61b) R = β-OAc
(61c) R = O–polymer

enzyme[1,98,99]. Ultraviolet spectrophotometric titration of the isomerase indicates that one of the three tyrosines in the isomerase titrates normally (pK_a 9.5–10.0), whereas the other two have substantially higher pK_a values (12–13)[100]. Benisek and Ogez[97] noted that aromatic resonances in the proton NMR spectrum of the isomerase undergo a substantial upfield shift upon binding to the competitive inhibitor 17β-estradiol. They concluded that these spectral changes might be due to interaction between the steroid and one or more active site tyrosine residues. Jones and Wigfield[21] have suggested that one of the tyrosines of the enzyme may function as an acid to protonate the 3-oxo group of the substrate.

In support of the possible participation of tyrosine in the catalytic mechanism, Tyr-55 is located close to the site of attachment (Asn-57) of the active-site-directed irreversible inhibitor 5, 10-seco-5-estryne-3, 10, 17-trione[101]. Thus, it is reasonable to suspect that Tyr-55 might be present at the active site also. X-ray evidence, to be discussed later, also indicates that Tyr-55 is at the active site.*

4. Asparagine 57

There is some evidence that Asn-57 plays a role in steroid binding and/or catalysis. Batzold and Robinson[102,103] have shown that the 3-oxo-5, 10-secosteroids **59a** and **59b** are suicide substrates of the isomerase. These acetylenic steroids act as substrates for the isomerase and undergo enzymatic conversion to a mixture of allenic ketones, which in turn cause rapid and irreversible inactivation of the enzyme (equation 24)[1,104]. The covalent adduct between **59a** and the isomerase was isolated and digested with Proteinase K. A modified tetrapeptide containing residues 55–58 was isolated from the reaction, and it was determined that Asn-57 had been converted to aspartic acid[101,105] during the inactivation process. Although amides are not generally regarded as nucleophiles, it was suggested that the side-chain of Asn-57 forms a covalent bond with the electrophilic allenic steroid[101,106], and may by analogy act as a base during the catalytic reaction.



(24)

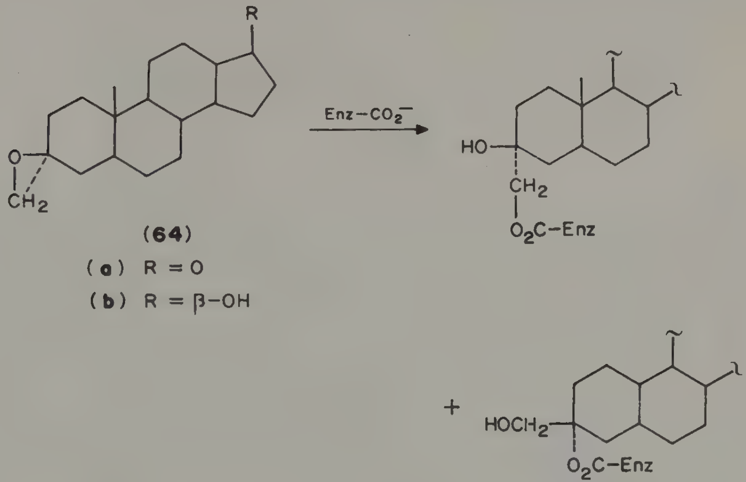
**Note added in proof*: Site-directed mutagenesis of the isomerase suggests that Tyr-55 is not catalytically important, but that Tyr-14 is (A. Kuliopulos, A. S. Mildvan, D. Shortle and P. Talalay, *FASEB J.* 2 (Abs. 1704), p. AS89 (1988)).

*5. Aspartic acid 38**

The involvement of a carboxylate residue in the isomerase mechanism has been demonstrated by inactivation studies. Martyr and Benisek[107] reported that irradiation ($\lambda > 300$ nm) of the isomerase in the presence of the competitive inhibitor 19-nortestosterone acetate (**61b**) causes irreversible inactivation of the enzyme. The major reaction accompanying the inactivation is a photodecarboxylation of Asp-38, yielding an alanine at this position[108,109]. Hearne and Benisek[110–112] subsequently identified a second mechanism of inactivation and isolated a peptide covalently bound to Asp-38 from the photoinactivation of the isomerase by the solid-phase reagent Δ^6-testosterone-agarose (**61c**). Since the A and B rings of the steroid are the photoreactive parts of the molecule and the large agarose side-chain at $C_{(17)}$ should effectively preclude binding of the D ring in the interior of the active site, they concluded that Asp-38 must lie at the base of the binding pocket in the isomerase.

Additionally, Benisek and coworkers[113] have shown that Asp-38 is hyperreactive towards amidation with amines in the presence of *N*-ethyl-*N'*-(3-dimethylamino)propyl carbodiimide (EDAC). When the isomerase is treated with EDAC in the presence of various amines (glycine ethyl ester, taurine, cystamine or ammonium ion) at pH 4.75, there is a rapid pseudo-first-order loss of enzyme activity (for > 3 half-lives). A detailed analysis of the kinetics of enzyme inactivation and amide formation with cystamine indicates that the data are in excellent agreement with a kinetic model in which one carboxyl group per enzyme subunit is rapidly amidated and 14 other carboxyl groups per subunit each react about 100-fold more slowly. The rate of enzyme inactivation under the same conditions agrees with the rate of rapid amidation of the single carboxylate in this kinetic model. The modified amino acid was identified as Asp-38.

Asp-38 was also identified at the active site in affinity alkylation studies with 3β- and 17β-oxiranyl steroids (e.g. **64** and **65**)[80,114]. In short-term experiments, these oxiranes are



(**64**)

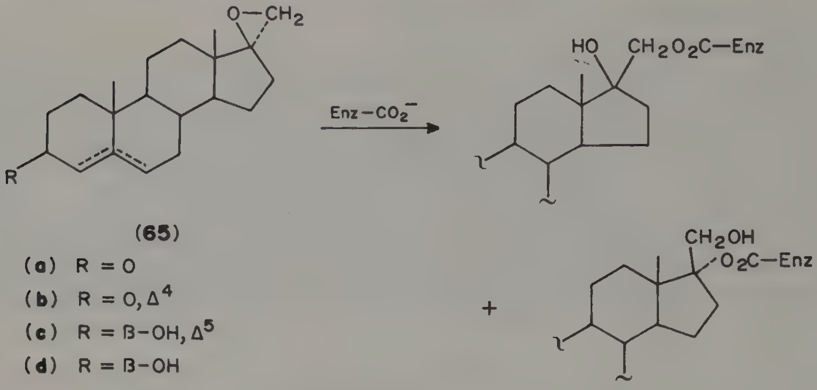
(**a**) R = O

(**b**) R = β-OH

(25)

---

*There was some controversy about the identification of several residues of the isomerase. Residues 22, 24, 33 and 38 were originally assigned to asparagine by Benson and coworkers[72] whereas Ogez and collaborators reported aspartic acid at these positions[109]. Recent sequencing of the gene confirms that these residues are all aspartic acid[133,136]. Residue 77, which was assigned as glutamine in the protein sequence[72], has been reassigned as glutamic acid by gene sequencing[133,136].



(65)

(a) $R = O$
(b) $R = O, \Delta^4$
(c) $R = \beta\text{-}OH, \Delta^5$
(d) $R = \beta\text{-}OH$

(26)

competitive inhibitors of the isomerase, whereas upon longer incubation they form covalent bonds with Asp-38. Neither the 3α-nor the 17α-oxiranes, however, are irreversible inhibitors. Alkylation occurs at both the methylene and spiro carbons of the oxiranes with the 3*β*- and 17*β*-oxiranes (equations 25 and 26). The pH dependence for the reaction of (3*S*)-spiro[5α-androstan-3, 2′-oxiran]-17-one (**64a**) with the isomerase shows p*K* values of 4.75 and 4.90 for the free enzyme and the enzyme–inhibitor complex, respectively[115]. These values agree well with p*K*s determined for the isomerization of the nonspecific substrate 5(10)-estren-3, 17-dione ($pK_E = 4.57$ and $pK_{ES} = 4.74$), suggesting that Asp-38 is involved in the catalytic reaction (Figure 1).

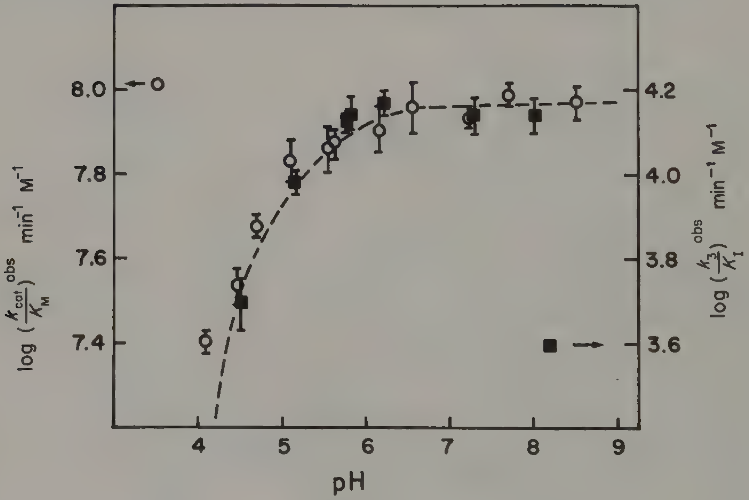
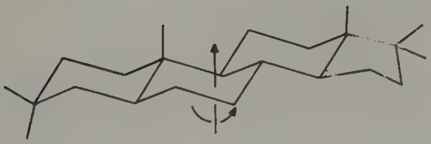


FIGURE 1. Comparison of the pH–rate profiles for log $(k_{cat}/K_M)^{obs}$ for the isomerization of 5(10)-estrene-3,17-dione (○) and log $(k_3/K_I)^{obs}$ for the inactivation by (3*S*)-spiro[5α-androstane-3,2′-oxiran[-17]one (■). The line is theoretical for a simple titration curve with $pK = 4.75$. Reproduced with permission from R. M. Pollack, S. Bantia, P. L. Bounds and B. M. Koffman, *Biochemistry*, **25**, 1905 (1986). Copyright (1986) American Chemical Society

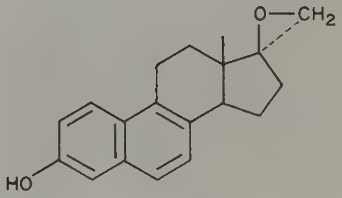
Further evidence that Asp-38 is catalytically important comes from the studies of Linden and Benisek[116]. They reported that, although the amino acid sequence of the 3-oxo-Δ^5-steroid isomerase from *Pseudomonas putida* demonstrates only 34% overall homology with the related *testosteroni* enzyme, 100% homology is seen in a region encompassing Asp-38 (residues 33–41). These authors suggest that this highly conserved region must be important for catalysis.

E. Backwards Binding

Since 3β- and 17β-oxiranes each form covalent bonds with Asp-38, steroids must be capable of binding to the isomerase in at least two modes, allowing both A-ring and D-ring reactive groups proximity to the same amino acid (Asp-38). Analysis of the steroid products released upon base hydrolysis of the enzyme-steroid adducts resulting from reaction between the isomerase and oxirane enriched with ^{18}O in the oxiranyl oxygen, indicates that alkylation of the enzyme occurs via nucleophilic attack of Asp 38 on the oxirane at the α-face of steroid for both the 3β- and 17β-oxiranes (equations 25 and 26)[80,81,114,117]. These observations suggest that the two modes of binding are related by a rotation of 180° about an axis perpendicular to the plane of the steroid nucleus (**66**). This conclusion is supported by the detection of a transient enzyme steroid complex in the irreversible inhibition of the isomerase by the 17β-oxirane (17*S*)-spiro[estra-1, 3, 5(10), 6, 8-pentaen-17, 2′-oxiran]-3-ol (**67**)[118,119]. X-ray crystallographic determination of the structures of analogous 3β- and 17β-oxiranes shows that 3β-oxiranes and backwards* 17β-oxiranes have similar steric characteristics, consistent with this hypothesis (Figure 2)[120].



(66)

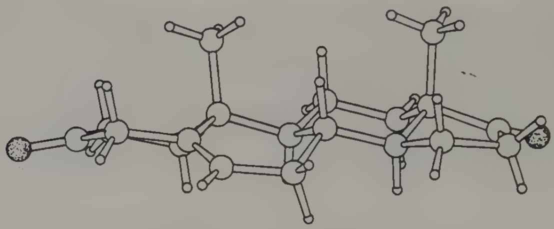


(67)

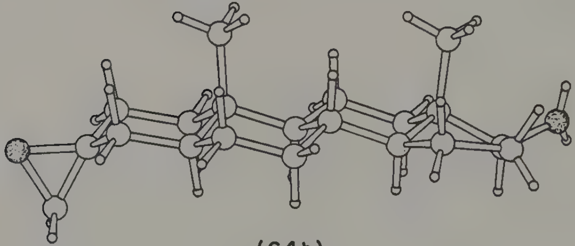
The ability of steroids to bind in more than one mode to the active site of the enzyme has important consequences for the interpretation of structural and mechanistic data of the isomerase, since it is possible that the observed complex (in X-ray or NMR investigations, for example) is not the catalytically active one. The finding that Asp-38 reacts from the α-side of the bound 3β-oxiranes was initially interpreted[81] in terms of the existence of two bases at the active site, as proposed by Viger and coworkers[85,86]. If Asp-38 is localized at the α-side of bound steroids, it cannot be the base involved in the catalytic mechanism, since proton transfer is predominantly 4β to 6β. Asp-38, however, could be the α-side base. Alternatively, it may be that steroids can bind ‘upside down’ as well as ‘backwards’, making it possible for Asp-38 to have access to both faces of a steroid molecule at the active site, but not at the same time. Although there is no evidence for this mode of binding for the isomerase, it has been proposed for other steroid binding enzymes[121–124].

---

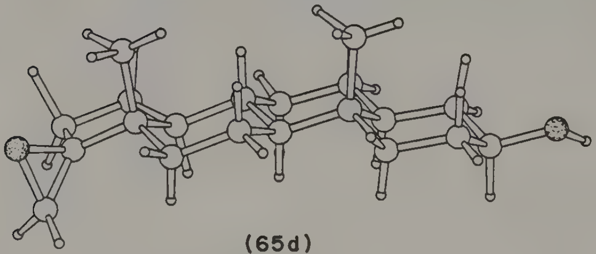
*Backwards refers to a steroid rotated 180° about an axis perpendicular to the plane of the steroid as in **66**.



5-Androstene-3, 17-dione



(64b)

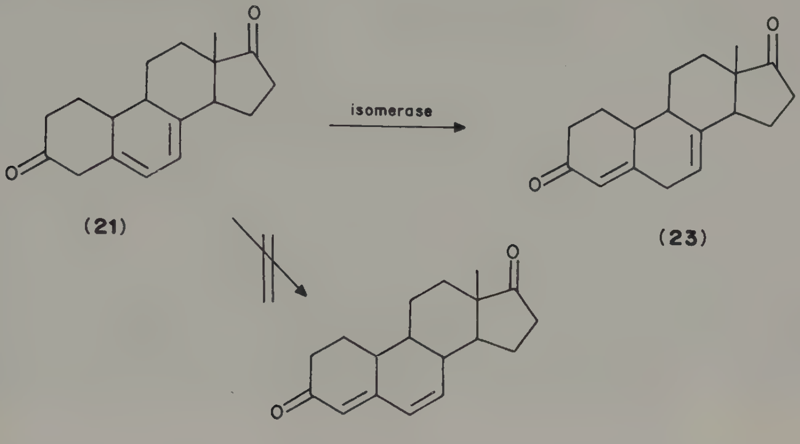


(65d)

FIGURE 2. Comparison of 5-androstene-3, 17-dione with (3*S*)-spiro[5α-androstan-3, 2′-oxiran]-17β-ol (**64b**) and (17*S*)-spiro[5α-androstan-17, 2′-oxiran]-3β-ol (**65d**) viewed along the C- and D-ring plane. Large open circles are carbon atoms, stippled circles are oxygen atoms and small open circles are hydrogen atoms. Reproduced with permission from S. Kashino, H. Katz, J. P. Glusker, R. M. Pollack and P. L. Bounds, *J. Am. Chem. Soc.*, **109**, 6765 (1987). Copyright (1987) American Chemical Society

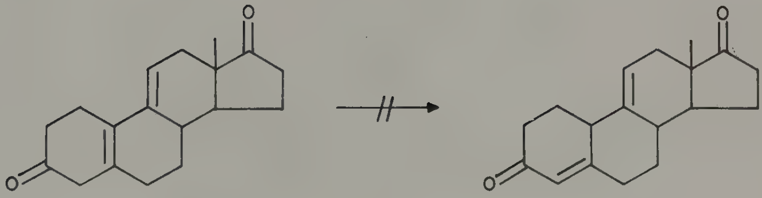
F. Evidence for an Intermediate Enol

Recent evidence that a dienol or dienolate is an intermediate on the reaction pathway comes from studies of the isomerase-catalyzed conversion of 5, 7-estradiene-3, 17-dione (**21**) to 4, 7-estradiene-3, 17-dione (**23**) (equation 27)[125]. Although **21** has an extra conjugated bond compared to normal substrates, it is an excellent substrate for the isomerase and is converted to **23** at a rate (k_{cat}/K_m) only slightly slower than that for the specific substrate 5-androstene-3, 17-dione. It is of interest that the fully conjugated ketone **24** is not formed, presumably because the active site base cannot reach $C_{(8)}$ to donate a proton, although nonenzymatic ketonization of the intermediate trienol also gives no **24** as product. Surprisingly, the analogous diene in the 5(10) series, estra-5(10), 9(11)-diene-3, 17-dione (**68**), is not a substrate for the isomerase, even though it is a good competitive inhibitor[84] (equation 28).



(21) (23) (24)

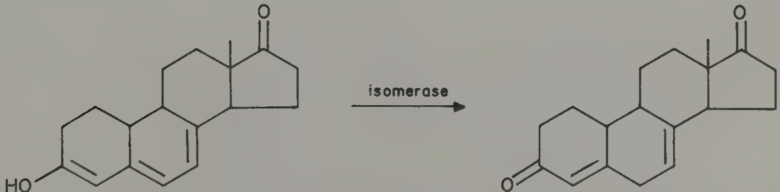
(27)



(68) (69)

(28)

Although the vast majority of enols are not isolable, the putative intermediate trienol (**22**) in this reaction can be synthesized chemically. When **22** is treated with the isomerase, it is converted to **23** at a rate that is comparable to the reaction of **21**[125] (equation 29). Thus, the putative intermediate is converted to product by the isomerase at a rate sufficient to implicate it in the overall catalytic mechanism. More recent unpublished work in our laboratory has shown that the dienol **19** from 5-androstene-3, 17-done is also a substrate for the isomerase.



(22) (23)

(29)

G. Magnetic Resonance and X-Ray Diffraction Data

The paucity of detailed information on the structure of the isomerase has posed a serious limitation to the conclusions that may be drawn from studies of the mechanism. The bacterial isomerase was first crystallized in 1960[71] and X-ray crystallographic studies were initiated by Westbrook and collaborators in 1971[126]. Difficulties were encountered during initial attempts to study a monoclinic crystal form of the enzyme grown at pH 7.0, and an alternative hexagonal crystal form grown from solution at pH 5.5 was chosen for study[127]. These crystals were found to be catalytically active and the crystal structure was solved at 6 Å resolution[82,128]. The location of the steroid binding site was determined with the competitive inhibitor 4-acetoxymercuriestradiol[82]. The steroid apparently binds in a pit which lies near the contact interface between the two monomers, and it was suggested that the binding site of each monomer might be influenced by the opposing monomer.

Refinement of the enzyme structure at 2.5 Å resolution is underway[129], and preliminary results of this work have been combined with magnetic resonance studies (NMR and EPR) to derive a model of the isomerase–steroid binding complex. Kuliopolis and coworkers[130] analyzed interactions between the isomerase and the spin-labelled steroid, spiro[doxyl-2,3′-5′α-androstan]-17β-ol (**70**). The paramagnetic effects of the spin label on the longitudinal relaxation rates of the resolved protein resonances were used to calculate distances from the nitroxide to those protons. On the basis of the calculated distances the

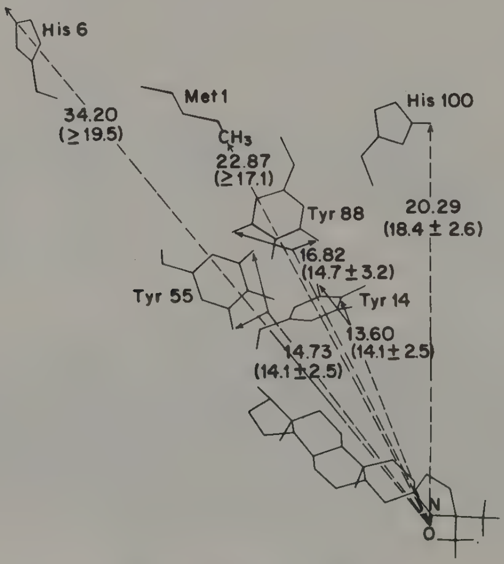
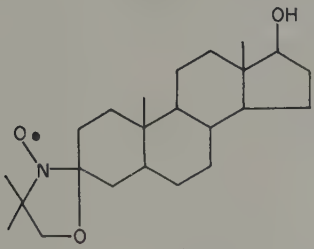


FIGURE 3. Computer-graphics representation showing the location of bound **70** at the active site of 3-oxo-Δ^5-steroid isomerase. Indicated root-mean-sixth average distances in angstroms are those measured by NMR (in parentheses) together with distances derived by positioning the spin label into the X-ray structure. The errors in the latter distances are ± 2 Å. Reproduced with permission from A. Kuliopulos, E. M. Westbrook, P. Talalay and A. S. Mildvan, *Biochemistry*, **26**, 3927 (1987). Copyright 1987, American Chemical Society

steroid molecule was 'docked' in the partially refined 2.5 Å resolution X-ray structure (Figure 3), and several resonances were assigned to specific residues, although the possibility of multiple binding modes of steroids with the isomerase complicates the interpretation.



(70)

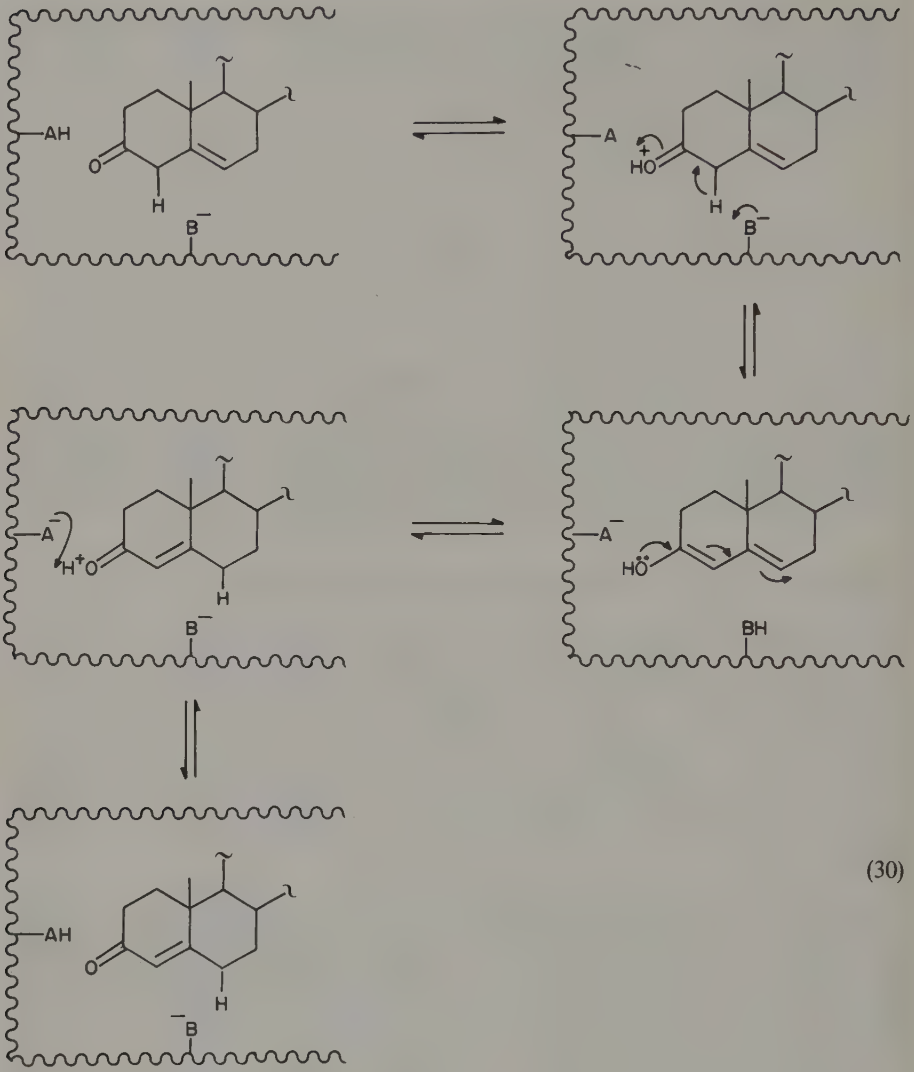
In agreement with previous results, it was found that Asp-38, Asn-57 and Tyr-55 are present at the active site, as well as Thr 35, Tyr 14, Tyr 88, Asp 32 and Glu 37. Binding of steroids seems to be controlled by hydrophobic interactions with three phenylalanine residues (82, 86 and 100) and Val 74 from the other subunit.

H. Models of the Active Site and Proposed Catalytic Mechanisms

By analogy to the mechanisms for the nonenzymatic catalysis of the isomerization of β,γ-unsaturated ketones, it is possible to write mechanisms involving either an enol or enolate ion as an intermediate in the isomerase reaction. A stepwise mechanism through a neutral enol (equation 30) would require the donation of a proton from an acid at the active site to the carbonyl, followed by abstraction of the 4β proton to produce a dienol, and subsequent reprotonation at $C_{(6)}$. Alternatively, deprotonation/reprotonation at carbon may not require prior protonation at oxygen but only hydrogen bonding of a dienolate ion intermediate (equation 31). A concerted mechanism that bypasses the formation of both a protonated ketone and a dienolate ion can also be written (equation 32).

In order to understand the mechanism of action of the isomerase, it is necessary to determine whether the reaction intermediate is a dienol or a dienolate ion and to specify the identity and functions of each of the amino acids involved in the mechanism. Furthermore, an analysis of the energetics of both the enzyme-catalyzed reaction and the corresponding nonenzymatic reaction should be carried out to determine the contributions of each of the active-site amino acids to catalysis. Although at present there is insufficient evidence to complete this analysis, substantial progress has been made.

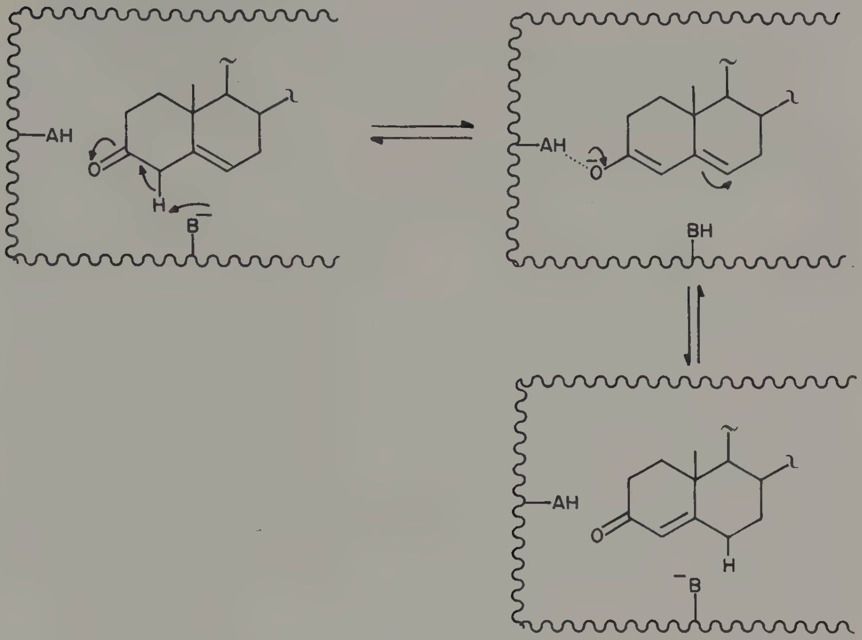
Malhotra and Ringold[18] sought to distinguish between neutral enols and their conjugate enolate anions in terms of the preferred site of protonation during acid-catalyzed interconversion of 3-oxo-Δ^4 and Δ^5 steroids. The neutral enol is preferentially protonated at $C_{(6)}$ to form the conjugated enone product[18], while the enolate anion undergoes protonation at $C_{(4)}$ to generate the thermodynamically unstable β,γ-unsaturated ketone[36]. Malhotra and Ringold[18] drew parallels between the acid-catalyzed model reaction and the enzymatic reaction. Like the enzymatic isomerization, the acid-catalyzed reaction proceeds via an almost exclusive $C_{(6)}$ protonation in the β position[18]; thus, the stereospecific protonation seen with the enzyme reaction might simply be explained in terms of the inherent chemical reactivity of substrate, and would be predicted if the enzyme proceeded via an acid-catalyzed mechanism. In the model studies, acid-catalyzed isomerization of 3-oxo-Δ^5-steroids shows a primary deuterium isotope effect



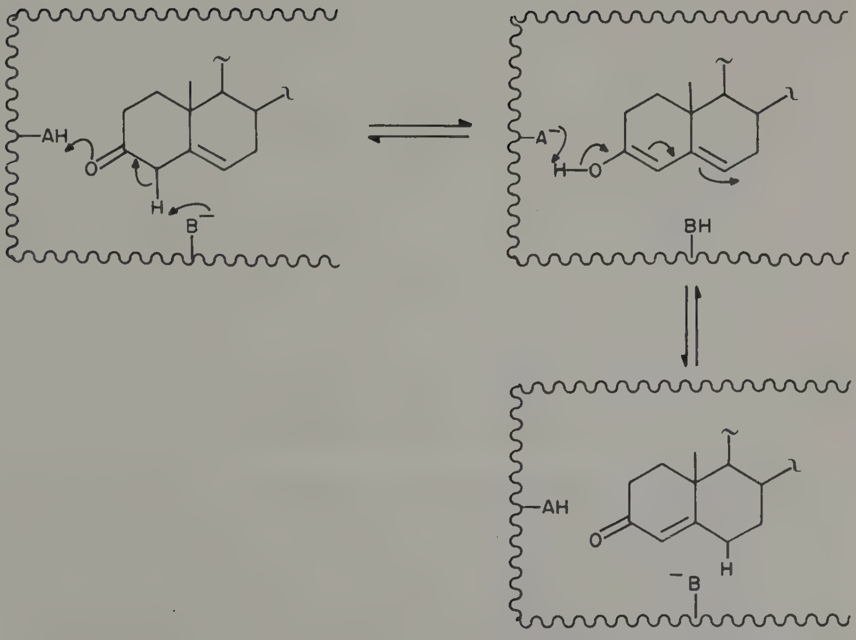
(30)

(k_{4H}/k_{4D}) of 4.1[18], and the enol protonates faster at $C_{(6)}$ than at $C_{(4)}$. The enzymatically catalyzed intramolecular $C_{(4)}$ to $C_{(6)}$ proton transfer in 5-androstene-3, 17-dione has a primary deuterium isotope effect ($k_{cat(4\beta H)}/k_{cat(4\beta D)}$) of 5.3, which is consistent with an acid-catalyzed mechanism. However, since the same proton that is abstracted from $C_{(4)}$ is transferred to $C_{(6)}$, the isotope effect could arise from either deprotonation at $C_{(4)}$ or protonation at $C_{(6)}$. If the enzymatic mechanism is indeed catalyzed by an acidic group and a neutral enolic intermediate is formed, then, based on the model studies, one might conclude that deprotonation at $C_{(4)}$ is the rate-limiting step.

The similarities between the acid-catalyzed and enzyme-catalyzed reactions concerning kinetic isotope effects and the site of protonation prompted Malhotra and Ringold[18] to



(31)



(32)

propose a catalytic mechanism involving a neutral enol intermediate. In their mechanism, an acidic residue (AH) acts to protonate the ketone substrate and facilitate the proton abstraction and transfer carried out by a basic residue (B^-) at the β face of bound steroid. The studies of Viger and coworkers[85] supported the mechanism of Malhotra and Ringold, with the inclusion of an α-side base (B'^-) to account for their observation of competitive abstraction of the 4α-proton.

The finding that the isomerase is inactivated by oxiranyl steroids is also consistent with an enolic mechanism, since epoxides are relatively inert toward nucleophilic attack unless protonated[131,132]. A comparison of the X-ray crystal structures of the steroidal oxiranes, (3*S*)-spiro[5α-androstan-3, 2′-oxiran]-17β-ol and (17*S*)-spiro[5α-androstan-17, 2′-oxiran]-3β-ol, with the structure of the substrate 5-androstene-3, 17-dione (Figure 1) demonstrated that the oxiranyl oxygen of the steroid epoxide and the 3-oxo oxygen of the substrate are similarly positioned relative to the steroid nucleus[120]. Thus, it is not unreasonable that the oxygens of the steroidal oxiranes and the substrate might be protonated by the same group on the enzyme surface.

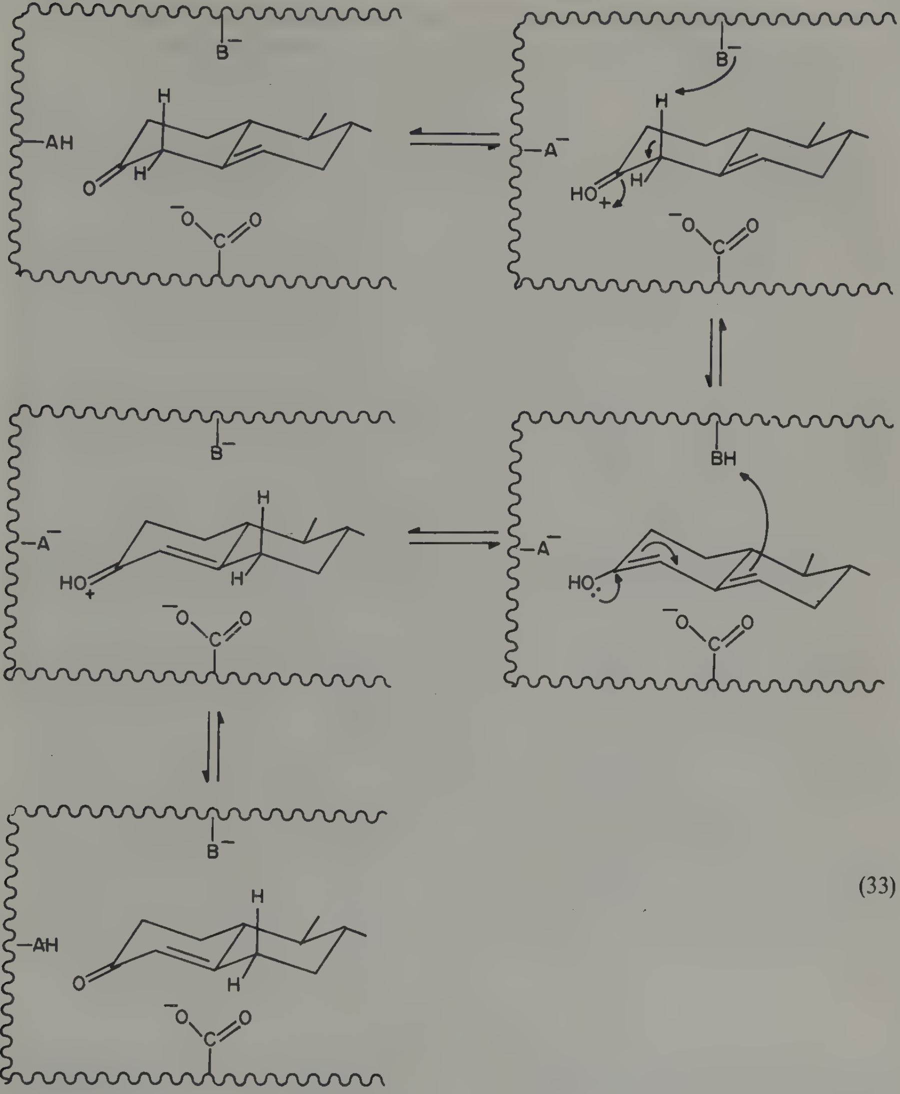
Based on the finding that Asp-38 attacks the oxiranyl steroids from the α-side of the steroid, we proposed that this group may act as an electrostatic catalyst to stabilize protonated ketone intermediates along the reaction pathway to and from a neutral dienol intermediate, analogous to the function of Asp-52 of lysozyme (equation 33)[81]. Kuliopulos and collaborators[130] modified this suggestion by proposing that the electrostatic catalyst is not Asp-38, but rather the negative end of an α-helix dipole, in addition to a carboxylate at the α face of the steroid (probably Glu-37). This proposal was based upon an interpretation of their data that places Asp-38 at the β face of the bound steroid.

The mechanisms proposed by Malhotra and Ringold[18] and subsequently by others[21,81,85,130] suggest that the substrate ketone group is protonated prior to or concurrent with abstraction of the 4β-proton. However, it is also possible that the enzyme functions through the formation of a dienolate ion, analogous to the base-catalyzed isomerization. The protons at $C_{(4)}$ are substantially more acidic (p*K* 12.7)[38] than would be expected for a saturated ketone (p*K ca* 18)[39,68,69], due to the β,γ-unsaturation, implying that protonation of the ketone may not be a prerequisite for proton abstraction. An anionic mechanism, in which the ion is stabilized by hydrogen bonding to the negatively charged oxygen of the intermediate, is a distinct possibility.

Studies by Wang and coworkers[83] in the early 1960s on the ultraviolet spectra of several competitive inhibitors bound to the active site of the isomerase may shed some light on this matter. The potent competitive inhibitor 19-nortestosterone exhibits an ultraviolet spectrum characteristic of an α,β-unsaturated ketone, having a maximum at 248 nm (in water)[83]. This spectrum undergoes a bathochromic shift to 258 nm in the presence of the isomerase, with the difference spectrum having a maximum of 270 nm. This shift was attributed to conversion of the enone in the active site to either a dienol or a dienolate intermediate, although a distinction between the two cannot be made on the basis of these data. This conclusion was strengthened by the observation that excess isomerase catalyzes the incorporation of deuterium from bulk solvent (D_2O) into 19-nortestosterone and other 3-oxo-Δ^4 steroids[83]. Unfortunately, the site of incorporation of deuterium was not determined.

Wang and coworkers[83] also demonstrated that the ultraviolet absorption spectrum of the competitive inhibitor 17β-estradiol in the presence of the isomerase resembles that of the ionized phenolate form, and suggested that a basic residue of the enzyme deprotonates the 3-hydroxyl group of the steroid. Similar findings were reported for both the ultraviolet and fluorescence spectra of 17β-dihydroequilenin complexes with the enzyme[83], and analogous complexes are transiently formed during the irreversible inactivation of the isomerase by (17*S*)-spiro[estra-1, 3, 5(10), 6, 8-pentaen-17, 2′ oxiran]-3-ol (**67**)[118,119].

Although it may be argued that the phenolic protons of these steroids are more acidic



(33)

(pK_a *ca* 10) than the hydrogen α to the 3-oxo group of the substrate, the ionization constant for 5-androsten-3,17-dione in aqueous solution (pK_a 12.7) shows that this ketone is considerably more acidic than typical saturated ketones, and it may be that proton transfer to the oxygen of the intermediate is not required for stabilization of the intermediate. It is possible that sufficient stability of an intermediate anion may be obtained simply by hydrogen bonding to an acidic group (or groups) of the enzyme. The pK_a of the intermediate dienol has not as yet been determined, but it is likely to be approximately 10 to 11 in aqueous solution, on the basis of other dienols[67]. Thus, proton transfer from a tyrosine ($pK_a \sim 9$–10) may provide little or no stabilization of a dienolate intermediate, although hydrogen bonding is probably important.

On the basis of current evidence, it appears certain that the isomerase acts through either an enol or enolate ion. Although definitive evidence allowing a choice to be made between the two is lacking, the acidity of 5-androstene-3, 17-dione suggests that a dienolate mechanism should not be ruled out. In either case, acidic groups on the enzyme can act to protonate the ketone (for an enol) or hydrogen bond (for an enolate ion).

The identity of the β-side base that mediates the catalytic proton transfer of the 4β-proton is also not clear. The stereochemical aspects of the reaction of the 3β- and 17β-oxiranyl steroids with the isomerase clearly indicate that Asp-38 reacts at the α face of the steroid nucleus[81,114]. However, in the model of the enzyme active site proposed by Kuliopolis and collaborators[130] Asp-38 is tentatively identified as the β-side base, although Glu-37 and Asp-32 are not ruled out. Since the isomerase can bind steroids in at least two orientations that differ by rotation about an axis perpendicular to the long axis of the steroid[80,114,119], and other steroid transforming enzymes can bind steroids in multiple orientations that involve flip-flopping of the α and β faces of the steroid[121,124], any positioning of specific residues with respect to the steroid nucleus must be made with caution. The model proposed[130] could be redrawn to place Asp-32 at the β face (for proton transfer) and Asp-38 at the α face (for electrostatic catalysis).

The evidence for the existence of a separate α-side base in the catalytic mechanism also depends on whether steroids can bind 'upside down'. An α-side base was initially invoked by Viger and coworkers[85] to rationalize nonproductive competitive abstraction of the 4α-proton during the catalytic reaction. However, if the isomerase can bind steroids either β-side 'up' or α-side 'up', then a single base could carry out both catalytic transfer of the 4β-proton and competitive abstraction of the 4α-proton. In the single base mechanism, the lack of proton transfer from the 4α-position to the 6β-position can be accounted for if steroid is not free to rotate about the long axis when it is bound.

In spite of the intense effort that has been mounted in several laboratories, the exact mechanism by which the isomerase functions is still unclear. There is agreement that the intermediate is either a dienol or dienolate, but no compelling evidence exists that can allow a choice to be made between the two. Although a reasonably detailed crystal structure is available, the catalytic functions of specific amino acid residues at the active site are unknown. In addition, the ability of the isomerase to bind steroids in more than one orientation makes a description of the productive complex hazardous. Perhaps site-directed mutagenesis experiments, facilitated by the recent cloning of the isomerase[133–136], will allow a more complete description of the mechanism.

V. ACKNOWLEDGMENT

Work from the authors' laboratory described in this chapter has been supported by the National Institutes of Health, the American Cancer Society, and the Petroleum Research Fund, administered by the American Chemical Society. We wish to thank Professors A. J. Kresge and R. L. Schowen for helpful comments.

VI. REFERENCES

1. F. H. Batzold, A. M. Benson, D. F. Covey, C. H. Robinson and P. Talalay, *Adv. Enzyme Regul.*, **XIV**, 243 (1976).
2. F. S. Kawahara, S.-F. Wang and P. Talalay, *J. Biol. Chem.*, **237**, 1500 (1962).
3. A. Fersht, *Enzyme Structure and Mechanism*, 2nd edn., W. H. Freeman and Co., New York, 1985.
4. K. Brocklehurst and A. Cornish-Bowden, *Biochem. J.*, **159**, 165 (1976).
5. J. Albery and J. R. Knowles, *Biochemistry*, **15**, 5627 (1976).

6. J. Hine, S.-M, Linden, A. Wang and V. Thiagarajan, *J. Org. Chem.*, **45**, 2821 (1980).
7. J. Hine, V. M. Kanagasabapathy and P. Ng, *J. Org. Chem.*, **47**, 2745 (1982).
8. J. Hine, *Structural Effects on Equilibrium in Organic Chemistry*, Wiley, New York, 1975, pp. 270–276.
9. J. Hine and M. J. Skoglund, *J. Org. Chem.*, **47**, 4758 (1982).
10. W. R. Nes, E. Loesser, R. Kirdant and J. Marsh, *Tetrahedron*, **19**, 299 (1963).
11. N. Heap and G. H. Whitham, *J. Chem. Soc. (B)*, 164 (1966).
12. D. L. Whalen, J. F. Weimaster, A. M. Ross and R. Radhe, *J. Am. Chem. Soc.*, **98**, 7319 (1976).
13. M. I. Page and W. P. Jencks, *Proc. Natl. Acad. Sci. U.S.A.*, **68**, 1678 (1971).
14. T. C. Bruice, A. Brown and D. O. Harris, *Proc. Natl. Acad. Sci. U.S.A.*, **68**, 658 (1971).
15. W. P. Jencks and M. I. Page, *Biochem. Biophys. Res. Commun.*, **57**, 887 (1974).
16. W. P. Jencks, *Adv. Enzymol. Relat. Subj. Biochem.*, **43**, 219 (1975).
17. U. Westphal and J. Schmidt-Thome, *Chem. Ber.*, **69**, 889 (1936).
18. S. K. Malhotra and H. J. Ringold, *J. Am. Chem. Soc.*, **87**, 3228 (1965).
19. D. S. Noyce and M. Evett, *J. Org. Chem.*, **37**, 394 (1972).
20. D. S. Noyce and M. Evett, *J. Org. Chem.*, **37**, 397 (1972).
21. J. B. Jones and D. C. Wigfield, *Can. J. Chem.*, **47**, 4459 (1969).
22. A. Kergomard, L. Q. Xang and M. F. Renard, *Tetrahedron*, **32**, 1989 (1976).
23. A. Kergomard and M. F. Renard, *Tetrahedron*, **28**, 2111 (1972).
24. P. Talalay and V. S. Wang, *Biochem. Biophys. Acta*, **18**, 300 (1955).
25. R. W. Taft, Jr., Office of Naval Research Contract No. 656(03), Project NRO 55-295, Final Report (1960).
26. T. Okuyama, A. Kitada and T. Fueno, *Bull. Chem. Soc. Jpn.*, **50**, 2358 (1977).
27. E. J. Corey and R. A. Sneen, *J. Am. Chem. Soc.*, **78**, 6269 (1956).
28. H. L. Carrell, J. P. Glusker, D. F. Covey, F. H. Batzold and C. H. Robinson, *J. Am. Chem. Soc.*, **100**, 4282 (1978).
29. G. Kruger, *J. Org. Chem.*, **33**, 1750 (1968).
30. G. Dzingeleski, S. Bantia, G. Blotny and R. M. Pollack, *J. Org. Chem.*, **53**, 1540 (1988).
31. N. A. C. Rogers and A. Sattar, *Tetrahedron Lett.*, 1471 (1965).
32. S. K. Malhotra and H. J. Ringold, *J. Am. Chem. Soc.*, **86**, 1997 (1964).
33. K. Sudarshan, S. K Malhotra and H. J. Ringold, *J. Am. Chem. Soc.*, **85**, 1538 (1963).
34. T. Okuyama, T. Sakagami and T. Fueno, *Tetrahedron*, **29**, 1503 (1973).
35. T. Okuyama, T. Fueno and J. Furukawa, *Tetrahedron*, **25**, 5409 (1969).
36. H. J. Ringold and S. K. Malhotra, *Tetrahedron Lett.*, 669 (1962).
37. S. K. Perera, W. A. Dunn and L. R. Fedor, *J. Org. Chem.*, **45**, 2816 (1980).
38. R. M. Pollack, J. P. G. Mack and S. Eldin, *J. Am. Chem. Soc.*, **109**, 5048 (1987).
39. P. Pruszynski, Y. Chiang, A. J. Kresge, N. P. Schepp and P. A. Walsh, *J. Phys. Chem.*, **90**, 3760 (1986).
40. Y. Chiang, A. J. Kresge, Y. S. Tang and J. Wirz, *J. Am. Chem. Soc.*, **106**, 460 (1984).
41. Y. Chiang, A. J. Kresge and J. Wirz, *J. Am. Chem. Soc.*, **106**, 6392 (1984).
42. A. M. Ross, D. L. Whalen, S. Eldin and R. M. Pollack, *J. Am. Chem. Soc.*, **110**, 1981 (1988).
43. A. J. Birch, *J. Chem. Soc.*, 1551, 2325 (1950).
44. P. Y. Bruice and T. C. Bruice, *J. Am. Chem. Soc.*, **100**, 4793 (1978).
45. P. Y. Bruice and T. C. Bruice, *J. Am. Chem. Soc.*, **100**, 4802 (1978).
46. M. Emly and D. L. Leussing, *J. Am. Chem. Soc.*, **103**, 628 (1981).
47. P. Y. Bruice, *J. Am. Chem. Soc.*, **105**, 4982 (1983).
48. A. J. Kresge and Y. Chiang, *J. Am. Chem. Soc.*, **95**, 803 (1973).
49. P. Y. Bruice, *J. Am. Chem. Soc.*, **106**, 5959 (1984).
50. R. H. Kayser and R. M. Pollack, *J. Am. Chem. Soc.*, **97**, 952 (1975).
51. R. M. Pollack and R. H. Kayser, *J. Am. Chem. Soc.*, **98**, 4174 (1976)
52. R. M. Pollack and M. Brault, *J. Am. Chem. Soc.*, **98**, 247 (1976).
53. M. Brault, R. M. Pollack and C. L. Bevins, *J. Org. Chem.*, **41**, 346 (1976).
54. M. Brault, R. H. Kayser and R. M. Pollack, *J. Org. Chem.*, **43**, 4709 (1978).
55. W. F. Benisek and A. Jacobson, *Biory. Chem.*, **4**, 41 (1975).
56. W. P. Jencks, *Catalysis in Chemistry and Enzymology*, Chap. 4, McGraw-Hill, New York (1969).
57. J. Hine, B. C. Menon, J. H. Jensen and J. Mulders, *J. Am. Chem. Soc.*, **88**, 3367 (1966).

58. M. L. Bender and A. Williams, *J. Am. Chem. Soc.*, **88**, 2502 (1966).
59. J. Hine, J. C. Craig, Jr., J. G. Underwood II and F. A. Via, *J. Am. Chem. Soc.*, **92**, 5194 (1970).
60. J. A. Barltrop and J. Wills, *Tetrahedron Lett.*, 4987 (1968).
61. M. J. Jorgenson, *J. Am. Chem. Soc.*, **91**, 198 (1969).
62. I. A. Skinner and A. C. Weedon, *Tetrahedron Lett.*, **24**, 4299 (1983).
63. A. C. Weedon, *Can. J. Chem.*, **62**, 1933 (1984).
64. C. S. K. Wan and A. C. Weedon, *J. Chem. Soc., Chem. Commun.*, 1235 (1981).
65. R. M. Duhaime, D. A. Lombardo, I. A. Skinner and A. C. Weedon, *J. Org. Chem.*, **50**, 873 (1985).
66. R. M. Duhaime and A. C. Weedon, *J. Am. Chem. Soc.*, **107**, 6723 (1985).
67. R. M. Duhaime and A. C. Weedon, *J. Am. Chem. Soc.*, **109**, 2479 (1987).
68. Y. Chiang, M. Hojatti, J. R. Keeffe, A. J. Kresge, N. P. Schepp and J. Wirz, *J. Am. Chem. Soc.*, **109**, 4000 (1987).
69. Y. Chiang, A. J. Kresge and P. A. Walsh, *J. Am. Chem. Soc.*, **104**, 6122 (1982).
70. R. M. Pollack, J. P. G. Mack and G. Blotny, *J. Am. Chem. Soc.*, **109**, 3138 (1987).
71. F. S. Kawahara and P. Talalay, *J. Biol. Chem.*, **235**, PCl (1960).
72. A. M. Benson, R. Jarabak, P. Talalay, *J. Biol. Chem.*, **246**, 7514 (1971).
73. H. Weintraub, F. Vincent, E.-E. Baulieu and A. Alfsen, *Biochemistry*, **16**, 5045 (1977).
74. W. F. Tivol, E. D. Beckman and W. F. Benisek, *J. Biol. Chem.*, **250**, 271 (1975).
75. A. M. Benson, A. J. Suruda and P. Talalay, *J. Biol. Chem.*, **250**, 276 (1975).
76. H. Weintraub, F. Vincent and E.-E. Baulieu, *FEBS Lett.*, **37**, 82 (1973).
77. F. Vincent, H. Weintraub, A. Alfsen and E.-E. Baulieu, *FEBS Lett.*, **62**, 126 (1976).
78. J. Ogez and W. F. Benisek, *Biochem. Biophys. Res. Commun.*, **85**, 1082 (1978).
79. T. M. Penning, E. M. Westbrook and P. Talalay, *Eur. J. Biochem.*, **105**, 461 (1980).
80. R. H. Kayser, P. L. Bounds, C. L. Bevins and R. M. Pollack, *J. Biol. Chem.*, **258**, 909 (1983).
81. C. L. Bevins, S. Bantia, R. M. Pollack, P. L. Bounds and R. H. Kayser, *J. Am. Chem. Soc.*, **106**, 4957 (1984).
82. E. M. Westbrook, O. E. Piro and P. Sigler, *J. Biol. Chem.*, **259**, 9096 (1984).
83. S.-F. Wang, F. S. Kawahara and P. Talalay, *J. Biol. Chem.*, **238**, 576 (1963).
84. H. Weintraub, E.-E. Baulieu and A. Alfsen, *Biochem. J.*, **185**, 723 (1980).
85. A. Viger, S. Coustal and A. Marquet, *J. Am. Chem. Soc.*, **103**, 451 (1981).
86. A. Viger and A. Marquet, *Biochim. Biophys. Acta*, **485**, 482 (1977).
87. H. Weintraub, A. Alfsen and E.-E. Baulieu, *Eur. J. Biochem.*, **12**, 217 (1970).
88. J. R. Knowles, *CRC Crit. Rev. Biochem.*, **4**, 165 (1976).
89. W. W. Cleland, *Adv. Enzymol. Relat. Areas Mol. Biol.*, **45**, 273 (1977).
90. M. Dixon and E. C. Webb, *Enzymes*, Academic Press, New York, 1980.
91. R. M. Pollack, unpublished observations.
92. R. Kluger and K. Nakoaka, *Biochemistry*, **13**, 910 (1974).
93. S. Shaltiel and M. Cortijo, *Biochem. Biophys. Res. Commun.*, **41**, 594 (1970).
94. A. Molrad, G. Hegyi and G. Toth, *Acta Biochim. Biophys. Acad. Sci. Hung.*, **2**, 19 (1967).
95. R. B. Wallis and J. J. Holbrook, *Biochem. J.*, **133**, 183 (1973).
96. P. Talalay, *Annu. Rev. Biochem.*, **34**, 347 (1965).
97. W. F. Benisek and J. R. Ogez, *Biochemistry*, **21**, 5816 (1982).
98. O. M. Colvin and P. Talalay, *Fed. Proc., Fed. Am. Soc. Exp. Bi.*, **27**, 523 (1968).
99. P. Talalay and A. M. Benson, in *The Enzymes* (Ed. P. D. Boyer), Vol. VI, 3rd edn., Academic Press, New York, 1972, p. 591.
100. R. Jarabak, M. Colvin, S. H. Moolgavkar and P. Talalay, *Methods Enzymol.*, **15**, 642 (1969).
101. T. M. Penning and P. Talalay, *J. Biol. Chem.*, **256**, 6851 (1981).
102. F. H. Batzold and C. H. Robinson, *J. Am. Chem. Soc.*, **97**, 2576 (1975).
103. F. H. Batzold and C. H. Robinson, *J. Org. Chem.*, **41**, 313 (1976).
104. D. F. Covey and C. H. Robinson, *J. Am. Chem. Soc.*, **98**, 5038 (1976).
105. T. M. Penning, D. F. Covey and P. Talalay, *J. Biol. Chem.*, **256**, 6842 (1981).
106. T. M. Penning, D. N. Heller, T. M. Balasubramanian, C. C. Fenselau and P. Talalay, *J. Biol. Chem.*, **257**, 12589 (1982).
107. R. J. Martyr and W. F. Benisek, *Biochemistry*, **12**, 2172 (1973).
108. R. J. Martyr and W. F. Benisek, *J. Biol. Chem.*, **250**, 1218 (1975).
109. J. R. Ogez, W. F. Tivol and W. F. Benisek, *J. Biol. Chem.*, **252**, 6151 (1977).
110. M. Hearne and W. F. Benisek, *Biochemistry*, **24**, 7511 (1985).
111. M. Hearne and W. F. Benisek, *J. Protein Chem.*, **3**, 87 (1984).

112. W. F. Benisek and M. Hearne, in *Protein Tailoring for Food and Medical Uses* (Eds. R. E. Feeney and J. R. Whitaker), Marcel Dekker, Inc., New York, 1986, p. 243.
113. W. F. Benisek, J. R. Ogez and S. B. Smith, *Ann. N.Y. Acad. Sci.*, **346**, 115 (1980).
114. P. L. Bounds and R. M. Pollack, *Biochemistry*, **26**, 2263 (1987).
115. R. M. Pollack, S. Bantia, P. L. Bounds and B. M. Kaufman, *Biochemistry*, **25**, 1905 (1986).
116. K. G. Linden and W. F. Benisek, *J. Biol. Chem.*, **261**, 6454 (1986).
117. S. Bantia, C. L. Bevins and R. M. Pollack, *Biochemistry*, **24**, 2606 (1985).
118. C. L. Bevins, R. H. Kayser, R. M., Pollack, D. B. Ekiko and S. Sadoff, *Biochem. Biophys. Res. Commun.*, **95**, 1131 (1980).
119. C. L. Bevins, R. M. Pollack, R. H. Kayser and P. L. Bounds, *Biochemistry*, **25**, 5159 (1986).
120. S. Kashino, H. Katz, J. P. Glusker, R. M. Pollack and P. L. Bounds, *J. Am. Chem. Soc.*, **109**, 6765 (1987).
121. R. C. Strickler, D. F. Covey and B. Tobias, *Biochemistry*, **19**, 4950 (1980).
122. F. Sweet and B. R. Samant, *Biochemistry*, **19**, 978 (1980).
123 J. B. Adams and D. McDonald, *Biochim. Biophys. Acta*, **664**, 460 (1981).
124. D. J. Saxman, A. Ko and C. Walsh, *J. Biol. Chem.*, **258**, 11937 (1983).
125. S. Bantia and R. M. Pollack, *J. Am. Chem. Soc.*, **108**, 3145 (1986).
126. E. M. Westbrook, P. B. Sigler, H. Berman, J. P. Glusker, G. Bunick, A. Benson and P. Talalay, *J. Mol. Biol.*, **103**, 665 (1976).
127. E. M. Westbrook, *J. Mol. Biol.*, **103**, 659 (1976).
128. E. M. Westbrook and P. B. Sigler, *J. Biol. Chem.*, **259**, 9090 (1984).
129. E. M. Westbrook, personal communication.
130. A. Kuliopulos, E. M. Westbrook, P. Talalay and A. S. Mildvan, *Biochemistry*, **26**, 3927 (1987).
131. F. A. Long and J. G. Pritchard, *J. Am. Chem. Soc.*, **78**, 2663 (1956).
132. F. A. Long and J. G. Pritchard, *J. Am. Chem. Soc.*, **78**, 2667 (1956).
133. K. Y. Choi and W. F. Benisek, *Gene*, **58**, 25 (1987).
134. K. Y. Choi and W. F. Benisek, personal communication.
135. A. Kuliopulos, D. Shortle and P. Talalay, *Biochemistry*, **26**, 4167 (abstr.) (1987).
136. A. Kuliopulos, D. Shortle and P. Talalay, *Proc. Natl. Acad. Sci. U.S.A.*, **84**, 8893 (1987).
137. Y. Chiang, A. J. Kresge, J. A. Santaballa and J. Wirz, *J. Am. Chem. Soc.*, **110**, 5506 (1988).

ISBN 0 471 91563 7